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ADVANCES IN PEDIATRICS

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Preface to the Second Edition

A plethora of literature has been published in the field of pediatrics during the past few decades. In the last five years there has been a many folds increase in the knowledge. With each passing moment our knowledge-base, has expanded dramatically, with the resultant emergence of various super- and subspecialties. We, in this edition of *Advances in Pediatrics*, have tried to add the latest management protocols for various diseases. There are some articles which cannot be found in any textbook but are invaluable for the pediatrician who is fresh in practice. The book will also be of great help to a postgraduate appearing in the examination as it gives consolidate information on a number of topics. The efforts put in by us in the past few months have resulted in a unique collation of expertise, clinical application and incisive opinions on the latest in our fields. It has been our pleasure to have a host of eminent academicians and practitioners, both international and national, as a part of this endeavor, each lending their imprint into the development of a thorough and comprehensive compendium. We, in India, are still struggling with abysmal health indices and they are a matter of shame. With the economic upturn, we need to see that the benefits of this percolate down to the poorest of the poor. We have a huge human resource of health care professionals but they are concentrated in the cities. The facility for updating the knowledge are not very good. We hope that the book will go a long way in bridging the gap for updating the knowledge of pediatricians. We are happy that the organizing committee of the PEDICON 2012 have decided that it is very important to disseminate knowledge and towards this end, they are giving a copy of the book to each and every delegate attending the conference. The need of the hour is to be well prepared to meet the adversities that come our way as professionals. Whether we are good, better or the best, we should never let it rest, until our good is better, and our better, the best. That has been the philosophy of our book, and that is the spirit that we would encourage to inculcate in all our readers. A beginning has been made and to see a generation benefit from this vast resource would be most gratifying for us.

Anupam Sachdeva

AK Dutta

Preface to the First Edition

A plethora of literature has been published in the field of Pediatrics during the past few decades. With each passing moment our knowledge base has expanded dramatically, with the resultant emergence of various super and sub specialties. The very notion that a practicing pediatrician, and for that matter even a post graduate student, must be competent to deliver holistic care for the child patient at every juncture and in each of these ramifications of pediatrics, is a challenging prospect and highlights the need for continuing education and enhancement of one's skills. To meet these needs, we considered tracking the current trends of pediatric practice in the form of a concise book. The labors of the past few months have resulted in a unique collation of expertise, clinical application and incisive opinions on the latest in our fields. It has been our pleasure to have a host of eminent academicians and practitioners, both international and national, as a part of this endeavor, each lending their imprint into the development of a thorough and comprehensive compendium. The issues that we have addressed through "Advances in Pediatrics" reflect the health afflictions of the Indian child specifically, both urban as well as rural. Our nation suffers from perhaps one of the highest infant - and under five - mortality rates across the globe, reflecting the non availability and delivery of the neonatal health care system. In such a scenario, the importance of neonatal care assumes principal significance. In the same breath, infectious diseases are perhaps a major cause for mortality too and their management and prevention with appropriate vaccination have been the focus of attention. Our purview extends to include gastroenterology, hemato-oncology, nephrology, pediatric cardiology, emergency and respiratory diseases and neurology amongst others. The need of the hour is to be well prepared to meet the adversities that come our way as professionals. Whether we are good, better or the best, we should never let it rest, until our good is better, and our better, the best. That has been the philosophy of our book, and that is the spirit that we would encourage to inculcate in all our readers. A beginning has been made and to see a generation benefit from this vast resource would be most gratifying for us.

I shall be telling this with a sigh
Somewhere ages and ages hence:
Two roads diverged in a wood, and I—
I took the one less travelled by,
And that has made all the difference.

AK Dutta
Anupam Sachdeva

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Section 1

Neonatology

Editor
Neelam Kler

CHAPTER 1

Setting Up of Neonatal Intensive Care Unit

Ashish Mehta

Setting up an neonatal intensive care unit (NICU) is a challenging job which requires a lot planning and contemplation on many fronts.

A well organized neonatal unit is the back-bone on which clinicians and nurses work to produce the desired outcome. Without a well organized unit, medical and paramedical staff may struggle to apply their skills in a timely and efficient manner, which ultimately affects over-all outcome of the unit. Setting up a good NICU is not a single-handed job, it is a team work. While designing, a lot needs to be planned before putting into practice. Experts with knowledge and skills—like architects, civil and electrical engineers, fire-personnel, interior designers, bio-medical engineers - form a core team. This team works and designs a plan based on requirements of clinicians, nurses and supporting staff.

In a developed country recommended standards of newborn ICU are already made and they are revised at regular intervals. Unfortunately we do not have such standards. National Neonatal Forum has already specified requirements to establish various levels of care in NICU but guidelines to design such units in our country are not there.

Recommended standards of materials, meant suitable for environment of developed country and usage may not be suitable/required for our NICU. One may need to spend a lot to procure such materials. In that case, we need to look at what is best available in our country. Materials that are harmless and durable should be used.

Thus before embarking upon the design of an NICU, following requirements need to be kept in mind:

- Available space for NICU (carpet area)
- Number of beds required (current and future)
- Number of staff required: clinical, personnel in each shift to handle babies and other services.
- Equipment: movable and non-movable
- Light source: emergency and regular

- Acoustic effect: internal and external
- Heating, ventilation system and air conditioning (HVAC).

Once this is decided, following can be planned:

- Space planning: visualized 3D space
- Operational planning-traffic pattern
- Functional location of beds and equipment
- Ancillary services location
- Interior planning
- Surface – floor, walls and ceiling material planning
- HVAC - designing outlets.

Based on the above, a blue-print is prepared. Inputs are required at every level before execution of the design.

NICU LOCATION WITHIN THE HOSPITAL

Ideally, NICU should be in close proximity to the birthing unit in the hospital. If that is not possible, an elevator just adjacent to birthing unit with facility for key operation is desirable. Traffic for other services/disciplines should not pass through NICU. Those NICUs where babies are received from outside, NICU should have direct access to hospital transport receiving area.

Space Requirement

Depending upon the complexity of care rendered, bed space can be planned-Keeping in mind family's involvement in care of an infant.

Traditional design of NICU is of “multiple bed NICU”, where a single big area is designed with multiple beds. Current and more popular concept in developed world is of “single family room NICU”, where mother stays with baby in NICU. Such units not only require huge space, but also more staff. Evidence supports that such designs are practical, popular and justified by increasing awareness of the impact of the sensory environment on premature and ill newborns.

In resource limited set ups such concept may not be viable. In that case, a well spaced multiple bed NICU also serves equal purpose. For level 3 multiple bed NICU, infant bed space should be 120 sqft of unobstructed space. The distance between two baby beds should be 8-12 feet, so that the area adjacent to each infant space will have a minimum width of 4 feet. Each infant space should be designed to allow privacy for infant and family.

Infant space for intensive care infant beds situated in a single infant room should be at least 150 sq.ft per infant to provide adequate space for both equipment and family. The width of aisle in multiple bedroom should be enough to allow for easy movement of all equipment which might be brought to the infant's bedside, as well as for easy access of maternal bed. Aisle width of 8 feet is good enough for this purpose.

FAMILY SUPPORT AREA

Adequate space is required immediately adjacent to the NICU for families. The family hold area should have space for gowns, hand washing, secured storage for their belongings, a small pantry and toilet. The sitting should be comfortable and play area with entertainment material for children should be provided. These rooms should have emergency call and telephone or intercom linkage with NICU staff. It is a good idea to provide internet and education material in this area.

STAFF SUPPORT AREA

Adequate space should be provided within the NICU to meet the professional, personal and administrative needs of the staff. These areas include lockers, lounges, counseling space, education and conference space. On call rooms with adequate facilities are required for relaxation.

MOTHER'S ROOM

A mother's room is an important part of any well-designed NICU. These rooms should be within or immediately adjacent to the NICU. These rooms should be sufficient equipped and sized to accommodate parents and people from various disciplines (clinicians, nurses, social workers, etc.) who may need to meet the parents in private. The aim of these rooms is to encourage over-night stay by parents of the infants in NICU when opportunities arise to do so. The number of rooms will depend on number of growing babies in the NICU, and regional practices. These rooms need to have medical gas and suction outlets. Light music and TV facilities along with educational video/ material are desirable.

SUPPORT SPACE FOR ANCILLARY SERVICES

Specialized feeding preparation area or room should be provided in the NICU, which is away from the bedside.

This area will require hands-free hand washing station, counter for work space, and storage area for formula. A dedicated fridge is required for refrigerated and frozen breast milk.

Other ancillary services such as respiratory therapy, laboratory, pharmacy, radiology, developmental therapy are part of NICU. Distance, size and access are to be decided based on overall working pattern of the hospital, e.g. for multispecialty hospital, all these services can be centralized.

ADMINISTRATIVE SPACE

The disciplines that provide services to the unit, on a daily basis need distinct areas to carry out their responsibilities. Such disciplines can share a single room.

GENERAL SUPPORT SPACE

Adequate facilities should be provided for clean, soiled utilities, medical equipment storage and unit management services.

Clean utility areas are for storage of supplies frequently used in newborn care. Soiled utility room is essential for storing used and contaminated material before its removal from care area. It is desirable to have hand washing facility and covered waste receptacle with foot control. This area should have negative air pressure with 100% air exhausted to the outside. More important would be its location in the NICU. It should be located in such a way that soiled material can be removed without passing from infant care area.

Adequate charting space in form of separate area or desk for tasks like complying detailed records, completing requisitions and telephone communication should be provided.

Ideally three zone storage system is desirable. The first storage area should be control supply of the hospital. Second storage zone is the clean utility area. Third storage zone is for items frequently used at the infant's bedside (in the form of bedside cabinets). While designing third storage zone and charting area, ease of access to the staff, infection and noise control should be considered.

For laundry facility, separate laundry room with washing machine and dryer is required. Commercial grade washer, dryer should be installed.

ISOLATION ROOM

An air-borne infection isolation room is a part any good NICU. This room should have negative air pressure with 100% air exhausted to the outside. Adequate hands free hand washing station, area for gowning and a separate area for clean and soiled material is required near the entrance of the room. At least a single occupancy isolation room should be available for infant suspected with

air-borne infection. A space within the NICU should also be available to safely isolate infants infected with common air borne pathogen. Isolation room should have self closing devices on exit doors.

HAND WASHING STATIONS

Hand washing station should be no closer than 3 feet from an infant bed or clean supply store. NICU where a single infant concept is used, a hands free hand washing station shall be provided with each infant room. In multiple bed room NICU, every infant bed shall be within 20 ft of a hands-free hand washing station.

The sink should be large enough to control splashing and should be designed to avoid standing or retained water. The minimum dimensions for hand washing sink are 24 inches wide × 16 inches front to back × 10 inches deep from bottom of the sink to the top of its rim (61 cm × 41 cm × 25 cm). Hand washing instruction in written and pictorial should be provided above the sinks. There should be no aerator on the faucet.

Sink location, construction material and related hardware should be chosen with durability, ease of operation, ease of cleaning and noise control in mind.

ELECTRICAL GAS SUPPLY AND MECHANICAL NEED

Electrical and gas outlets near each infant bed should be organized, to ensure safety, easy access and maintenance. From available resources in the market, a system should be chosen which can include race ways for electrical conduit and gas piping. There should be minimum 18 to 20 simultaneously accessible electrical outlets.

Minimum number of gas outlets is 3 for air, 3 for oxygen and 2 for vacuum. A provision should be made to allow data transmission to a remote location.

GENERAL LIGHTING

Illumination plays an important role in the healing environment and inappropriate lighting can have negative effect on the health of sick babies. On one side perception of skin tone is critical in NICU, and on the other side continuous exposure to bright light in preterm infants can cause harmful effects.

Ambient lighting levels in infant space should be adjustable through a range of at least 10 to 600 lux as measured at each bedside. Both natural and electrical light sources should have controls that allow immediate darkening of any bed position, sufficient for trans-illumination when necessary. A master switch is desirable when rapid darkening of the room is required. Control of lights should be accessible to staff and families. No direct view of electrical light or sun in infant space should be provided. So as to avoid any infant's direct line of sight to the fixture.

To perform the procedures, separate lighting capable of providing no less than 2000 lux is required. This lighting should be adjustable to the required level when required. Lighting fixtures should be easily cleanable.

In the NICU which has lot of natural light, the issue of fluctuation in ambient temperature should be addressed. The thermal effect can cause fluctuation in ambient temperature. The window glass should be double glazed units with appropriate U-factors and solar factors.

At least one source of daylight should be visible from infant care area. Such windows should also be of double glazed glass and should be situated at least 2 feet from any part of the infant bed to minimize radiant heat loss.

FLOOR SPACE

Floor surfaces should be easily cleanable and should minimize growth of microorganisms. Floors should be highly durable to withstand frequent cleaning and heavy traffic. Consideration should also be given to glossiness, their acoustical properties and density of the material used. Polyvinyl chloride or vinyl is common in flooring materials. The production of PVC generates Dioxin, a potent carcinogen. Dioxin releases are not associated with materials such as polyolefin, rubber (latex) or linoleum. Resilient sheet flooring (medical grade rubber or linoleum) is suitable flooring. While laying the flooring, seams should be heat or chemically welded. Careful carpeting should provide impermeable backing.

WALL SURFACES

As with floors, the ease of cleaning, durability and acoustic properties of wall surfaces must be considered. The outer surfaces of walls must be created with materials that have antibacterial solid mineral surface and should be bacteriostatic.

CEILING FINISHES

False ceilings should be modular type and ideally hermetically sealed. Suspended ceiling should be structured by means of nontoxic silicon application for cleaned rooms, such that an air-tight environment is created in NICU.

AMBIENT TEMPERATURE AND THE VENTILATION

The air temperature of the NICU should be 20 to 26°C (72 to 78°F) and a relative humidity of 30 to 60%.

A minimum of six air changes per hour is required with a minimum of two changes being outside air. Ventilation air delivered to the NICU should be filtered with at least 3 micron HEPA filters. Filters should be located outside the infant care area so that they can be changed easily and safely.

ACOUSTIC ENVIRONMENT

The permissible noise criteria of an hourly L_{eq} is of 45 dB and an hourly L_{10} is of 50 dB. Transient sound should not cross 65 dB. To achieve these conditions, the noise criteria for surroundings should be considered.

Apart from engineering requirements, to run NICU at distinctive level, requires addressing lot many other issues like:

- Protocol based management
- Training of medical and paramedical staff
- Software specifically designed for NICU
- Follow-up clinics

- Maintenance services for medical and nonmedical gadgets.

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CHAPTER 2

Neonatal Resuscitation Programme 2010: Changes and the Way Beyond

Vikram Datta

INTRODUCTION

Of the nearly 100 million babies born annually worldwide majority of newborns do not require any assistance for transition from intrauterine to extrauterine life, however 10 percent newborns require intervention while <1 percent require extensive resuscitation.^{1,2}

This article will review the current practices, new recommendations' and special considerations in neonatal resuscitation.

Over the years there have been constant changes in Neonatal Resuscitation Programme (NRP) based on the currently available evidence. The International Liaison Committee on Resuscitation (ILCOR) was formed in 1992 and comprises the eight international resuscitation organizations: American Heart Association (AHA), European Resuscitation Council (ERC), Heart and Stroke Foundation Canada (HSFC), Resuscitation Council of Asia (RCA), Resuscitation Council of Southern Africa (RCSA), Australia and New Zealand Council on Resuscitation (ANZCOR), Inter American Heart Foundation (IAHF).

ILCOR provides a mechanism by which the international science and knowledge relevant to cardiopulmonary resuscitation and emergency cardiovascular care is identified and reviewed and periodically develop and publish a consensus on resuscitation science. ILCOR uses a formal evidence evaluation process to identify and prioritize questions and assign reviewers.

The task of evaluating published research is daunting and to make the process easier, several scientists have outlined categories of evidence and stratified them.

The levels of evidence outline by Sackett and his colleagues in 2000 are as follows:

- 1A = Systematic review of randomized controlled trials (RCTs)
- 1B = RCTs with narrow confidence interval

- 1C = All or none case series
- 2A = Systematic review cohort studies
- 2B = Cohort study/low quality RCT
- 2C = Outcomes research
- 3A = Systematic review of case-controlled studies
- 3B = Case-controlled study
- 4 = Case series, poor cohort case controlled
- 5 = Expert opinion.

Hadorn and his colleagues outlined another way of classifying categories of evidence:

- *Level A:* Well-conducted RCT with 100 patients or more (including multicenter and meta-analyses); well-conducted RCT with fewer than 100 patients (one or institutions and meta-analysis; well-conducted study).
- *Level B:* Well-conducted case-control study, poorly controlled or uncontrolled (including RCT with one or more major or three or more minor methodological flaws), observations studies with high potential for bias, case series or case reports, conflicting evidence with more support.
- *Level C:* Expert opinion

Since publication of the 2005 *International Consensus on CPR and ECC Science With Treatment Recommendations*,³⁻⁵ several controversial neonatal resuscitation issues have been identified. The literature was researched and a consensus was reached on the assessment of oxygenation and role of supplementary oxygen, peripartum management of meconium, ventilation strategies, devices to confirm placement of an advanced airway (e.g. tracheal tube or laryngeal mask airway), medications, maintenance of body temperature, postresuscitation management, and considerations for withholding and discontinuing resuscitation.

International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations: 2010

- Newborns born at term actively crying with good tone should not be separated from the mothers, should be put on the mothers chest to dry and to warm.
- All others need to be assessed to determine their need for one or more of the following actions in sequence
 - A. Initial steps in stabilization (dry and provide warmth, position, assess the airway, stimulate to breathe).
 - B. Ventilation.
 - C. Chest compressions.
 - D. Medications or volume expansion.

Each step should be completed in 30 sec, the successful completion of the first step permits progression to the next and is initially based on simultaneous assessment of 2 vital characteristics: heart rate and respirations.

Major Changes in 2010 and Rationale

1. Progression to the next step following the initial evaluation is now defined by the simultaneous assessment of 2 vital characteristics: heart rate and respirations.
2. Oximetry should be used for evaluation of oxygenation because assessment of color is unreliable.
Class I, Level of Evidence B.
3. For babies born at term it is best to begin resuscitation with air rather than 100 percent oxygen.
Level of Evidence B, Class II B.
4. Administration of supplementary oxygen should be regulated by blending oxygen and air should regulate administration of supplementary oxygen, and the concentration delivered should be guided by oximetry.
Class IIb, Level of Evidence C.
5. The available evidence does not support or refute the routine endotracheal suctioning of infants born through meconium-stained amniotic fluid, even when the newborn is depressed.
Class IIb, Level of Evidence C.
6. The chest compression-ventilation ratio should remain at 3:1 for neonates unless the arrest is known to be of cardiac etiology, in which case a higher ratio of 15:2 should be considered.
Class IIb, Level of Evidence C.
7. Therapeutic hypothermia should be considered for infants born at term or near-term with evolving moderate to severe hypoxic-ischemic encephalopathy, with protocol and follow-up coordinated through a regional perinatal system.
Class IIa, Level of Evidence A.
8. Cord clamping should be delayed for at least 1 minute in assessments, auscultation of the heart is the most accurate, babies who do not require resuscitation. Evidence is insufficient to recommend a time for clamping in those who require resuscitation.
Level of Evidence 1.

9. It is appropriate to consider discontinuing resuscitation if there has been no detectable heart rate for 10 minutes. Many factors contribute to the decision to continue beyond 10 minutes.
Class IIb.

Rationale

1. Heart rate should remain the primary vital sign by which to judge the need for and efficacy of resuscitation. Auscultation of the precordium should remain the primary means of assessing heart rate. There is a high likelihood of underestimating heart rate with palpation of the umbilical pulse, but this is preferable to other palpation locations.⁵⁻⁷
2. For babies who require ongoing resuscitation or respiratory support or both, the goal should be to use pulse oximetry as color is a poor indicator of oxygenation and both hypoxia and hyperoxia are detrimental. The sensor should be placed on the baby's right hand or wrist before connecting the probe to the instrument.⁸
3. In term babies 100 percent oxygen conferred no advantage over air in the short-term and resulted in increased time to first breath or cry or both.^{9,10}
4. Because many preterm babies of 32 weeks' gestation will not reach target saturations in air, blended oxygen and air may be given judiciously and ideally guided by pulse oximetry. Both hyperoxemia and hypoxemia should be avoided. If a blend of oxygen and air is not available, resuscitation should be initiated with air.¹¹
5. In healthy neonates suctioning of the mouth and nose can cause cardiorespiratory complications. In infants who are intubated, sedated, or paralyzed following resuscitation, endotracheal suctioning in the absence of secretions may result in a decrease in oxygenation, an increase in cerebral blood flow and intracranial pressure, and a decrease in compliance.¹²⁻¹⁴
6. Adequate ventilation is essential to reverse asphyxia arrest and increasing the chest compressions will result in decreased ventilation, which is not desired in post-asphyxia newborns.¹⁵
7. There are several RCTs confirming the benefits of induced hypothermia in postasphyxia newborns associated with significantly fewer deaths and less neurodevelopmental disability at 18-month follow-up. It should begin within 6 hours of birth, continue for 72 hours after birth, and rewarm over at least 4 hours.¹⁶⁻¹⁸
8. Newborns with delayed cord clamping have higher iron stores in infancy, lesser incidence in intracranial hemorrhage, better blood pressure, lesser need for blood transfusions.¹⁹
9. The following guidelines must be interpreted according to current regional outcomes.^{20,21}

- Resuscitation is not indicated in extreme prematurity (gestational age 23 weeks or birth weight 400 g), anencephaly, and some major chromosomal abnormalities, such as trisomy 13 (Class IIa).
- Resuscitation is nearly always indicated in babies with gestational age 25 weeks and those with most congenital malformations (Class IIa).
- In conditions associated with uncertain prognosis in which survival is borderline, the morbidity rate is relatively high, and the anticipated burden to the child is high, parental desires concerning initiation of resuscitation should be supported (Class Indeterminate).

VENTILATION STRATEGIES

Ventilation strategies were examined from 4 perspectives:

- Characteristics of the initial assisted breaths and the role of positive end-expiratory pressure (PEEP)
- Continuous positive airway pressure (CPAP) during or following resuscitation
- Devices to assist ventilation
- Strategies when resources are limited.

Positive Pressure Ventilation (PPV)

To establish initial lung inflation in apneic newborn infants, initiation of intermittent positive-pressure ventilation at birth can be accomplished with either shorter or longer inspiratory times. However, initial peak inflating pressures necessary to:

- Achieve an increase in heart rate or
- Movement of the chest are variable and unpredictable and should be individualized with each breath.²²

Pressures: An initial inflation pressure of 20 to 25 cm of H₂O may be effective in preterm babies, but a pressure of 30 to 40 cm H₂O may be necessary in some term babies.

If pressure is not being monitored, the minimal inflation required to achieve an increase in heart rate should be used.²³

Over inflation of chest in preterms during resuscitation should be avoided.

Assisted ventilation should be delivered at a rate of 40 to 60 breaths per minute to promptly achieve or maintain a heart rate 100 per minute.²⁴

CONTINUOUS POSITIVE AIRWAY PRESSURE

Spontaneously breathing preterm infants who have respiratory distress may be supported with CPAP or intubation and mechanical ventilation. The most appropriate choice may be guided by local expertise and preferences.²⁵

Assisted Ventilation

Ventilation of the newborn can be performed effectively with a flow-inflating bag, a self-inflating bag, or a pressure-limited T-piece resuscitator.

Laryngeal Mask Airway

The laryngeal mask airway indications:

If face mask and tracheal intubation is unsuccessful or not feasible.

The laryngeal mask airway may be considered as an alternative to a face mask for positive-pressure ventilation among newborns weighing 2000 g or delivered at 34 weeks' gestation.²⁶

Use has not been evaluated in:

- Meconium-stained amniotic fluid
- During chest compressions, or
- For administration of emergency intratracheal medications.

Endotracheal intubation may be indicated at several points during neonatal resuscitation:

- Initial endotracheal suctioning of nonvigorous meconium-stained newborns
- If bag-mask ventilation is ineffective or prolonged
- When chest compressions are performed
- For special resuscitation circumstances, such as congenital diaphragmatic hernia or extremely low birth

Indicator of Endotracheal Intubation

- Prompt *increase in heart rate* is the best indicator that the tube is in the tracheobronchial tree and providing effective ventilation.
- Exhaled CO₂ detection is the recommended method of confirmation of endotracheal tube placement (LOE 5).
- Other clinical indicators — condensation in the endotracheal tube, chest movement, and presence of equal breath sounds bilaterally, have not been systematically evaluated in neonates.

Medications and Fluid Administration

Epinephrine

If adequate ventilation and chest compressions have failed to increase the heart rate to >60 beats per minute, then it is reasonable to use epinephrine.

Dose: 0.01 to 0.03 mg/kg *intravenously* (Class IIa)

If intravenous access is not available it can be given by endotracheal route.

Dose: 0.05 mg/kg to 0.1 mg/kg (Class Indeterminate).^{27,28}

Volume Expansion

- Early volume replacement with crystalloid or red cells is indicated for babies with blood loss, not responding to resuscitation. Because blood loss may be occult, a trial of volume administration may be considered in babies who do not respond to resuscitation (Class IIb, LOE C).²⁹
- An isotonic crystalloid solution or blood is recommended for volume expansion in the delivery room rather than albumin (Class IIb). The recommended dose is 10 ml/kg.

Other Drugs

Very rarely a narcotic antagonist (naloxone), sodium bicarbonate or vasopressors may be useful after resuscitation. However, these are not used routinely.³⁰ If naloxone has to be used heart rate and color must first be restored using adequate ventilation. Only IV or IM use is recommended, in absence of clinical data use via endotracheal route is not recommended (Class Indeterminate).

Supportive Therapy

Temperature Control

Newborn infants of 28 weeks' gestation should be completely covered in a polythene wrap or bag up to their necks without drying immediately after birth and then placed under a radiant heater and resuscitated or stabilized in a standard fashion (Class IIa, LOE 2,4,5). Delivery room temperatures should be at least 26°C for infants of 28 weeks' gestation.³¹

Changes Modifiable in Future (Table 1)

- *Delayed cord clamping in nonvigorous babies:* Cord clamping being delayed in babies not requiring resuscitation has been validated however in nonvigorous newborns the data is insufficient. If adequate techniques develop in future, proper resuscitation can be provided with the added benefits of delayed cord clamping.
- *PEEP in early resuscitation:* There are not enough studies at present evaluating the benefits of PEEP in early resuscitation. However in view of the improved functional residual capacity and lung compliance PEEP may provide added benefits in resuscitation.
- *Tidal volume measurement during ventilation:* Both hyperinflating and inadequate inflation can have deleterious effects on the lungs of the preterm hence monitoring of tidal volume in resuscitation may be beneficial to prevent lung injuries.
- *Colorimetric CO₂ detection to assess ventilation in nonintubated patients;* though insufficient data regarding its use, can be used in future to detect obstruction.

Among the prominent changes is now three questions are relevant as compared to the earlier four with color being removed from assessment of signs and more emphasis being laid on placing the baby on the mother's chest for skin-to-skin contact. Precordial auscultation better than umbilical cord palpation for detection of heart rate with increase in heart rate as sensitive indicator of resuscitation efficacy. Pulse oximetry is recommended for assessment of oxygenation and attach probe to right hand or wrist (measure preductal saturations). Shift from 100 percent to 21 percent O₂ for term babies needing PPV,

supplemental oxygen to be started at 90 sec from birth in case of no improvement and use of blender and pulse oximetry is recommended for term babies also. CPAP is now mentioned in the algorithm for persistent cyanosis or labored breathing.

Cord clamping to be delayed till 1 min in neonates not needing resuscitation.

Naloxone is not recommended in routine resuscitation.

Newer Guidelines: Efficacy in Indian Scenario

In this era of evidence based medicine the newer changes advocated in recent guidelines are derived from large studies conducted in several tertiary care centers. Even though the human physiology and effects and management of asphyxia is similar it is the application of these methods that may differ in the Indian rural setting. These guidelines can be adapted without any changes in the tertiary care centers in our country. However, some modifications in the recommendations are warranted to make it more adaptable to our scenario. Some areas of changes which may be considered are:

- Use of pulse oximetry in all preterm babies may not be practically possible in a majority of our newborn care corners and birthing places. Not only is it financially impractical but also the logistics of maintenance and upkeep will be major challenges precluding the introduction of pulse oximeters in the delivery rooms across India. Till such time we may continue with the practice of using color as an assessment tool. Laryngeal mask airway requires expertise and may not be the best option in our setting.
- The use of oxygen blender and CPAP though justified and rational can be used in our tertiary centers, however seems improbable in the rural and more so in the noninstitutional deliveries due to cost logistics of maintenance and the supply of uninterrupted electricity.
- The current recommendation not providing any recommendation with respect to meconium in non-vigorous babies needs to be viewed with caution as meconium is a problem largely seen in the Indian sub-continent and at this point it may seem unethical to deny our vast majority of meconium stained babies' tracheal suction when they need it.

CONCLUSION

About 10 percent of newborns require resuscitation at birth and the prompt availability of trained personnel's can drastically reduce neonatal mortality. Hence, all health workers should be updated regarding the changes in resuscitation guidelines and to be put to use in the best possible way in accordance with the local practices in rural settings.

Table 1: Comparisons for the changes in recommendations

<i>Resuscitation step</i>	<i>Recommendations (2005)</i>	<i>Recommendations (2010)</i>
1. Assessment for need of resuscitation	Four questions <ul style="list-style-type: none"> • Gestation—term or not? • Amniotic fluid—clear or not? • Tone—Good? • Breathing/Crying? 	Three questions <ul style="list-style-type: none"> • Gestation—term or not? • Tone—Good? • Breathing/Crying?
2. Routine care (given if answer to all three question is YES)	<ul style="list-style-type: none"> • Provide warmth • Clear airway • Dry • Assess color 	<ul style="list-style-type: none"> • Provide warmth • Assure open airway • Dry • Ongoing evaluation (color, activity and breathing)
3. Initial steps	<ul style="list-style-type: none"> • Provide warmth • Position; clear airway (if required) • Dry, stimulate, reposition 	<ul style="list-style-type: none"> • Provide warmth • Open airway (no routine suction) • Dry, stimulate
4. Assessment (after initial steps and ongoing)	<i>Look for 3 signs</i> <ul style="list-style-type: none"> • Respiration 	<i>Look for 2 signs</i> <ul style="list-style-type: none"> • Heart rate
4.1. Assessment for need for progressive steps after initial steps	<ul style="list-style-type: none"> • Heart rate • Color 	<ul style="list-style-type: none"> • Respiration (labored, unlabored, apnea, gasping)
4.2. Assessment of heart rate	Palpation of umbilical cord pulsation for 6 sec and multiply by 10	Auscultation of heart at the precordium is the most accurate
5. Positive pressure ventilation (PPV)	<i>Indications are (any 1 out of 3)</i> <ul style="list-style-type: none"> • Heart rate <100/min • Apnea or gasping 	<i>Indications (1 out of 2)</i> <ul style="list-style-type: none"> • Heart rate <100/min • Apnea or gasping
5.1. Indication for PPV	• Persistent central cyanosis despite free flow oxygen	Heart rate
5.2. Assessment of effectiveness of resuscitation steps once PPV is started	Heart rate Color Respiration	Pulse oximetry Respiration
6. Initial oxygen concentration for resuscitation in case of PPV	<i>Term babies (≥37 weeks)</i> <ul style="list-style-type: none"> • Start with 100% O₂ during PPV • If room air resuscitation is started O₂ up to 100% should be given if no improvement within 90 seconds • In case nonavailability of O₂— start room air <i>Preterm babies (<32 weeks)</i> <ul style="list-style-type: none"> • Start with oxygen between 21 and 100% • Advocates use of blender for graded O₂ • Pulse oximetry for targeting SpO₂—85–95% 	<i>Term babies (≥37 weeks)</i> <ul style="list-style-type: none"> • Start with room air (21%) • No improvement in heart rate or oxygenation — use up to 100% to attain target saturations • Use blender for graded increased in delivered oxygen concentrations <i>Preterm (<32 weeks)</i> <ul style="list-style-type: none"> • Initiate resuscitation using O₂ concentration between 30–90% • Uses blended air oxygen mixture judiciously guided by pulse oximetry
7. Peripartum suctioning for neonates born through meconium stained amniotic fluid	<ul style="list-style-type: none"> • No routine oropharyngeal and nasopharyngeal suction • Tracheal suction only in nonvigorous babies born through meconium stained amniotic fluid (MSAF) 	<ul style="list-style-type: none"> • No routine oropharyngeal and nasopharyngeal suction required • Tracheal suction of nonvigorous babies with MSAF still to be continued though evidence for the same is conflicting
8. Initial breath strategy positive pressure ventilation (PPV)	<ul style="list-style-type: none"> • No specific recommendation for short or long inflation time • No specific PIP recommendation • No specific recommendation for PEEP • Guiding of PPV looking at chest rise and improvement in heart rate 	<ul style="list-style-type: none"> • No specific recommendation for short or long inflation time as evidence is conflicting • PIP— for initial breaths 20–25 cm H₂O for preterm and 30–40 cm H₂O for term • PEEP likely to be beneficial for initial stabilization of preterm infants, if provided with suitable equipment (T-piece or flow inflating bags) • Guide the PPV looking at heart rate and oxygenation especially in preterm, chest rise less reliable

Contd...

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9. CPAP in delivery room	Suggested for preterm babies (<32 weeks) with respiratory distress	Spontaneously breathing preterm infants with respiratory distress may be supported with CPAP or ventilation as per local practice
10. Airway management	Exhaled CO ₂ detection is recommended except in cardiac asystole where direct laryngoscopy may have to be done	Exhaled CO ₂ detection is recommended except in cardiac asystole where direct laryngoscopy may have to be done
10.1. Confirmation of endotracheal tube placement		LMA may be used for infants >2000 g and ≥ 34 weeks in case bag and mask is ineffective and tracheal intubation is unsuccessful or not feasible
10.2. Laryngeal mask airway	For near term and term infants >2500 g may be used with no definite mention of indications	
11. Chest compression	<ul style="list-style-type: none"> • Ratio of compression 3:1 • Two thumb technique better than two finger technique • The compression is applied at the lower one-third of sternum • The depth of compression should be one-third of the anteroposterior diameter of the chest 	<ul style="list-style-type: none"> • Ratio of compression 3:1 unless cardiac arrest is due to a clear cardiac etiology where ratio of 15:2 may be considered • Two thumb technique better than two finger technique • The compression is applied at the lower one-third of sternum • The depth of compression should be one-third of the anteroposterior diameter of the chest
12. Drugs		
12.1. Naloxone	Naloxone considered in case of infants born to mothers with history of opioid exposure within 4 hours of delivery and there is persistent respiratory depression even after restoration of heart rate and color by effective PPV	<ul style="list-style-type: none"> • Naloxone is not recommended as part of initial resuscitation in babies with respiratory depression. • Focus needs to be on effective ventilation
13. Supportive care		
13.1. Therapeutic hypothermia	No sufficient evidence to recommend routine use of modest systemic or selective cerebral hypothermia after resuscitation in infants with suspected asphyxia.	Therapeutic hypothermia (whole body or selective head cooling) recommended for infants ≥36 weeks with moderate to severe hypoxic ischemic encephalopathy as per the protocol used in major cooling trials with provision for monitoring for side effects and long-term follow-up
13.2. Delayed cord clamping	Avoid hyperthermia in such cases Not recommended	For uncomplicated births both term and preterm not requiring resuscitation — delay cord clamping by at least 1 minute

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CHAPTER 3

Practical Approach to Fluid and Electrolyte Management in Newborns

Anup Jalan

Fluid and electrolyte therapy is a very important component of overall care of a sick neonate. Fluid and electrolyte requirements are a very dynamic phenomenon and require alterations depending on gestation, age or sickness. Premature neonates, particularly those with low birth weight, frequently require parenteral fluids, whose quantity and composition can be highly variable. Correction of fluid and electrolyte derangements is not only important for improving their survival but also is very essential in ensuring good neurodevelopmental outcome.

This topic covers the basic mechanisms for maintaining fluid and electrolyte homeostasis and outlines the factors that govern fluid and electrolyte requirements for term and preterm infants. I describe methods for monitoring fluid and electrolyte balance, discuss potential complications and practical approaches of fluid and electrolyte imbalances.

BODY FLUID COMPOSITION IN THE FETUS AND THE NEWBORN

At birth, the percentage of body weight represented by water is approximately 75 percent in term infants and greater in premature infants (Fig. 1). As gestational age increases, total body water and extracellular water decrease and intracellular fluid content increases. An infant born at 32 weeks' gestation has a total body water and extracellular fluid bodyweight percentage of approximately 83 percent and 53 percent, respectively.

POSTNATAL CHANGES IN BODY WATER COMPARTMENTS

During the first 7 to 10 days of life, all infants experience a reduction in bodyweight, which, in part, represents inadequate calorie intake during this period. However, this physiologic weight loss is largely the result of a

reduction in the extracellular compartment of body water. The precise mechanism for the postnatal contraction of the extracellular fluid compartment is unclear. However, it has been well documented that infants with low birth weight lose approximately 10 percent to 15 percent of the extracellular fluid during the first 5 days of life. This phenomenon is associated with a concurrent diuretic phase resulting in negative fluid and sodium balance.

It is important to recognize that in the first few days of life, physiologic weight loss in an infant with low birth weight represents isotonic contraction of body fluids. The contraction of the extracellular fluid space appears to be part of a normal transitional physiologic process. Perturbations of this normal transitional physiology can lead to

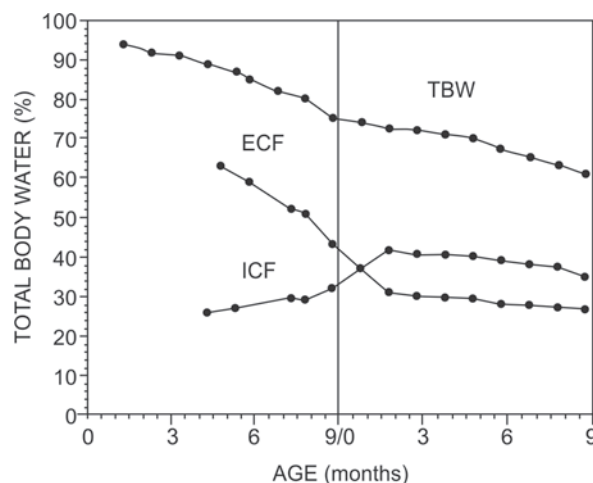


Fig. 1: Total body water (TBW) content and its distribution between the extracellular fluid (ECF) and intracellular fluid (ICF) compartments in the human fetus, newborn and infant from conception until 9 months of age

imbalances in sodium and water homeostasis. In particular, high fluid intake resulting in a lack of extracellular fluid compartment contraction may be associated with a higher incidence of symptomatic patent ductus arteriosus and necrotizing enterocolitis.

FLUID AND ELECTROLYTES CALCULATION

Calculation of fluid requirements in the newborn is based on maintenance needs, deficits and ongoing losses. Critical factors that determine these fluid requirements include gestational age, renal function, ambient air temperature, ventilator dependence, presence of drainage tubes and gastrointestinal losses.

Maintenance Fluids

Maintenance fluid requirements are the quantities of water needed to preserve neutral water balance in the typical preterm or term newborn. The total amount of maintenance fluid required is equal to urine production plus insensible losses. A summary of maintenance fluid requirements during the first month of life for full-term and preterm infants is listed in Table 1. The values in Table 1 are only guidelines; they are to be used as a starting point for prescribing maintenance fluid for infants with low birth weight during the first week of life. Further adjustments must be based on the clinical situation. In particular, close attention must be paid to the patient's volume status and assessment of factors that could increase or decrease the baseline fluid requirements if the clinician is to provide appropriate management of the infant.

Insensible Losses

Insensible water losses are primarily evaporative losses via skin and respiratory tract. In newborn infants, one-third of insensible water loss occurs through the respiratory tract, and the remaining two-thirds occurs through the skin. A number of physiologic, environmental and therapeutic factors (Level of maturity, environmental temperature, humidity, skin breakdown such as burns, omphalocele, phototherapy, double-walled incubator) can influence insensible water loss, making it the most variable component of the maintenance fluid requirements in

newborns. The most important variable is the maturity of the infant because there is an inverse relationship between bodyweight and insensible water loss. A 26 week ELBW baby under a radiant warmer on day 1 may lose over 150 ml/kg/day. Mature babies will lose <30 ml/kg/day. Insensible losses decrease after first few days, as skin thickens.

Urinary Losses

The quantity of water required for the formation of urine depends on two major factors: The degree of renal function and the renal solute load. Under normal conditions, a major determinant of renal water requirement is renal solute load. Renal solute load is derived from exogenous and endogenous sources.

During the first day or two of life, the exogenous solute load of infants with low birth weight is minimal because they usually do not receive electrolytes or protein. Because they are not usually fed enterally, however, delivery of calories by intravenous glucose-containing solutions does not meet basal energy needs. For instance, in the first day or two of life, the basal energy requirement for infants with low birth weight is approximately 50 kcal/kg body weight. If they are given 70 to 90 ml/kg per day of a 10 percent glucose solution, the caloric intake is 35 kcal/kg per day. The infants, therefore, must derive the remaining mandatory energy requirement from an endogenous source; in other words, they must derive energy from catabolism.

The catabolic state produces approximately 6 mOsm/kg per day of an endogenous solute load presented to the kidney. Assuming the infant can produce a maximum urinary concentration of 600 mOsm/kg, then a minimum of 10 ml/kg per day of free water is required to excrete this solute load. As the infant ages, the exogenous intake from parenteral and enteral sources increases, resulting in increased caloric intake. The exogenous solute load therefore increases, whereas catabolism decreases, resulting in a decreased endogenous solute load.

By 2 or 3 weeks of age, an infant consuming 80 to 120 kcal/kg per day has a total solute load of approximately 15 to 20 mOsm/kg per day. Assuming that the infant can produce a maximum urinary concentration of 800 mOsm/kg by this age, thus 20 to 25 mL/kg per day of free water is required to excrete the solute load.

Table 1: Maintenance fluid requirements during the first month of life

Birth weight (g)	Insensible water loss (ml/kg/day)	Water requirements (ml/kg/day) by age		
		Day 1–2	Day 3–7	Day 8–30
<750	100–200	100–200 +	150–200 +	120–180
750–1000	60–70	80–150	100–150	120–180
1001–1500	30–65	60–100	80–150	120–180
>1500	15–30	60–80	100–150	120–180

Other Fluid Losses

Water loss through the gastrointestinal tract from stool output is minimal during the first few days of life, particularly in infants with low birth weight. Once enteral feeds begin, the water loss in the stool is 5 to 10 ml/kg per day. In a growing infant, the amount of water required for new tissue formation should be considered in calculating maintenance fluid requirements. Because infants grow at the rate of 10 to 20 g/kg per day and new tissue contains 70 percent water, the maintenance fluid should provide a net water balance of 10 to 15 ml/kg per day.

Electrolyte Requirements

Maintenance sodium and chloride are usually not provided during the first 1 to 2 days of life due to the relatively volume expanded state of the newborn. Similarly, potassium is not provided in parenteral fluid until urinary flow has been established and normal renal function is ensured. From postnatal days 3 to 7, maintenance sodium, potassium and chloride requirements are approximately 1 to 2 mEq/kg per day. Beyond the first week of life, 2 to 3 mEq/kg per day or more of sodium and chloride are required to maintain the positive electrolyte balance that is necessary for the formation of new tissue. Because of high urinary sodium losses, premature infants may require up to 4 or 5 mEq/kg of sodium per day during the first few weeks of life.

Estimating Pathologic Losses and Deficit Replacement

Many clinical situations require careful estimates of ongoing pathologic losses and replacement of deficits. Commonly encountered conditions include diarrhea with dehydration, chest tube drainage, surgical wound drainage and excessive urine losses from osmotic diuresis. The important guiding principle in managing patients with these conditions is to accurately measure the volume and composition of the pathologic losses. Electrolyte losses can then be calculated by multiplying the volume of fluid losses by the electrolyte content of the respective body fluids.

Estimating replacement for pathologic fluid and electrolyte losses can be difficult, particularly in infants who accumulate fluid and electrolytes in static body fluid compartments. This phenomenon, commonly referred to as third spacing, occurs in several conditions including sepsis, hydrops fetalis, hypoalbuminemia and intra-abdominal infections, as well as following abdominal or cardiac surgery. An infant with necrotizing enterocolitis, for example, often accumulates fluid in the mucosal and submucosal tissues of the small and large intestine as well as in the peritoneal cavity. Under these circumstances, large amounts of fluid, electrolytes and protein can leak into the interstitial tissue and cannot be accurately quantified. Because fluid lost into these tissue spaces does not

contribute to effective arterial blood volume and circulatory balance, these patients can appear edematous even though their intravascular volume is decreased. The most appropriate strategic approach to managing these infants is to replenish the extracellular fluid compartments with colloid and crystalloid.

Monitoring Fluid and Electrolyte Balance

Interpretation of key clinical feedback is a critical part of successful fluid and electrolyte management strategies in newborns. Fluid and electrolyte balance can be achieved by using a meticulous and organized system that obtains pertinent data and applies the physiologic principles outlined in the beginning of this chapter. A careful assessment of clinical indicators of volume status, including heart rate, blood pressure, skin turgor, capillary refill, oral mucosa integrity and fullness of the anterior fontanelle is essential. Other pertinent data that must be monitored include body weight, fluid intake, urine and stool output, serum electrolytes and urine osmolality or specific gravity.

During the first few days of life, appropriate fluid and electrolyte balance is reflected by a urine output of approximately 1 to 3 ml/kg per hour, a urine specific gravity of approximately 1.008 to 1.012 and an approximate weight loss of 5 to 15 percent in term infants and in premature infants with very low birth weight, respectively. Sampling of serum electrolytes can be done at 8- to 24-hour intervals, depending on illness severity, gestational age, and fluid-electrolyte balance. Extracellular volume depletion is manifest by excessive weight loss, dry oral mucosa, sunken anterior fontanelle, capillary refill greater than 3 seconds, diminished skin turgor, increased heart rate, low blood pressure, elevated blood urea nitrogen or metabolic acidosis. Serum sodium, which reflects sodium concentration but not sodium content, could be normal, decreased, or increased in states of volume depletion. Bedside monitoring of weight gain, as an indicator of volume status and growth, is essential for monitoring the adequacy of fluid and calorie intake in sick neonates. Beyond the first week of life, infants should gain approximately 20 to 30 g per day.

Practical Approach to Fluid Therapy

- Most cardiorespiratory stable infants can be started on feeds even on day one. We may start full enteral feeds on infant ≥ 32 week (60 ml/kg).
- In stable infants < 32 wk, small amount of enteral feeds are started and rest of fluid requirements are met with IV fluids. Respiratory support *per se* is not a contraindication to start enteral feeds.
- Most unstable infants are started on IV fluids. IV fluid may be dextrose alone or may be PN (with lipid and

amino acid). Consider starting PN in all infants, on whom significant enteral intake is unlikely in next 4 to 5 days. Otherwise start with plain dextrose solution at rate as per estimated fluid limit. Start at GIR 4-6 mg/kg/min. We may use D10 percent as initiating fluid as long as fluid rate is 60-100 ml/kg. if fluid rate is too low (as in HIE/ATN) or too high (as in extreme prematurity, polyuria etc), we may need to use variable dextrose concentrations so as to match desired GIR of 4-6 mg/kg/min.

- Dextrose concentration of required fluid may be calculated by following formula:

$GIR (mg/kg/min) = Fluid\ rate (ml/kg/day) \times Dextrose\ concentration \times 0.007$

- Once we have calculated required fluid volume and desired dextrose concentration (D), we may make this fluid by mixing two dextrose solutions, one with higher concentration (H) and another with lower (L) concentration. This is done using following computations:
- $Lower\ dext\ conc.\ volume = Total\ volume \times (H-D)/(H-L)$
- $Higher\ dext\ conc\ volume = Total\ volume - Lower\ dext\ conc.\ volume$
- Make desired fluid by mixing calculated amount of these two fluid and give over 24 hr
- Monitor blood sugars intermittently (target range 50-150 mg/dl)
- Guidelines for initiating and adjusting fluid and electrolytes (Table 2)

ELECTROLYTE DISTURBANCES

Hyponatremia

Definition: Serum sodium <130 mEq/L

Causes: Hyponatremia could be either due to:

- a decrease in serum sodium relative to body water content (less often)
- excess of free water (more often).

Pseudohyponatremia is a condition in which concentration of sodium per liter of serum volume is decreased due to addition of serum solids such as hyperlipidemia, hyperproteinemia, however sodium concentration per liter of serum water is normal. Diagnosis can be made by a difference in calculated osmolality ($2 \times Na + BUN/2.8 + Glu/18$) and measured osmolality (by ion electrode method), with later being normal in pseudohyponatremia. Correction factors for raised proteins and lipids:

$Triglycerides (mg/dl) \times .002 = mEq/L\ decrease\ in\ Na$

$Plasma\ protein\ level [g/dl] - 8 \times 0.25 = mEq\ decrease\ in\ Na$

In practice, pseudohyponatremia is extremely uncommon in neonates. Hyperproteinemia is unknown in neonatal period. In settings of hyperlipidemia, a rise in triglyceride by 500 mg/dl will lead to fall in serum Na by 1 mEq/L. Thus, even in situation of s triglycerides as high as 1000 mg/dl, serum sodium will fall by 2 mEq/L. Hence, apart from inherited disorders with hyperlipidemia, hyperlipidemia is an unlikely cause of Hyponatremia.

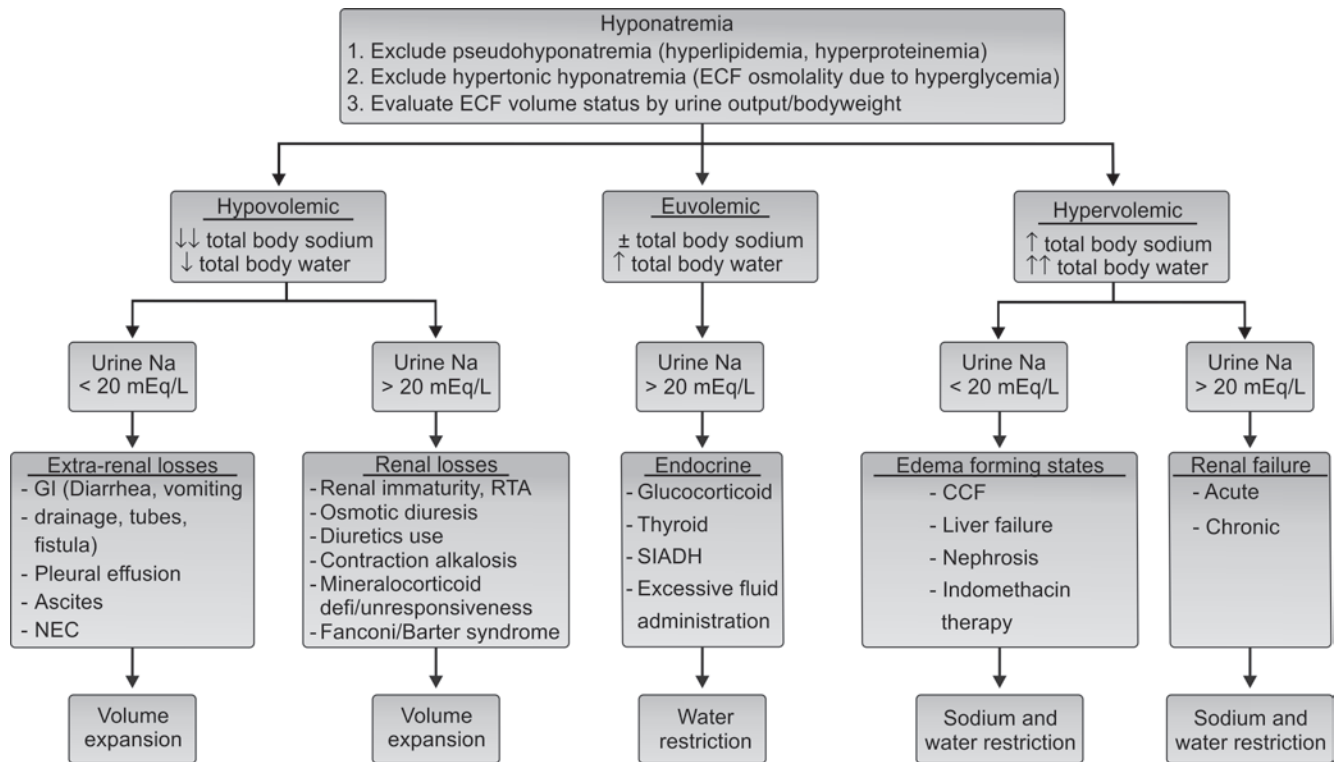
Approach to Hyponatremia (Flow chart 1)

- Hyponatremia is detected either incidentally on routine investigations or on workup of a symptomatic infant.
- Once hyponatremia is detected, evaluated for cause of hyponatremia. Assess weight pattern, urine output and other losses during last 24-48 hrs. (If required investigate for urine sodium and osmolality).
- If there is hyponatremia along with abnormal weight gain: this is a setting of free water access (either due to excessive administration of fluids or due to decreased urine output. Urine sodium and osmolality will be high with ARF and low with SIADH, CCF, liver failure or nephritic syndrome. Treatment required is fluid restriction.

Table 2: Guidelines for initiating and adjusting fluid and electrolytes

	Postnatal Day 1	Adjustment during the prediuretic phase	Adjustment during the diuretic/natriuretic phase
Water	<25 wk: ~150 ml/kg/d 25 - 27 wk: 120 ml/kg/d 28 - 30 wk: 100 ml/kg/d 30 - 34 wk: 80 ml/kg/d >34 wk: 60 ml/kg/d	Increase if: weight loss is >2%/day or serum sodium increases Decrease if: weight increases or serum sodium decreases	Increase by 10 to 30 ml/kg per day if: weight loss is >5%/d or serum sodium is > 150 mEq/L with no sodium intake Decrease by 10 to 30 ml/kg per day if: weight loss is <1%/d
Sodium	None	Usually no sodium is required	Begin 1 to 2 mEq/kg per day if: serum sodium is <135 mEq/L with weight loss or serum sodium is <130 mEq/L with no change or gain in weight
Potassium	None	Usually no potassium is required	Begin 1 to 2 mEq/kg per day if: serum potassium is <5mEq/L and not increasing and urine output is >1 ml/kg/hour

Flow chart 1: Algorithmic approach to hyponatremia



- If there is hyponatremia in absence of abnormal weight gain: This is a setting of total body sodium deficit. This might be due to excessive diuresis/natriuresis or losses through other routes. Urine sodium and osmolality will be high in renal salt wasting and low with extra renal loss. Treatment is replacement of sodium and fluid deficits and increasing daily maintenance to compensate for ongoing losses.

Given below is algorithmic approach to Hyponatremia:

Treatment of Hyponatremia

- In case of free water access, treatment is simply fluid restriction. Target fluid limit should be adjusted so as to achieve a negative fluid balance (less than sum of insensible losses + urine output). This may at times require fluid limit less than 40 to 50 ml/kg/day. (In such setting, we need to give fluid with high dextrose concentration so as to maintain required GIR 4-6 mg/ kg/ min. This will need insertion of central line). Repeat serum sodium every 24 to 48 hr.
- In case of body sodium deficit, replace body sodium. Calculation for sodium deficit is done by following formula:

$$\text{Sodium deficit (mEq)} = 0.6 \times \text{weight} \times (\text{desired Na} - \text{Actual Na})$$
 Correct the deficit by adding calculated sodium in 24 hr maintenance fluid. For every one mEq add 2 ml of 3% saline or 6.5 ml of normal saline.
 Usually, a deficit of 12 mEq/ L should be corrected over every 24 hr. However, if hyponatremia is symptomatic or

serum sodium is less than 120 mEq/L, a rapid correction to a level up to 120 mEq/L is recommended to prevent/control seizures. Give the calculated amount of sodium (to target serum sodium to 120 mEq/L) over 4 to 6 hr as separate infusion and give rest of sodium (maintenance plus remaining deficit) in 24 hr fluid as infusion.

Hypertatremia

Definition: serum sodium >150 mEq/L

Causes:

- Increased sodium intake: Less common (in this there is no weight loss)
 - excessive NS administration
 - excessive sodabibcarb administration
- Decrease body water (hypertatremic dehydration): More common
 - Lactational failure, poor intake, faulty feeding
 - High insensible losses (extremely preterm infant under warmer/phototherapy)
 - Polyuria (DI), diarrhea.

Management of True Hypertatremia

Management of true hypertatremia is simply restriction of sodium intake and monitoring till levels normalize.

Management of Hypertatremic Dehydration

Hypertatremic dehydration is usually a state of both salt and free water deficit with free water deficit being more than sodium deficit, hence resulting in increase sodium

concentration in serum. Treatment consists of correction of both sodium and fluid deficit.

Principle of therapy is to correct both sodium and fluid deficit gradually, so that there is no rapid change in serum osmolality. Any rapid fall in osmolality will lead to transcellular shift of water and hence brain edema.

Goal of Therapy

- Fall of serum sodium 10 to 12 mEq/ kg/ day
- Correction of 7% fluid deficit per day (that means 70 ml/ kg fluid deficit correction over every 24 hr).

Calculations for hypernatremic dehydration are as follows:

Calculate Fluid Deficit

This is equal to degree of dehydration. For example, if there is 10 percent dehydration, that means fluid deficit of 100 ml/kg. If dehydration is 20 percent, it is equal to 200 ml/kg of fluid deficit. As classical clinical signs of dehydration are not reliable in estimating degree of dehydration, estimation of fluid deficit is done by estimating weight loss.

Fluid deficit = expected or preillness weight – current weight

- In older infant, it is easy to get preillness weight, as there are not large variations in body weight over days to weeks and any weight measurement during last close visit may be regarded as true weight. But in a neonate, there is a constant significant change in body weight over even short span.
- There is a weight loss during first few days with regain of birth weight by 7 to 14 days. Subsequently, there is a steady weight gain by 10 to 15 gm/kg/day, provided there is adequate caloric balance.
- If adequate caloric intake has been ensured, then a weight difference from the expected weight (as per scheme given above) should be considered as fluid deficit. For example, if a neonate with birth weight 3 kg comes at day 7 of life with weight of 2500 gm (he was expected to regain his birth weight by this time, hence his expected weight was 3000 gm), fluid deficit may be assumed to be $3000 - 2500 = 500$ gm.
- However, in most circumstances, particularly those associated with poor feeding or lactational failure, there is inadequate caloric intake, and hence assuming a growth velocity of 10-15 gm/kg/day will be erroneous. Rather there might be a negative balance and there may be loss of lean body mass in addition to dehydration. Therefore, all the estimated weight difference cannot be attributed to fluid deficit though the estimation proportion of fluid deficit will be difficult and approximate value only.
- Example: if an infant with 3 kg birth weight presents at 3 weeks of life with poor feeding and hypernatremic dehydration. With his present weight of 2.0 kg, his serum sodium is 180 mEq/L. As per physiologic pattern, he must have regained his birth weight by 7 days

and then for next 2 weeks, he is expected to gain 10 gm/kg of his birth weight every day ($30 \text{ gm daily} \times 14 \text{ days} = 420 \text{ gm}$) so expected current weight is $3 \text{ kg} + 420 \text{ gms} = 3.42 \text{ kg}$ and fluid deficit will be $3.42 - 2.0 = 1.42 \text{ kg} = 41\%$.

- But a calorie deprived infant is not expected to gain and will rather lose 5-10 gm/kg every day. So, if we expect 5-10 gm/kg loss every day (with average of 7 gm/kg, i.e. $21 \text{ gm daily} \times 21 \text{ days} = 440 \text{ gm}$), then expected weight will be $3 \text{ kg} - 440 \text{ gm} = 2.56 \text{ kg}$. The fluid deficit will be $2.56 - 2.0 = 560 \text{ gm} = 22\%$
- Earlier calculation of fluid deficit was overestimation and perhaps later estimate is closer to true fluid deficit in this setting.
- However, in settings of excessive losses (e.g. diarrhea, diabetes insipidus, excessive insensible loss), majority of weight difference may be attributed to fluid loss rather than lean mass loss.

Calculate Free Water Deficit

Free water deficit (liter) = $\text{actual Na} - \text{desired Na} \times 0.6 \times \text{Expected weight (Kg)}$

In this case S. Na at admission is 180 mEq/ L, and desired S. Na will be 145 mEq/L.

Free water deficit: $180 - 145 / 180 \times .6 \times 256 = 0.298 \text{ L} = 298 \text{ ml}$

- As a rough rule, free water deficit is 3 to 4 ml/ kg for each mEq rise in serum sodium. Take factor of 4 if there is pure free water deficit (as in diabetes insipidus) and factor of 3 if there is combined free water and sodium deficit.
- For example, in this case serum sodium has risen by 35 mEq/L (s. sodium is 180 mEq/L and desired is 145 mEq/L). weight for calculation of free water deficit will be $3 \times 2.56 \times 35 = 269 \text{ ml}$.

In this case Na deficit = $0.560 - 0.298 \times 0.6 \times 180 = 28 \text{ mEq}$.

Calculate Final Fluid Composition

Our goal will be to correct the fluid deficit of 560 ml (22%) and Sodium difference of 30 mEq/L (Actual Na 180 mEq/L – Desired Na 145 mEq/L) over 3 days. [goal of therapy is to correct 7 percent fluid deficit per day and 10 mEq/L of fall in S. Na per day]. That means 186 of fluid deficit (560 ml/3) and (sodium deficit of 9.3 mEq (28 mEq/3) sodium deficit to be added in each day's maintenance fluid.

Total fluid for day 1 = maintenance fluid + deficit (186 ml)

Total sodium for day 1 = maintenance Na + deficit (9.3 mEq)

Similarly, fluid is calculated for next two days by adding same amount of fluid and Na deficit in next 2 day's maintenance fluid.

Estimating maintenance fluid requirement for each day: Standard calculation for maintenance fluid requirement is insensible losses + urine output. Only difference

is that urine output may be very low in dehydrated state. Hence, for the first day do not assume maintenance requirement to be in range of 150 ml/kg. In fact, it may be in range of 50 to 100 ml/kg.

- Take caution in estimating maintenance fluid requirements of a neonate with hypernatremic dehydration. Urine output is expected to be low initially during dehydrated state hence it may be appropriate to estimate maintenance fluid requirement approximately 25-50 ml/kg/day or 1-2 ml/kg/hr.
- Add each day's sodium and fluid deficit to this maintenance fluid. In current example, this means 50 ml/kg maintenance fluid + 186 ml/kg of fluid deficit (total 236 ml fluid at rate of 10 ml/hr). Sodium maintenance will be 2-3 mEq/kg = approx 6 mEq + deficit 9.3 mEq = total 15 mEq approx.
- Monitor weight and urine output every 4 to 6 hr and adjust fluid rate to achieve target weight gain of 2 percent every 6 hr or 8 percent in 24 hr. Do not overshoot the weight gain as it will lead to precipitous fall in serum sodium. If weight gain is inappropriately high (urine output is lower than estimated), decrease fluid rate and if weight gain is slow (urine output is higher than estimated), increase the fluid rate. Maintain target weight gain 2 percent every 2 hr or 8 percent every 24 hr.
- Repeat serum sodium every 6 to 8 hr target fall in serum sodium by 3 mEq/L in every 6 hr or 12 mEq/L in every 24 hr. increase fluid rate if fall in serum Na is slow and decrease the fluid rate, if fall is rapid.
- On subsequent days maintenance fluid amount may be increased, as per increase in urine output.

An Alternative Simple Regimen may be as Follows

- It's not that we have to always go through the twisting calculations for correction of hypernatremic dehydration. Though calculations customize the fluid type and volume for the infant's need, they are also based on our assumptions about body losses and may be wrong. Moreover calculation errors may be a disaster. Hence, if one is not comfortable, he may skip calculations to the following regimen.
- You may use N/3 to N/5 saline in D5% as the type of fluid for correction of hypernatremic dehydration. Use N/5 solutions if pure free water deficit is there (diabetes insipidus, etc.) and use N/3 if significant sodium deficit is there along with fluid deficit (diarrhea and other scenarios with body salt losses). In settings of decreased intake, take strength in between two (use N/4 to N/5).
- Fluid rate is calculated in same manner as above. Add maintenance fluid, which should be approximately 50 ml/kg for first day plus 8 percent or 80 ml/kg of fluid deficit over every 24 hr, i.e. a total of 50+80 =130 ml/kg of N/4 saline in D5%. Fluid rate may be later adjusted as per weight gain pattern, as discussed above.

- Over next day you may increase maintenance fluid amount, as urine output improves. Add 80 ml/kg as deficit in maintenance fluid. (for example you may take 100 ml maintenance plus 80 ml deficit. That means a total of 180 ml/kg N/4 to N/5 D5% for second day and so on.
- Keep monitoring weight, urine output and serum sodium every 4 to 6 hr and make appropriate adjustments, till sodium is <150 mEq/L.
- If patient requires acute correction of fluid deficit because of shock, it should be done with NS only @ 20 ml/kg/hr.

One of the most important points in understanding the management of hypernatremic dehydration is anticipating its presence. This entity should be expected in any neonate, who comes with significant weight loss/ poor weight gain/ failure to thrive, etc. If hypernatremic dehydration is not suspected at admission and high rate of hypotonic fluids are started, then enough damage might have incurred by the time serum sodium report is available. Be reasonable in starting fluids in such scenarios. Do not give rapid boluses unless really needed. Try to get serum sodium report as quickly as possible.

HYPERKALEMIA

- Normal S. potassium = 5.5 ± 0.5 mEq/L
- Hyperkalemia >6 mEq/L
- *Causes*
 - Excess administration (calculation error)
 - Acidosis
 - Decreased K clearance: ARF, oliguria, CAH
 - Increase K release: Tissue destruction, hemolysis, internal bleeding, asphyxia, IVH
 - Miscellaneous: Blood/ exchange transfusion
 - Pseudohyperkalemia: Excessively squeezed/ hemolysed sample
- *Clinical Signs*
Brady or tachyarrhythmia, cardiovascular instability or collapse
- *ECG*
Changes progress with increasing K levels
 - Peaked T waves
 - Flattened P waves and increasing PR intervals
 - QRS widening and slurring
 - Finally, SVT/VT, bradycardia and VF
- *Other investigations:*
Blood gas (for metabolic acidosis), calcium, electrolytes, renal functions, urine output
- *Management*
 - Remove all sources of exogenous potassium
 - Rule out spurious hyperkalemia—trauma, thrombocytosis, hyperleukocytosis (TLC >50,000/mm³)
- Repeat serum K (to reconfirm)
- ECG to be done (to look for electrophysiologic effect of hyperkalemia)

- Treatment varies based on the fact whether hyperkalemia is symptomatic or asymptomatic (detected incidently) and on severity of hyperkalemia. If hyperkalemia is asymptomatic and serum potassium levels are <7 mEq/L, conservative management with elimination of potassium from IV fluids and close monitoring may be sufficient.
- If hyperkalemia is severe and/or it is symptomatic, then additional measures are required.
- Goal of therapy is to:
 - Stabilize myocardium (by IV calcium gluconate)
 - Promote intracellular shift (by insulin infusion). In presence of acidosis give bicarbonate correction.
 - Enhance elimination (by exchange resins).

Approach

- Give *Calcium gluconate* (10%) carefully under cardiac monitoring 1 to 2 ml/kg IV as a slow infusion. Repeat as required, till hyperkalemia resolves.
- *Insulin*: Give a bolus of insulin and glucose (0.05-0.1 units/kg of regular insulin with 2-4 ml/kg of 10 percent dextrose. This is followed by continuous infusion of insulin 0.05-0.1 Unit/kg/hr with a parallel neutralizing dextrose infusion drip (250-500 mg/ kg/ hr). run insulin and dextrose infusion separately so that adjustment in dextrose infusion rate can be done so as to maintain euglycemia. 5 units of insulin can be diluted in 50 ml NS and given as 0.1 unit/kg/hr. Dextrose infusion can be given as Dextrose 10 percent at rate of 2.5-5 ml/ kg/hr. Rate may be adjusted according to blood sugars, which should be monitored periodically. If fluid restriction is warranted due to oliguria or overhydration, you may use dextrose 25 percent (through central line) at rate of 1-2 ml/kg/hr.
- *Beta-2-adrenergic stimulation*: Enhances K uptake via stimulation of Na-K ATPase. Salbutamol may be given as Nebulization, though rarely used as primary therapy.
- *Alkalemia*: Sod. bicarbonate may be used 1-2 ml/kg IV, particularly if acidosis is present.
- *Exchange resins*: Na polystyrene sulfonate (Kayexelate) given rectally (1gm/kg with 0.5 g/ml of DW/NS) with a minimum retention time of 30 minutes, repeat every 4-6 hrly (*mainstay of therapy*).

Furosemide: 1 mg/kg iv may increase K excretion, particularly in state of fluid overload.

Peritoneal dialysis and double-volume exchange transfusion in case of refractory threatening hyperkalemia.

Suggested Algorithm

Serum K >6 , Normal ECG

- Eliminate exogenous supplementation
- Monitor K every 6-12 hrly

Serum K >7 , Normal ECG

- Eliminate exogenous supplementation
- Exchange resin (Kayexelate)
- Monitor K every 4-6 hrly.

Arrhythmias/ Serum K >8

- All above measures plus
- Calcium gluconate
- Insulin infusion (with neutralizing dextrose drip)
- NaHCO_3 , if warranted
- Diuretics, if warranted.

Refractory Hyperkalemia

- All above measures plus
- Peritoneal dialysis/exchange transfusion.

HYPOKALEMIA

- Normal S potassium 5.5 ± 0.5 mEq/L
- Significant hypokalemia: Serum potassium <3.5 mEq/L
- *Causes*
 - Spurious hypokalemia: High WBC-Sample in room air uptake of K by WBC
 - Alkalosis (an increase in pH by 0.1 leads to fall in K of 0.6 mEq/L)
 - NG loss, ileostomy drainage, diarrhea, persistent vomiting
 - Renal tubular defects
 - Hyperaldosteronism
 - Drugs: Chronic diuretic use, steroids, digoxin, amphotericin B, aminoglycosides, β -agonist, insulin therapy
- *Clinical features*
 - Hypotonia, ileus, urinary retention
 - Respiratory failure, failed weaning
 - Hypotension
 - Ventricular arrhythmias
 - Cardiac arrest
- *ECG changes*: Prominent U waves, bifid T-waves, flattened T, QTc prolongation
- *Evaluation*: Obtain serum and urine electrolytes and ABG and ECG
- *Management*
 - Reduce/replace renal/GI loss
 - Correct alkalosis, if present
 - Increase potassium intake as needed. Preferable route—Oral if possible. IV Potassium if oral route is not possible or hemodynamically unstable. Increase the potassium supplementation from normal 2 mEq/kg/day to 3-5 mEq/kg/day as infusion over 24 hr). Continue hemodynamic monitoring. Repeat S. potassium every 6 to 12 hr.

- One suggested regimen for potassium concentration in infusate is as follows:

Serum potassium level (mEq/L)	Potassium conc in infusate (mEq/L)
3 – 3.5	30 mEq/L
2.5 – 3	40 mEq/L
2 – 2.5	60 mEq/L
<2 or arrhythmia/hypoventilation	KCl drip 0.5–1 mEq/kg/hr

HYPOCALCEMIA

- Normal calcium value = 9-11 mg/dl
- Hypocalcemia defined as <8 mg/dl in term infant and <7 mg/dl in PT infant
- Total calcium is influenced by serum albumin concentration. A decrease in S. albumin by 1 gm/dl will lead to a decrease in total calcium by 1 mg/dl.
- Physiologically important component is ionized calcium which should be >4 mg/dl.
- In sick infant low total calcium may be because of associated hypoalbuminemia. Ionized calcium may be unaltered in this situation.
- Serum calcium levels are primarily regulated by Vit-D and PTH levels rather than calcium intake.

Causes of Hypocalcemia

- *Early hypocalcemia (1-4 days)*
 - Prematurity
 - Asphyxia
 - Perinatal stress
 - IUGR
 - Maternal diabetes
 - Maternal anticonvulsants
- *Late hypocalcemia (5-10 days)*
 - Hyperphosphatemia
 - Hypomagnesemia
 - Alkalosis, alkali therapy, citrated blood transfusion, furosemide, xanthine use, lipid infusion, phototherapy
 - Vit D deficiency
 - PTH resistance (transient neonatal pseudohypoparathyroidism)
 - Primary hypoparathyroidism (agenesis/DiGeorge syndrome)
 - Secondary hypoparathyroidism (due to maternal hyperparathyroidism)
 - Acquired/inherited disorders of Vit D metabolism
 - Skeletal dysplasia (osteopetrosis)

Evaluation

- *History*
 - Maternal diabetes/hyperparathyroidism
 - Intrapartum events/asphyxia, PT/IUGR
 - Nutritional supply of mother/infant
 - History of drugs intake
- *Physical examination*
 - Features of hypocalcemia: jitteriness, cyanosis, seizures
 - Associated features: PT, CHD, dysmorphism (DiGeorge syndrome)
- *Investigations*
 - Total/ionized calcium
 - Blood gas
 - Magnesium, phosphorus
 - Urinary calcium, phosphorus, magnesium, creatinine
 - Chest X-ray (for thymic shadow)
 - Vit-D metabolite, PTH, calcitonin levels (in unexplained refractory hypocalcemia).

Treatment

- For asymptomatic hypocalcemia in PT infants, treatment threshold is <6 mg/dl.
- For symptomatic hypocalcemia, IV calcium gluconate 10 percent is indicated. Give IV bolus (slow over several minutes) at dose of 2 ml/kg. Subsequently IV calcium should be continued at dose of 75 mg/kg/d of elemental calcium (8 ml/kg/day of 10 percent calcium gluconate) either as 6 hrly boluses or as continuous infusion in par-enteral fluid. Take care of extravasation into soft tissue.
- Usually 2 to 3 days of therapy is sufficient.
- If requirement is prolonged, shift to oral therapy, once infant is ready to tolerate oral feed. Same dose of elemental calcium should be given in form of susp osteocalcium (except in setting of hyperphosphatemia).
- A poor response to calcium therapy may result from concurrent magnesium deficiency. If magnesium deficiency is present (Magnesium level <1.6 mg/dl), magnesium should be given IV/IM, as 50 percent magnesium sulfate in a dose of 0.1 to 0.2 ml/kg, repeat 12 to 24 hr, if needed. Usually, one or two doses are sufficient.
- If hyperphosphatemia is the underlying cause, give oral calcium salt (as carbonate) with low phosphorus formula.
- If vit D deficiency is suspected/proved, 1000 to 2000 IU vit D for 4 weeks is sufficient. Hypoparathyroidism is also treated similarly with 1000 to 2000 IU Vit-D supplementation.

HYPERCALCEMIA

- Defined as serum total calcium >11 mg/dl.
- Clinical signs (unusual below 13 mg/dl) are vomiting, dehydration, hypotonia, seizures, bradycardia, HT, renal function impairment, polyuria, hypercalciuria, nephrocalcinosis, hematuria.

Causes

- *Iatrogenic*: Calcium salts, vit A, vit D, thiazide diuretics, hypophosphatemia
- Neonatal hyperparathyroidism/maternal hypoparathyroidism
- Familial hypocalciuric hypercalcemia
- Distal RTA
- Subcutaneous fat necrosis
- Carbohydrate malabsorption
- William's syndrome
- Blue diaper syndrome
- Hyperprostaglandin E syndrome
- Hypophosphatasia
- Tumor – related

Evaluation

- *History*
 - Rule out iatrogenic causes first
 - Familial/maternal disease
 - Traumatic birth
 - Maternal/neonatal vit A/vit D supplementation, thiazide use.
- *Physical examination*
 - Lethargy, dehydration, hypertension
 - Associated features: elfin facies, CHD, MR, subcutaneous fat necrosis
- *Investigations*
 - Total/ionized calcium, phosphorus, magnesium, alkaline phosphatase, blood gas, protein, creatinine
 - Urinary calcium, phosphorus, creatinine, pH
 - ECG: short QT interval
 - Chest and long bone X-ray (identify demineralization/lytic lesions)

- Renal ultrasound
- PTH, 25 OH- vit-D level, vit-A level

Treatment

- Conservative management is appropriate in mild hypercalcemia.
- If hypercalcemia is associated with hypophosphatemia (due to poor phosphorus supply) emphasis on phosphorus supplementation.
- In moderate to severe hypercalcemia more aggressive treatment is needed.

Discontinue oral/IV calcium and vit D supplementation

- Increase excretion by giving 1.5 to 2 times maintenance fluids
- Furosemide may enhance renal excretion.
- In extreme of case, corticosteroids (prednisolone 2 mg/kg for short period in case of Vit-D excess), calcitonin, bisphosphonates, dialysis and total parathyroidectomy should be considered as appropriate.

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CHAPTER 4

Parenteral Nutrition in Neonatal Intensive Care Unit

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ABSTRACT

Newborn nutrition is a vital part of the well-being of an infant. The period of rapid growth in infancy requires careful nutritional support to continue the growth and development that began at conception. The main objectives in feeding infants are meeting nutritional needs, preventing nutritional deficiencies and promoting growth. Moreover, recent evidence suggests that early nutrition has biological effects on the individual with important implications for later health. The goal of nutrition management in preterm infants is the achievement of postnatal growth at a rate that approximates the intrauterine growth of a normal fetus at the same postconceptional age.

INTRODUCTION

Adequately supplying the nutritional needs of preterm infants remains a significant clinical challenge, especially for very low birth weight (VLBW) and extremely low birth weight (ELBW) infants. Although rates of survival of these infants have improved, growth failure is nearly universal, and multiple recent studies have documented the poor growth and the nutritional deficits in this population of infants. At the time of birth, only about 18 percent of ELBW infants are less than the 10th percentile for weight and length, but at 36 weeks corrected gestational age, as they near discharge most of these same ELBW infants are less than the 10th percentile for weight and length. In these infants, full enteral feedings are generally delayed because of the severity of medical problems associated with prematurity, such as immature lung function (which often requires endotracheal intubation and mechanical ventilation), hypothermia, infections, and hypotension. In addition, early enteral feeds are also delayed because of concerns that aggressive feeding may lead to complications such

as feeding intolerance or necrotizing enterocolitis. As a result, the nutritional requirements of VLBW infants are rarely met by enteral feeds in the first two weeks after birth.¹ The impact of early malnutrition can have long-lasting negative effects on central nervous system development and growth. Parenteral nutrition (PN) can meet the goal of providing nutrition at this time.

MAIN CONTENT

Goals of Parenteral Nutrition

There is growing evidence that inadequate nutrition in the first weeks of life of premature infants results in growth failure that is often difficult to correct and may lead to permanent detrimental effects.² The early use of adequate PN minimizes weight loss, and improves growth outcome. Increased protein and energy intakes in the first weeks of life also are associated with improved neurodevelopmental outcome.³ Because adequate enteral nutrition cannot be established in most VLBW infants in their early weeks, PN is initiated to correct *in utero* growth restriction and to prevent subsequent growth failure.

Indications for Starting TPN

- Premature infants <30 weeks gestation and/or <1000g.
- Wt <1500 not expected to receive full enteral feeds for >3 days (Ventilator dependent—HMD, BPD; NEC, major surgeries, etc.)
- Wt >1500 not expected to receive enteral feeds for >5 days (Severe birth asphyxia, ventilator dependent, fulminant sepsis, etc.)
- Absorption problems as in short bowel syndrome
- Surgically correctable GI malformations (Omphalocele, gastroschisis, TE fistula, malrotation, etc.)
- GI catastrophes as NEC

PN for the premature infant includes the following:

- Adequate calories for energy expenditure and growth
- Carbohydrates to prevent hypoglycemia and, in combination with lipids, provide the caloric intake to meet the energy needs of the infant
- Adequate protein intake including essential amino acids to achieve positive nitrogen balance required for growth
- Fatty acids to prevent essential fatty acid deficiency and maximize overall nonprotein energy intake
- Essential nutrients including minerals (i.e. calcium, magnesium, and phosphorus), electrolytes, vitamins, and trace elements (e.g. copper, zinc, and selenium) are needed for growth.

The recommended nutrient needs for medically stable and growing premature infants receiving either parenteral or enteral nutrition is shown in Table 1.

Calorie Requirements

In premature infants, energy requirements must cover both energy needed for energy expenditure (resting metabolic rate, activity and thermoregulation) and for growth. The resting metabolic rate has been estimated to be 40 to 60 kcal/kg per day in parenterally fed neonates maintained in a thermoneutral environment. Each gram of weight gain for growth, including the stored energy and the energy costs of component synthesis, requires between 3 and 4.5 kcal. Thus, an ideal daily weight gain of 15g/ kg (which estimates daily fetal growth) requires an additional caloric requirement of 45 to 67 kcal/ kg above the estimated resting metabolic rate.⁴ The premature infant has an energy requirement of 80 to 100 kcal/ kg per day when nourished parenterally, which is generally lower than the energy requirement needed with enteral nutrition. This lower energy requirement is due to less fecal energy loss (energy excreted), and usually lower energy needs for activity and thermoregulation because of their controlled thermoneutral environment.

Carbohydrates and fat primarily provide the calories for energy. Protein intake including essential amino acids should be sufficient to attain positive nitrogen balance by covering the needs generated by protein turnover (protein

catabolism) and tissue growth. The distribution of non-protein calories derived from carbohydrates and lipids is similar to that of human milk, which is generally about 40 and 45 percent of calories from fat and carbohydrates, respectively.

Studies have shown that mixtures that favor a higher distribution of glucose (i.e. carbohydrates) may result in adverse effects on respiratory metabolism. Surplus calories from glucose result in glucose conversion to fat, which increases the production of carbon dioxide and raises the partial pressure of carbon dioxide (PaCO₂) leading to an increased minute ventilation and respiratory quotient, and a possible rise in oxygen consumption.⁵ In addition, a balanced distribution of calories from glucose and fat favors protein accretion, while intake of glucose—only PN (i.e. without lipids) is associated with protein oxidation.⁶

Fluid Requirements

The percentage of total body water in fetuses decreases from approximately 95 percent early in development to 80 percent by 8 months' gestation and to 75 percent at term.⁷ During the first day after birth, term infants require a minimum of 60 mL/ kg per day to meet maintenance fluid needs (replacing net losses). As infants mature, fluid needs gradually increase to a total of 120 to 150 mL/kg per day to allow for increased renal solute load, stool water output, and growth. Preterm infants have more insensible water losses than term infants due to their large surface area, skin immaturity, and ensuing increased evaporation. Thus, fluid needs are higher on the first postnatal day at 80 to 100 mL/kg per day and increase by 10 to 20 mL/kg per day to a total of 130 to 180 mL/kg per day as preterm infants mature.⁷

Carbohydrate

Glucose is transported across the placenta via facilitated diffusion and is the principal energy substrate for the fetus. The primary storage form of glucose is glycogen, which is only produced during the third trimester. Glucose is the chief energy source for the neonatal brain and is of paramount importance for preterm infants who, in addition to having limited glycogen stores, also have especially metabolically active organs. Endogenous glucose production varies with age and was estimated to be 8 mg/kg per minute in term newborns and 6 mg/kg per minute in preterm infants.⁸ These production rates provide an appropriate starting point for glucose infusion rates in PN for term and preterm infants. The upper rate of glucose administration is dictated by the maximal glucose oxidative capacity for energy production and glycogen deposition. When glucose is given in excess, it is converted into lipid via lipogenesis. This conversion is inefficient, increases energy expenditure, and may have additional clinical consequences via increased carbon dioxide production and

Table 1: Composition of fluid, energy and nutritional intake for stable growing preterm infants

Components, units	Units/kg/day	
	Parenteral	Enteral
Water, ml	120–160	135–190
Energy, kcl	90–100	100–130
Protein, g	3.0–3.8	3.4–4.3
Fat, g	3–4	5.3–7.2
Carbohydrates, g	9.7–15	

exacerbation of lung disease.⁹ The maximum glucose oxidation capacity is 12 mg/kg per minute in term newborns and preterm infants receiving long-term PN and generally should not exceed this concentration.

The minimum recommended blood glucose concentration is 45 mg/dL (2.5 mmol/L). Despite limited glycogen storage capacity, ELBW infants often experience episodes of hyperglycemia during the first few postnatal days. This may be due to surges in glucose production caused by birth-related increases in catecholamines, possibly compounded by an exogenous supply of catecholamines and inotropic drugs, a decrease in endogenous production of insulin, and an increase in peripheral and hepatic insulin resistance.¹⁰ In addition, ELBW infants often fail to suppress endogenous glucose production completely in response to an exogenous supply of PN glucose. Although there is no consensus definition of hyperglycemia, especially in ELBW infants, a suggested range may be 150 to 220 mg/dL (8.3 to 12.2 mmol/L). The primary concern for hyperglycemia in infants is its association with death, prolonged hospitalization, intraventricular hemorrhage grades 3 and 4, necrotizing enterocolitis, and late-onset bacterial and fungal sepsis.¹¹ Early AA supplementation on the first day after birth seems to stabilize high blood glucose concentrations by stimulating endogenous insulin secretion. Other interventions for hyperglycemia include reducing the glucose infusion rate or treating with intravenous insulin.¹¹ Of note, a Cochrane review evaluating these two strategies for treatment of hyperglycemia found no difference in death or serious morbidities.

There is also a concern about the potential risk of lactic acidemia in infants receiving high insulin and glucose administration. Because the safety of insulin therapy and its impact on hyperglycemia-related morbidities have not been established, the consensus in the literature points toward incrementally decreasing the glucose infusion rate to approximately 4 mg/kg per minute and reserving insulin use for infants whose blood glucose concentrations are greater than 250 mg/dL (13.9 mmol/L) while receiving this infusion rate.

Proteins

The delivery of adequate intakes of both protein and energy, and an optimal mixture of essential/nonessential amino acids is required to achieve a positive nitrogen balance, which results in protein accrual and growth.¹² With no amino acid intake, VLBW infants lose the equivalent of 0.5 to 1 g/kg per day of protein due to protein catabolism in the first days after birth. The impact can be seen in the following example. A 26-week gestation 1,000 g birth weight infant begins with body protein stores of approximately 88 g. Without any protein intake, the infant loses approximately 1.5 percent of total body protein per day. At the same time, the fetus *in utero* accumulates

approximately 2 g/d of body protein. To achieve this rate of accretion, the placenta supplies substantially more than 2 g/kg per day of amino acids to the developing fetus.¹³ After only 3 days without protein intake, body protein stores are reduced by 5 percent from birth and are 10 percent less than a fetus of comparable age. It is obvious that significant body protein deficits can and most often do accumulate rapidly in ELBW infants in early postnatal life, particularly if the initiation of intravenous amino acids is delayed for even a few days after birth (Fig. 1).

Protein accretion rates by fetuses at 24 to 25 weeks', 27 to 28 weeks', and 30 to 32 weeks' gestation have been estimated to be 4.0, 3.6, and 3.3 g/kg per day, respectively.¹⁴ Infusion of AA with glucose as early as the first postnatal day decreases protein catabolism and enhances net protein accretion.¹⁵ Thus, reducing the number of hours that infants receive suboptimal nutrition (without AAs) has been emphasized recently as an important goal of neonatal intensive care. The purpose of early AA supplementation is to provide preterm infants with substrate that promotes protein deposition that closely approximates fetal energy production and growth. For most preterm infants, 1.0 to 1.5 g/kg per day of intravenous AA along with glucose prevents protein catabolism.¹⁶ When non-protein energy intake is 80 to 85 kcal/kg per day and AA intake is 2.7 to 3.5 g/kg per day, nitrogen retention and growth might actually approach the intrauterine rate. Recent studies have challenged the older practice of starting at 0.5 to 1 g/kg per day of AA and gradually advancing the AA infusion rate.^{17,18} In a retrospective study, Valentine and associates¹⁵ suggested that providing 3 g/kg per day of AA within 24 hours of birth to very low-birth weight (VLBW) infants was safe and associated with better weight gain and shorter duration of PN administration. ELBW infants may require up to 4 g/kg per day of intravenous AA to maintain stores and promote growth. More research is needed to establish the optimal AA requirements in critically ill infants and in those who have sepsis and renal and hepatic dysfunction. For a fixed nitrogen intake, nitrogen retention increases with increasing energy intake from 50 to 90 kcal/kg per day. As a result, one needs to consider both nitrogen and energy intake in order to optimize a positive nitrogen balance.

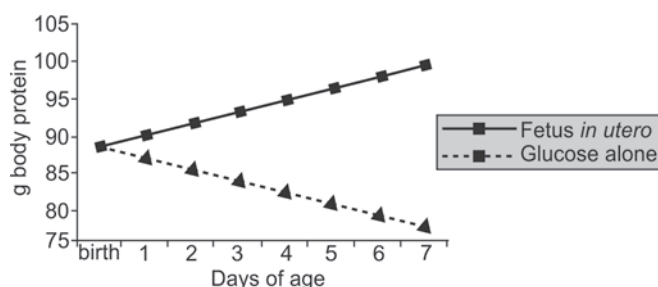


Fig. 1: Protein accretion in intrauterine life and if only glucose is given postnatally

The major concerns about early and aggressive delivery of AA, especially to ELBW infants, are the development of azotemia, hyperammonemia, and metabolic acidosis. These complications of PN were reported using earlier AA preparations and rarely occur with current crystalline solutions. Blood urea nitrogen (BUN) represents the complex interaction of hydration status, renal function, energy quality and quantity, and degree of illness. Rising BUN values are, therefore, not just a reflection of the ELBW infant's intolerance to AA infusion.

Composition

The essential amino acids in PN include isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, and valine. In the premature infant, other amino acids may be conditionally essential because the premature infant has a limited ability to synthesize them. They include *cysteine*, glutamine, glycine, histidine, taurine, and tyrosine.¹⁹

The first parenteral amino acid solutions used in neonates were hydrolysates of fibrin or casein. Concerns about these first-generation solutions included high concentrations of glycine, glutamate, and aspartate; the presence of unwanted peptides; and high acidity. Hyperammonemia and acidosis in the early 1970's were associated with the use of the first-generation solutions in neonates. The second generation of amino acid solutions consisted of crystalline amino acid mixtures. The amino acid pattern of these mixtures reflects that of high-quality dietary proteins, with large amounts of glycine and alanine and the absence of glutamate, aspartate, tyrosine, and cysteine.

The current solutions include modifications of crystalline amino acids for use in pediatric patients (Table 2). Aminosyn PF (Abbott Laboratories, North Chicago, IL) and TrophAmine (B Braun, Irvine, CA) are the two parenteral amino acid solutions commercially available in the United States that are recommended for use in neonates. Primene (Baxter Laboratories, Portugal) has an amino acid pattern closely resembling that of TrophAmine, although its composition was derived from fetal and neonatal cord blood amino acid concentrations. In India, Aminoven is the amino acid preparation made by Frasenius Kabi. There is no clear evidence that one amino acid mixture is superior to another in promoting nitrogen retention.

Cysteine and glutamine: It has been proposed that supplementation of *cysteine* and glutamine will improve patient outcome. One possible mechanism is supplementation of these two amino acids improves glutathione synthesis.²⁰ Glutathione is a major intracellular antioxidant and its primary function is to protect cells from free-radical damage (e.g. peroxides). The liver synthesizes glutathione from cysteine, glutamine, and glycine. However, in a trial that randomly assigned standard (45 mg/kg per day) and high dose of cysteine

Table 2: Composition of different amino acid preparations

	<i>Aminosyn-PF</i> (Abbott) (mg/dL) (10% solution)	<i>TrophAmine (B</i> <i>Braun)</i> (mg/dL) (10% solution)	<i>Primene</i> (Baxter) (mg/ dL) (10% solution)
Histidine	312	480	380
Isoleucine	760	820	670
Leucine	1,200	1,400	1,000
Lysine	677	820	1,100
Methionine	180	340	240
Phenylalanine	427	480	420
Threonine	512	420	370
Tryptophan	180	200	200
Valine	673	780	760
Alanine	698	540	800
Arginine	1,227	1,200	840
Proline	812	680	300
Serine	495	380	400
Taurine	70	25	60
Tyrosine	44	240*	45
Glycine	385	360	400
Cysteine	—	<16	189
Glutamic acid	820	500	1,000
Aspartic acid	527	320	600

(81mg/kg per day), there were no differences glutathione concentration and synthesis, and the plasma levels of cystine between the two groups.²¹

Lipids

Intravenous lipid administration provides essential fatty acids (i.e. linoleic and linolenic acids) that cannot be synthesized by humans and is an important nonprotein source of energy. Small amounts of essential fatty acids (approximately 4% of caloric intake or 0.5 g/kg per day) are required to prevent essential fatty acid deficiency. Without supplementation, clinical manifestations of fatty acid deficiency (such as dermatitis, thrombocytopenia, and increased likelihood of infection and failure to thrive) become apparent by the end of the first week after birth.

Intravenous fat emulsion (IL) formulations used in premature infants contain varying combinations of soybean, safflower, or fish oils, with glycerin and egg yolk phospholipids added as emulsifiers (Table 3). When given early as PN, intravenous lipid prevents essential fatty acid deficiency, provide needed energy for tissue healing and growth, and balance the distribution of non-protein calories.²²

Table 3: Composition of different IV lipid preparations

	Soy	Soy/Safflower	Soy/Olive	MCT/LCT
16:0 (%)	11	7.5	13	4.5
18:0 (%)	4	4	3	1.5
18:1 (%)	24	18	60	13
18:2n-6 (%)	55	66	18	27
18:3n-3 (%)	8	4	2	4
Triglyceride (g/L)	200	200	200	200
Phospholipid (g/L)	12	12	12	12
Glycerol (g/L)	22	22	22	22

IL has been given to premature infants who have been severely ill on the first day of life without short-term adverse effects.²³ In one review, there were no differences on growth, the risk of lung disease, and overall morbidity and mortality between early (defined as ≤ 5 days after birth) and late use of IL.²⁴

10 versus 20 percent IL: IL is available in two different concentrations, 10 and 20 percent solutions. In premature infants, at similar or even greater doses of IL, the 20 percent IL solution appears to be better tolerated because the 10 percent solution requires a larger administered volume and is associated with a poorer clearance of triglycerides due to interference from lipoprotein X. The accumulation of lipoprotein X appears to be due to the higher ratio of phospholipids to triglycerides in the 10 percent solution.²⁵ As a result, at the same dose of lipid, infants who receive 20 percent IL solution compared to those who receive 10 percent solution better tolerate and utilize the infused lipids as demonstrated by their lower serum concentrations of triglyceride, cholesterol, and phospholipid.

Continuous vs intermittent infusion: IL can be infused either continuously or intermittently. In the premature infant, intermittent infusion (administered over less than 24 hours) appears to produce higher and more variable serum triglyceride concentrations than continuous infusion (over a 24 hour interval) if both are given at the same lipid dose.²⁶ As a result, the use of continuous infusion of intralipids over 24 hours is advocated.

Measurement of serum triglycerides is the preferred method for monitoring clearance of infused intravenous lipid. Triglyceride concentrations up to 150 mg/dL (1.7 mmol/L) are acceptable; some intensive care units tolerate up to 200 mg/dL (2.3 mmol/L) before decreasing the lipid infusion.

Complications

IL complications in the neonate include the following:

- The risk of hyperlipidemia and hypertriglyceridemia increase with decreasing gestational age and sepsis. A short-term decrease in the lipid infusion rate is usually

sufficient to normalize serum lipid levels with a goal of maintaining serum triglyceride below 150 mg/dL.

- Although there is no direct evidence that IL increases indirect hyperbilirubinemia, there is a theoretical concern that fatty acids may displace bilirubin from albumin-binding sites leading to an increase in free serum bilirubin. As a result, IL rates are limited to less than 3 g/kg per day in causes of extreme hyperbilirubinemia.
- Some studies have shown that IL may interfere with pulmonary oxygenation by altering pulmonary vascular tone and pulmonary artery pressure through thromboxane-mediated pathways or by the formation of free radicals (e.g. hydroperoxides). However, other studies have shown that the use of IL, even when administered within the 12 hours of birth, was not associated with impairment of pulmonary function.

New lipid formulation: A newer IL formulation (Omegaven) utilizes fish oil, which contains long-chain polyunsaturated fatty acids (e.g. docosahexaenoic acid [DHA] and eicosapentaenoic acid [EPA]). This formulation was designed to replace the plant fatty acids (e.g. plant phytosterols) derived from soy-bean lipid emulsions, which have been thought to be proinflammatory and contribute to liver damage. In one study of infants with short bowel syndrome, reversal of cholestasis due to prolonged PN exposure was quicker in 18 infants who received Omegaven compared to 21 historical controls who received soybean emulsions (9.4 versus 44 weeks).²⁷ In addition, the Omegaven group compared to the soybean emulsion group had fewer deaths (2 versus 7) and liver transplantations (0 versus 2). However, randomized controlled trials are needed to determine whether this formulation is more beneficial than the standard IL formulations used in premature infants.

Practical Tips for Lipid Infusion

- Use of 20 percent lipid emulsion is preferable to a 10 percent solution to decrease the risk of hypertriglyceridemia, hypercholesterolemia, and hyperphospholipidemia.
- Initiate lipids at starting dose of 0.5 or 1.0 g/kg per day.
- Plasma triglycerides are monitored after each increase in dose, and concentrations are maintained at less than 200 mg/dL (2.26 mmol/L).
- If the infant has severe hyperbilirubinemia or severe respiratory disease without evidence of PVR, provide lipids at 0.5 to 1.0 g/kg per day, maintaining a serum triglyceride value of no greater than 200 mg/dL (2.26 mmol/L)
- Maximum lipid dosage is usually 3 g/kg per day.
- The lipid infusion hourly rate correlates best with plasma lipid concentrations. Hourly infusion should not exceed 0.12 g/kg per hour.

Minerals

Sodium, potassium and chloride are essential minerals for survival. In VLBW infants, sodium intake should be restricted during first phase of fluid balance to reduce risk of bronchopulmonary dysplasia.²⁸ Till 6 to 10 percent of weight loss has occurred sodium should not be added to PN. Potassium should not be added till diuresis sets in. Sodium and potassium are added to PN usually from day 3 onwards, depending on serum levels. Sodium and potassium can be given as chloride, lactate, or phosphate salts. Infants who receive electrolytes solely as chloride salts may develop hyperchloremic metabolic acidosis. Chloride is generally given as sodium chloride. Estimated and advisable intakes are based on accretion studies and urinary and fecal losses from balance studies completed in the late 1970s.

In premature infants, inadequate intakes of calcium and phosphorus result in bone undermineralization. Clinical manifestations depend upon the degree of impaired bone mineralization and may include osteopenia of prematurity, rickets, and fractures. Bone undermineralization may affect chest wall stability leading to atelectasis and an increased risk of chronic lung disease. Although the net retention is dependent upon the intake of these minerals, the intakes are limited by the solubility of Ca and P in PN solution. Because Ca and P solubility are affected by pH, amino acid concentration and source (e.g., cysteine increases Ca and P solubility), and temperature of the PN solution, adjustment of these factors can increase Ca and P solubility and intake.²⁹ To optimize solubility during PN preparation, P is added first and Ca is added as the last step. The optimal ratio of Ca to P in PN is generally between 1:1.3 and 1:1.7 by weight and nearly a 1:1 molar ratio. Lower ratios result in elevated urinary and serum P suggesting inadequate utilization of P because of insufficient Ca intake. Presently, phosphorus preparation is not available in India. Isolated calcium supplementation can lead to hypercalcemia and hypercalciuria, so calcium levels need to be monitored. The doses of various electrolytes and minerals are shown in Table 4.

Table 4: Recommended doses of electrolytes and minerals

Recommended doses of electrolytes and minerals

Electrolyte/Mineral	Intake
Sodium (meq/kg/d)	0–3
Potassium (meq/kg/d)	0–2
Chloride (meq/kg/d)	0–5
Calcium (mg/kg/d)	60–80
Phosphate (mg/kg/d)	45–60
Magnesium (mg/kg/d)	4.3–7.2

Vitamins

Parenteral vitamins are usually applied as a mixture of different vitamins. Vitamins should be added to lipid emulsion to increase stability and reduce peroxide formation.³⁰ Vitamin induced peroxide load can be reduced by shielding of tubing from light exposure.³¹ Except vitamin K, all vitamins should be supplemented daily. Adult MVI is the only preparation available in our country. It contains benzoic acid as stabilizer which is not recommended for neonates and should be used with caution. The dose of adult MVI is 0.5 ml/kg (comparing parenteral vitamin supplement doses as suggested by ESPGHAN with constitution of adult MVI).³² It is added on day 1. Pediatric MVI is currently not available in India. Separate preparations of fat-soluble and water-soluble vitamins suitable for neonates are not available in India.

Trace Elements

In utero accretion of trace elements primarily takes place in the final trimester of pregnancy. As a result, premature infants are at risk for deficiency of these nutrients because of their low body stores and increased requirements for growth. Calculated daily intake needs for the following trace elements are based upon the birth weight and intra-uterine accretion rate.³³

Recommended intakes for trace elements are as follows:

- Zinc: 400 µg/kg
- Copper: 20 µg/kg
- Chromium: 0.4 µg/kg
- Manganese: 10 µg/kg
- Selenium: 2 µg/kg.

The only trace elements recommended from the first day PN are zinc and selenium. The other trace elements are not needed until after two weeks of age. Iron, another trace element, is not needed in the first few weeks after birth and is not routinely added to PN. In India, the preparation of trace elements is available in form of Celecel.

Preparations of parenteral nutrition along with manufacturer are listed in Table 5.

Infusion Routes

PN may be infused via peripheral and central catheters. Peripheral infusion typically is used for short-term nutrition support. Peripheral vein osmolarity tolerance ranges from 700 to 1,000 mOsm/L. The osmolarity of glucose solutions rises from 255 to 1,020 mOsm/L with increasing concentration from 5 to 20 percent, respectively. Generally, glucose concentrations of 12.5 percent or less are well tolerated by peripheral veins as long as no other osmolarity-increasing agents are added. Central infusion of PN is delivered via central venous catheters and is the preferred route for long-term PN.

Table 5: Market preparations available in India

<i>Constituent</i>	<i>Preparation</i>	<i>Manufacturer</i>	<i>Availability</i>
Dextrose	5%, 10%, 25%, 50%		25, 100, 500
Amino acids	Aminoven infant 6%, 10%	Fresenius Kabi India pvt. limited	100 ml
	Primene	Baxter health care	100 ml
Lipids	Intralipid 10% PLR	Fresenius Kabi India Pvt. Ltd	100
	Intralipid 20% PLR	Fresenius Kabi India Pvt. Ltd	100
	Omegavan	Fresenius Kabi India Pvt. Ltd	100
	Clinoleic 20%	Baxter health care	500
Trace elements	Celecel 4	Claris health sciences	1,3,5
	Celecel 5	Claris health sciences	1,3,5

Table 6: Monitoring of parenteral nutrition

<i>Monitoring of parenteral nutrition</i>		
Parameter	Initial period	Established PN
Weight	Daily	Daily
Length		Weekly
Head circumference		Weekly
Blood sugar	Twice daily	Once daily
Urine sugar	Once daily	Once daily
Serum sodium, potassium, chloride	Every 24-48 hourly, can be done more frequently depending on clinical situation	Once weekly
Calcium, phosphorus, magnesium	Every 24-48 hourly, can be done more frequently depending on clinical situation	Once weekly
Urea, creatinine	48-72 hours	Once weekly
Serum triglyceride	Before initiating and with increment of each dose	Once weekly
Liver function tests	Before initiating lipids	Depending on clinical signs
Hemogram	Depending on clinical needs	Once weekly

Timing and Contents

In ELBW infants, PN should be administered within the first day of life to provide adequate nutrition to minimize early weight loss and protein breakdown, and improve growth outcome. Balancing the distribution of calories between nonprotein sources (i.e. lipids and carbohydrates) and protein sources is critical to optimize protein accretion and avoid adverse effects upon respiratory metabolism and protein oxidation.

The contents of early PN (on the day of birth or soon thereafter) include the following:

- Glucose starting at 4 mg/kg per minute (5 g/kg/day) and slowly increasing to 12 mg/kg/min over several days.
- Amino acids at 3 g/kg per day with increasing increments as tolerated to 4 g/kg per day.
- Lipids at 1 g/kg per day with increasing increments as tolerated to 3 g/kg per day. (See 'Lipids' above)

- Electrolytes are not initially included in early PN but added as needed based upon laboratory evaluation.
- *Other nutrients:* Calcium (60 to 80 mg/kg per day) and multivitamins.

Monitoring

Laboratory monitoring is required to adjust the contents of PN to avoid excesses or deficiencies of any given nutrient and to monitor for PN-associated complications, such as cholestasis and metabolic bone disease. The following laboratory tests should be obtained in any infant who is receiving PN (Table 6).

Complications

Monitoring and adjusting the PN contents can avoid many of the reported PN-associated complications in premature infants, such as electrolytes, glucose, Ca, and P abnormalities.

However, the following significant complications due to PN still may occur in premature infants:

- *Cholestasis*: Cholestasis is a serious complication of PN and is manifested by jaundice due to a direct hyperbilirubinemia.
- *Infection and sepsis*: Line infection is a common complication of PN in premature infants. The two most common bacterial agents are *Staphylococcus epidermidis* and *Staphylococcus aureus*. In the ELBW infants, candidal infections have increased in frequency and are associated with the administration of PN and the use of central venous catheters
- Other line complications include infiltration and potentially skin sloughing, and air embolus.
- Bone disease may occur if adequate nutrients are not provided.

Summary and Recommendations

In the first weeks after birth before adequate enteral nutrition can be established, parenteral nutrition is initiated to help treat *in utero* growth restriction and to lessen growth failure in very low birth weight premature infants (birth weight less than 1500 g).

Composition

- *Energy needs*: Parenteral nutrition (PN) should provide sufficient calories for energy expenditure (resting, metabolic rate, activity, and thermoregulation) and growth. The premature infant who receives parenteral nutrition has an energy requirement of 80 to 100 kcal/kg per day. Carbohydrates and fat primarily provide the calories for energy.
- *Carbohydrates*: Glucose is the carbohydrate used in PN and is a major source of caloric intake needed to meet energy needs. Exogenous glucose is needed after delivery to prevent hypoglycemia. In our practice, we start a glucose infusion rate at 4 mg/kg per minute and advance the rate daily, as tolerated, by 1 to 2 mg/kg per minute to a maximum of 11 to 12 mg/kg per minute. Serum glucose should be monitored because premature infants, especially extremely low birth weight (ELBW) infants (birth weights <1000 g), are susceptible to both hypo- and hyperglycemia.
- *Amino acids*: The delivery of adequate intakes of both protein and energy, and an optimal mixture of essential/ nonessential amino acids are needed to achieve a positive nitrogen balance required for growth and to prevent protein turnover. Early administration of amino acids within the first 24 hours of life prevents protein breakdown and is well tolerated. In our practice, we start an amino acid infusion rate at 3 g/kg per day with increasing increments as tolerated to 4 g/kg per day.

- *Lipids*: Intravenous lipid (IL) administration provides essential fatty acids (i.e. linoleic and linolenic acids) that cannot be synthesized by humans and is an important nonprotein source of energy (Table 4). We initiate IL infusion as a continuous infusion using a 20 percent solution at a dose of 1.0 g/kg per day and advance as tolerated to a target of 3 g/kg per day. A dose of 4 g/kg per day occasionally is used in a chronically-ill infant unable to tolerate enteral feedings. (See 'Lipids' above.)
- *Other nutrients*: Other essential nutrients include carnitine, minerals (calcium, magnesium, and phosphorus), vitamins, electrolytes (sodium, potassium, chloride, and acetate), and trace elements (copper, zinc, and selenium) required for growth.

Administration and Complications

- Parenteral nutrition (PN) can be infused through peripheral or central veins. The choice is dependent upon the expected duration of PN. If the infant is expected to require PN for more than two weeks, a central line should be inserted as a more concentrated formulation can be delivered providing calories required for growth.
- In ELBW infants, PN should be administered within the first day after birth to provide adequate nutrition to minimize early weight loss and protein breakdown, and improve growth outcome. The composition of early PN in ELBW includes glucose, amino acids, lipids, vitamins, calcium, and heparin.
- In patients who require ongoing administration of PN, caloric concentration is increased to provide adequate calories for growth. In addition, trace elements, phosphorus, magnesium, and cysteine are added to PN.
- Laboratory monitoring is required to adjust the contents of PN to avoid excesses or deficiencies of any given nutrient and to monitor for PN-associated complications. PN-associated complications include cholestasis, line infection and sepsis, infiltration and sloughing of the skin, and air embolus.

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CHAPTER 5

Feeding of Low-birth-weight Infants

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INTRODUCTION

Newborn nutrition is a vital part of the well-being of an infant. The period of rapid growth in infancy requires careful nutritional support to continue the growth and development that began at conception. The main objectives in feeding infants are meeting nutritional needs, preventing nutritional deficiencies and promoting growth.¹ Moreover, recent evidence suggests that early nutrition has biological effects on the individual with important implications for later health.

Low-birth-weight (LBW) infant is one who weighs less than 2500 grams at birth. Every year 20 million LBW infants are born in the developing world and 40 percent of these are born in India. Low-birth-weight infants are a heterogeneous group and would consist of preterm infants (born <37 weeks of gestation and weighing less than 2500 gm as well as full term infants if they weigh less than 2500 gm and the feeding guidelines would vary from one group to the other.

FEEDING PRINCIPLES FOR FULL TERM LBW INFANTS

Human milk is the recommended nutritional source for full-term infants for at least the first six months of post-natal life (54th WHA). The advantages of breastfeeding are not limited to childhood period but extend much beyond in adulthood as well.

- Reduction of infection (diarrhea, acute respiratory tract infections, otitis media, necrotizing enterocolitis, late onset sepsis)
- Protection against allergies: less chance of eczema, milk allergy and asthma
- Reduction of obesity/diastolic blood pressure by 2 mm Hg/ Type II DM/ leukemia/breast cancer

- Better cognition
- Saves money/social issues
- Reduction of under five child mortality by 13 to 15 percent in India
- Maternal benefits.

Knowing so many benefits of breastfeeding, it is strongly being emphasized by all agencies (WHO, AAP, IAP) to promote breastfeeding till 6 months but the exclusive breastfeeding rates in our country according to latest NFHS III is 46 percent which is low from all standards. Understanding that the incidence of true lactation failure is only 1 percent, there are other problems which can be sorted out by various practical solutions apart from increasing awareness:

- Establishment of antenatal clinic for breastfeeding promotion/nipple examination by obstetricians or pediatricians or any health care worker.
- Feeding in first hour of life to be emphasized which has been incorporated as essential part of Newborn Resuscitation Program and Kangaroo Mother Care.
- Employment of lactation nurses/Counselors in hospitals to help the mothers in actually initiating and maintaining lactation.
- Special emphasis on babies born to LSCS mothers like pain management/different positions/ bedding in/incision line care, etc.
- Promotion of breast milk expression techniques (by manual techniques or breast pumps) would help pre-term babies, working mothers or if mother and baby are separated because of any reason.

After breastfeeding, the second best option for milk in first one year of life is infant term milk formula with composition as close to mothers milk as possible. But the commonest milk consumed by Indian infants is cow's or buffalo's milk which is definitely with lots of side effects namely

iron deficiency anemia, vitamins C and D deficiency disorders, increased risk of infections, increased renal solute load to kidneys especially important during acute diarrhea episodes and most important lack of DHA in bovine milk which is of paramount importance for brain and retina growth. Because of these serious limitations American Academy of Pediatrics recommends against use of cow's milk till one year of age.^{2,3} Pediatric academies of Canada, Scotland and UK recommend not using cow's milk till 9 months of age. The age cut off of 9 to 12 months is based on the demonstration of microscopic bleeding from intestines in infants fed unmodified bovine milk till this age.

Supplementation of Exclusively Breastfed Infants

Because of widespread prevalence of vitamin D deficiency disorders in infants, AAP guidelines⁴ suggest to start vitamin D (400 IU/d) even in exclusively breastfed infants. Though there are concerns regarding exposure of infants to sunlight and later developments of skin cancer in white races; we do not have any Indian figures to support or negate these observations and as of now we do recommend sun exposure for vitamin D insufficiency.

Iron supplementation is started at 6 months of age as later supplementation has been associated with increased prevalence of iron deficiency states whereas earlier supplementation is also not without risks of infection (especially in malaria endemic zones) and poor growth.

FEEDING PRINCIPLES FOR PRETERM LBW INFANTS

This group can be subdivided in two smaller groups:

- Infants between 32 weeks and <37 weeks; 1800 gm to <2500 gm
- Infants <32 weeks and <1800 gm.

For the first group, the feeding principles should be on the same as that of full term infants in most situations and should be on direct breastfeeds. The special need of nutrition comes for the second group. The European Society of Paediatric Gastroenterology and Hepatology has given its recommendations for this group which is at a distinct disadvantage because of various physiological limitations.⁵

Very High Growth Rate

- Intrauterine weight gain 16 to 17 g/kg body weight per day (approx. 3 folds from 28th to 40th week). Gains around 20 cm in length
- Brain size increases three and half times.

Very Low Nutrient Stores

- Low fat and glycogen stores
- Lack of body building nutrients
- From 25 to 40th week body accumulates 20,000 mg of calcium.

Immature Organs

Gastrointestinal Tract

- Increased GI tract permeability leading to intestinal inflammation and injury
- Delayed gut colonization with Bifido bacteria.

Lack of Digestion and Absorption

- Smaller stomach capacity
- Delayed emptying of gastric content
- Low levels of intestinal lactase, lactose digestion is poor
- Low levels of pancreatic lipase and bile salts results in poor fat absorption.

Renal Function

- Low glomerular filtration rate
- Acidosis occurs early
- Poor urine concentration. Infant gets dehydrated readily.

Central Nervous System

- Uncoordinated sucking and swallowing
- Regurgitation and aspiration.

Respiratory System

- Resuscitation problems
- Hyaline membrane disease
- Vulnerable to chronic pulmonary insufficiency due to bronchopulmonary dysplasia.

The current concept of nutrition of very low birth weight infants is to provide aggressive nutrition as the ill effects of undernutrition are well established. During the acute phase of the disease, aim is to avoid catabolism and not growth. This is difficult in VLBW infants due to higher requirements, poor stores and reduced intake. After stabilization during the growing period, aim is to approximate *in utero* growth rate of a normal fetus of the same gestation with no functional impairment. There should be positive energy balance to sustain growth. Inadequate nutrition leads to poor postnatal growth which ultimately leads to impaired neurocognitive development.

Sources of nutrient recommendations for preterm infants include the American Academy of Pediatrics Committee on Nutrition, the European Society of Paediatric Gastroenterology Hepatology and Nutrition Committee on Nutrition (ESPGAN-CON), National Neonatology Forum⁶ and the reasonable ranges of nutrient intakes published by Tsang et al.⁷

CHOICE OF MILK FOR FEEDING PRETERM BABIES

The different choices of milk for preterm are breast milk, fortified human milk and preterm specialized formula milk. Breast milk remains the choice of feeding of all neonates. Breast milk confers significant advantage for

protection against infection and NEC in preterm infants. Breast milk in sufficient volume has been shown to achieve a desirable weight gain in preterm infants. Breast milk provides ideal whey casein ratio (60:40) and whey protein is easily digestible, contains long chain polyunsaturated fatty acid (LCPUFA) which is important for brain and retinal growth. It also contains oligosaccharides which help in host defense. The neurodevelopmental outcome also has been reported to be better with breastfeeding. However feeding exclusive breast milk to a preterm baby <32 weeks may have certain disadvantages. Though preterm milk initially contains higher protein but the protein content gradually declines over next 3 to 4 postnatal weeks. It also contains inadequate amounts of calcium and phosphate. A growing preterm needs higher protein, calorie, calcium, phosphate than can be provided by breast milk alone. Hence, the preterm babies may need additional supplements during the catch up growth if weight gain is not adequate. Table 1 shows recommended nutrient intakes as per ESPGHAN 2009.

NUTRITIONAL REQUIREMENTS OF PRETERM INFANTS FOR SOME IMPORTANT NUTRIENTS⁵

Energy

Recommendations for energy intake are based on growth and nutrient retention similar to intrauterine references. The recommendations should achieve not only weight gain but also body composition similar to intrauterine growth standards. It is also emphasized that rapid infant weight gain in term infants may be associated with adverse outcomes. Synthesis of new tissue is strongly affected by the intake of protein and other nutrients; thus, achieving an adequate energy to protein ratio is as important as providing adequate energy intake.

Based on intrauterine standards, a reasonable range of energy intake for healthy growing preterm infants with adequate protein intake is 110 to 135 kcal/ kg/ day. Increasing energy intake may not be appropriate for infants whose growth appears inadequate (without evidence of fat malabsorption) because it is more likely that other nutrients (e.g. protein) are rate limiting.

Proteins

Proteins are the main building blocks and a suboptimal intake of protein, energy, and other nutrients may lead to lower cognitive achievements. Protein accretion has been estimated at approximately 1.7 gm/kg/day for fetuses throughout the second half of gestation but is lower at the end of gestation. Obligatory protein losses are at least 0.7 gm/ kg/ day but may be higher if nitrogen losses from skin and breath could be measured. Based on the protein needs and nitrogen utilization, the protein intake

Table 1: Recommended intakes for macro- and micronutrients expressed per mg kg⁻¹ day⁻¹ and per 100 kcal unless otherwise denoted

<i>Min–Max</i>	<i>Per⁻¹ day⁻¹</i>	<i>per 100 kcal</i>
Fluid, mL	135-200	
Energy, kcal	110-135	
Protein, g <1kg body weight	4.0-4.5	3.6-4.1
Protein, g 1-1.8 kg body weight	3.5-4.0	3.2-3.6
Lipids, g (of which MCT <40%)	4.8-6.6	4.4-6.0
Linolenic acid, mg	385-1540	350-1400
α-linolenic acid, mg	>55 (0.9% of fatty acids)	>50
DHA, mg	12-30	11-27
AA, mg	18-42	16-39
Carbohydrate, g	11.6-13.2	10.5-12
Sodium, mg	69-115	63-105
Potassium, mg	66-132	60-120
Chloride, mg	105-177	95-161
Calcium salt, mg	120-140	110-130
Phosphate, mg	60-90	55-80
Magnesium, mg	8-15	7.5-13.6
Iron, mg	2-3	1.8-2.7
Zinc, mg	1.1-2.0	1.0-1.8
Copper, μg	100-132	90-120
Selenium, μg	5-10	4.5-9
Manganese, μg	≤27.5	6.3-25
Fluoride, μg	1.5-60	1.4-55
Iodine, μg	11-55	10-50
Chromium, μg	30-1230	27-1120
Molybdenum, μg	0.3-5	0.27-4.5
Thiamine, μg	140-300	125-275
Riboflavin, μg	200-400	180-365
Niacin, μg	380-5500	345-5000
Pantothenic acid, mg	0.33-2.1	0.3-1.9
Pyridoxine, μg	45-300	41-273
Cobalamin, μg	0.1-0.77	0.08-0.7
Folic acid, μg	35-100	32-90
L-ascorbic acid, mg	11-46	10-42
Biotin, μg	1.7-16.5	1.5-15
Vitamin A, μg RE, 1 μg~3.33 IU	400-1000	360-740
Vitamin D, IU/day	800-1000	
Vitamin E, mg (α-tocopherol equivalents)	2.2-11	2-10
Vitamin K ₁ , μg	4.4-28	4-25
Nucleotides, mg		≤5
Choline, mg	8-55	7-50
Inositol, mg	4.4-53	4-48

should be at least 3.0 gm/ kg/ day. Intrauterine weight gain can be matched at protein intakes <3 to 3.5 gm/ kg/ day accompanied by a high energy intake, but body fat percentage will then be much higher than observed in the fetus. Intakes in the range of 3 to 4.5 gm/ kg/ day will achieve acceptable plasma albumin and transthyretin concentrations. Some excess of protein intake over requirements was not shown to cause detrimental effects in preterms, but a small deficit will impair growth. ESPGHAN recommends 4.0 to 4.5 gm/ kg/ day protein intake for infants up to 1000 gm, and 3.5 to 4.0 gm/ kg/ day for infants from 1000 to 1800 gm. This will meet the needs of most preterm infants.

Lipids

Apart from providing much of its energy needs, dietary lipids also provide the preterm infants with essential polyunsaturated fatty acids, and lipid-soluble vitamins. Long chain polyunsaturated fatty acids (LCPUFAs) are important for cell membrane functions and the formation of bioactive eicosanoids. Brain grey matter and the retina are particularly rich in long-chain polyunsaturated fatty acids.

Assuming a daily intrauterine fat deposition of 3 g/kg, 10 to 40 percent loss from fat malabsorption, and 15 percent loss from unavoidable oxidation, and conversion of absorbed triglyceride to deposited triglyceride in tissue, a minimal dietary fat intake of 4.8 gm/ kg/ day is suggested.

Although some infants with restricted fluid and feed intakes may need high fat intakes to meet energy needs, for most preterm infants a reasonable range of fat intake is 4.8 to 6.6 gm/ kg/ day or 4.4 to 6.0 gm/100 kcal (40–55% of energy intake). The medium-chain triglyceride content in preterm formula, if added, should be in the range of up to 40 percent of the total fat content.

The recommended intakes are for DHA (docosahexaenoic acid) 12-30 mg/kg/day and for AA (arachidonic acid) 18-42 mg/kg/day with a ratio of AA:DHA::1-2:1. Eicosapentaenoic acid competes with AA and the levels are low in human milk; hence its supply should not exceed 30 percent of DHA supply.

Calcium

Calcium absorption depends on calcium and vitamin D intakes, and that calcium retention is additionally related to absorbed phosphorus. Various studies suggest that calcium retention ranging between 60 and 90 mg/ kg/ day decreases the risk of fractures, diminishes the clinical symptoms of osteopenia, and ensures appropriate mineralization in very-low-birth-weight (VLBW) infants. Thus, a calcium intake of 120 to 140 mg/ kg/ day with an absorption rate of 50 to 65 percent will lead to calcium retention of 60 to 90 mg/ kg/ day.

Phosphorus and Calcium to Phosphorus Ratio

- The calcium to phosphorus ratio may be an important determinant of calcium absorption and retention. The present recommendation for preterm formula is calcium to phosphorus ratio close to 2:1, but ideally this should be adapted taking into account nitrogen retention as well as bioavailability of the calcium salt. Considering a nitrogen retention ranging from 350 to 450 mg/ kg/ day and calcium retention from 60 to 90 mg/ kg/ day, the adequate phosphorus intake represents 65 to 90 mg/ kg/ day of a highly absorbable phosphate source (90%) with a calcium to phosphorus ratio between 1.5 and 2.0. Individual needs can be determined by measuring spot urinary calcium <6 mg/kg/d and urinary excretion of P >4 mg/ kg/ d.

Vitamin D

Vitamin D is important for supporting a large number of physiological processes such as neuromuscular function and bone mineralization. The requirements of vitamin D for optimal growth in VLBW and extremely-low-birth-weight infants are still matters for discussion. Studies have suggested a vitamin D intake of 800 to 1500 IU/ day which is necessary to reach a circulating 25(OH)D concentration above 75 nmol/ L. ESPGHAN recommends a vitamin D intake of 800 to 1000 IU/ day (and not per kilogram) during the first months of life.

Iron

Iron is essential for brain development, and many observational studies have shown an association between iron deficiency anemia and poor neurodevelopment in infants. Excessive iron supplementation of infants on the other hand may lead to increased risk of infection, poor growth, and disturbed absorption or metabolism of other minerals. Thus, one must prevent not only iron deficiency but also iron overload.

ESPGHAN recommends an iron intake of 2 to 3 mg/ kg/ day, given as a separate iron supplement, in preterm formula or in fortified human milk. Iron supplementation should be started at 2 to 6 weeks of age (2-4 weeks in extremely low birth weight infants). Infants who receive erythropoietin treatment and infants who have had significant, uncompensated blood losses may initially need a higher dose, requiring a separate iron supplement in addition to preterm formula or fortified human milk. Enteral iron doses >5 mg/kg/day should be avoided in preterm infants because of the possible risk of retinopathy of prematurity. Iron supplementation should be delayed in infants who have received multiple blood transfusions and have high serum ferritin concentrations. Iron supplementation should be continued after discharge, at least until 6 to 12 months of age depending on diet.

Table 2: Composition of various feeding options available for preterm infants per 100 ml of feed

<i>Per 100 ml</i>	<i>EBM</i>	<i>EBM and Lactodex HMF</i>	<i>EBM and Similac HMF</i>	<i>Lactodex</i>	<i>Dexolac</i>	<i>Enfamil</i>
Energy (Kcal)	67	82	81	80	68	68
Protein (gm)	1.1	1.5	2.1	2.16	1.7	1.4
Fat (gm)	3.5	3.6	3.9	4	3.5	3.7
Vitamin A (IU)	48	288	668	240	582	256
Vitamin D (IU)	8	84	128	72	69.6	54.4
Calcium (mg)	25.3	125	142	136	112.4	52
Phosphorus (mg)	14.5	64.5	81.5	68	56	29
Iron (mg)	0.09	0.09	0.44	1.9	1.23	1.22

Which milk is the best milk for preterms?

As evident from the above discussion, there are certain increased requirements for these preterm neonates and hence fortified human milk is the best available option to meet the nutritional requirements of preterm babies. Alternatively, a preterm formula would be required for this group of preterm neonates (Table 2).

Feeding Protocol for Preterm Babies, < 32 weeks and < 1800 gram

Choice of milk

First choice milk is maternal EBM (with HMF supplementation to 24 calories/30 ml when the baby is tolerating 100 ml/kg/day). *Second choice milk* would be Preterm formula.

Initiation of feeding

- Well babies
 - >30 weeks can be started immediately on total milk feeds.
 - <30 weeks: start feeds on D1 along with parenteral nutrition
 - <28 weeks: minimal enteral feeds on Day 2 or 3.
- Sick babies
 - >28 weeks, start enteral feeds when it is felt clinically appropriate.

Progression of feeds

- Well baby, no risk factors, baby tolerating feeds: Increase by 20 – 30 ml/ kg/ day
- Slow progression if baby shows features of feed intolerance
- In defining the rate of increase the following needs to be considered:
 - Gestation and weight of the baby
 - How sick the baby has been
 - How well the milk is being tolerated (vomits or large residuals)
 - Any abdominal signs, e.g. distention.

Final feed volume

Final feed needs to be individualized in each baby. A weight gain 15g/ kg/ day (range 10-25 g/kg/ day) should be targeted which can be achieved at a volume of around 180 ml/ kg/ day.

Nutritional assessment of the enterally fed premature infant

Component measured	Frequency
Fluid intake (ml/ kg/ day)	Daily
Nutrient intake	Daily
Energy intake (Kcal)	
Protein (g)	
Specific nutrient (unit)	
Anthropometry	
Body weight (g)	Same time each day
Length (cm)	Weekly
Head circumference (cm)	Weekly
Biochemical monitoring	
Hemoglobin, hematocrit	Weekly
Serum electrolytes	Twice weekly, then every 2 weeks
Calcium, phosphorus	Twice weekly, then every 2 weeks
Alkaline phosphatase	Twice weekly, then every 2 weeks
Albumin, BUN	Twice weekly, then every 2 weeks
Other assessments	
Renal USG	At 2 months of age (for nephrocalcinosis)

A daily weight gain of 1 to 1.5 percent of birth weight, length gain of approximately 0.9 cm/week and increase in head circumference of 0.7 to 0.9 cm/week are ideal desired targets.

Postdischarge Feeding

Most of the follow-up studies of VLBW and ELBW show that at discharge they are <10th centile and this growth failure continues in next few years. Though the current

feeding policies concentrate only on feeding practices during hospital stay, there is a need to have adequate calorie, protein and other mineral intake after discharge also. Policy of aggressive nutrition for preterm VLBW and ELBW infants should continue beyond discharge to improve growth during early infancy and childhood.

Practical guidelines at discharge

- For babies on direct human milk: continue calcium/phosphorus, iron and multivitamin drops and follow up on the growth chart. If continue to follow the target percentile; continue. If starts falling the percentile, add HMF.
- For babies on human milk but not direct feeds: <1800 gm—discharged on HMF, MV drops/iron. Calcium/phosphorus supplementation not required.
- Alternative is preterm special formulae.

GROWTH CHARTING

These babies should be followed on intrauterine growth charts (e.g. Fenton's charts) till 40 weeks of gestation and then subsequently on WHO growth standard charts.

CONCLUSION

There is ample evidence that most of the VLBW and ELBW infants suffer significant postnatal malnutrition. They remain <10th percentile for weight at discharge. Hence, one should adopt the policy of aggressive enteral nutrition from very early in life. As parenteral nutrition is

a difficult proposition in our country, one should attempt oral feeding as soon as the baby is stable. For high-risk babies at least minimal enteral nutrition should continue till the baby is ready for full feeds. Breastfed babies should get additional supplements with protein, minerals and vitamins which should continue even after discharge.

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CHAPTER 6

Acid-base Balance

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INTRODUCTION

A normal acid-base homeostasis is essential for intact functioning of all enzymatic processes and hence all organ systems of body. Blood gases are the basis for diagnosis and management of infants with cardiorespiratory diseases, metabolic disorders and other systemic illnesses. By integrating information derived from blood gas and clinical history, healthcare provider can accurately assess an infant's current condition and can take the appropriate steps to correct the imbalance so as to improve outcomes.

PHYSIOLOGY OF ACID-BASE BALANCE

In health, the normal range of hydrogen ions in ECF is 35 to 45 nmol/L. In clinical practice this is reflected as pH, which is negative logarithm of hydrogen ion concentration.

$$\text{pH} = -\log [\text{H}^+]$$

The corresponding pH value for normal range of hydrogen ion concentration is 7.35 to 7.45. The pH will be lower than 7.35, if hydrogen ion concentration is increased and will be higher than 7.45 if hydrogen ion concentration is decreased. This is called acidemia and alkalemia, respectively.

Acid load comes primarily from cellular respiration as carbon dioxide via carbonic acid (15,000–20,000 mmol H^+ /day) and to a lesser extent from the metabolism of fats and proteins (50 mmol/day). The concentration of hydrogen ions in blood plasma is very tightly regulated. The main organ systems that maintain pH in the normal range are respiratory system and kidneys. Some of these systems respond immediately to sudden alterations in hydrogen ion concentrations, whereas others respond more slowly.

Defence of normal body pH is achieved through the three following basic mechanisms:

- Respiratory control of the partial pressure of carbon dioxide in arterial blood (pCO_2) by the respiratory center, which is a rapid and powerful compensatory system. This regulates pH by changing rate of alveolar ventilation. The higher the concentration of $[\text{H}^+]$, the more CO_2 (which is a volatile acid) is expired from the lungs, and eventually pH will be normalized.
- Renal bicarbonate control and excretion of metabolic acids (nonvolatile acids). The kidneys are slower to compensate, but renal physiology has several powerful mechanisms to control pH by the excretion of excess acid or base. In responses to acidosis, tubular cells reabsorb more bicarbonate from the tubular fluid, collecting duct cells secrete more hydrogen and generate more bicarbonate, and ammoniogenesis leads to increased formation of the NH_3 buffer. In responses to alkalosis, the kidney may excrete more bicarbonate by decreasing hydrogen ion secretion from the tubular epithelial cells, and lowering rates of glutamine metabolism and ammonia excretion.
- Buffering by intracellular and extracellular anions and proteins, which minimizes acute changes. Buffer is a substance that has ability to bind or release hydrogen ion and hence can minimize changes in pH when acid or base is added to the system. The extracellular buffers, which include the bicarbonate-carbonic acid system, phosphate, and plasma proteins, act rapidly to return the extracellular pH toward normal. The intracellular buffers, which include hemoglobin, organic phosphates and bone apatite, act more slowly.

The most important extracellular buffer is plasma bicarbonate-carbonic acid buffer system, in which the acid component (carbonic acid $[\text{H}_2\text{CO}_3]$) is regulated by the lungs and the base component (bicarbonate $[\text{HCO}_3^-]$) is regulated by the kidneys.

The traditional approach to acid-base control centers round the Henderson-Hasselbalch equation, which describes the carbonic acid buffer system, fundamental to respiratory and renal control of pH. The reaction of

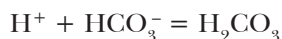
carbon dioxide with water forms carbonic acid, which dissociates to form bicarbonate and H^+ ions:

The buffer equation is



If hydrogen ion concentration increases for any reason, hydrogen combines with HCO_3^- , driving the buffer reaction toward greater production of H_2CO_3 and hence CO_2 . Increased CO_2 stimulates brain respiratory center, leading to increased alveolar ventilation and removal of CO_2 and normalization of pH. Similar compensation (in reverse direction) occurs in response to a decrease in hydrogen ion concentration with restoration of pH.

The Henderson-Hasselbalch equation can be modified as follows:



If by the law of mass action:

$$[H^+][HCO_3^-]/[H_2CO_3] = k \text{ (constant)}$$

Then by rearranging and taking logs of both sides:

$$pH = pK_a + \log ([HCO_3^-]/[0.03 \times pCO_2 \text{ mm Hg}])$$

where the pK_a value at $37^\circ C$ is 6.1.

From this equation, pH can be defined as the ratio of bicarbonate to carbon dioxide. Therefore, alterations in acid-base result from either changes in CO_2 (respiratory) or changes in HCO_3^- (metabolic) and compensatory mechanisms exist to maintain this ratio (normally 20:1).

Interpreting a Blood Gas Report

Usual blood gas report contains following parameters:

- pH
- PCO_2
- PO_2
- HCO_3^- (actual)
- HCO_3^- (standard)
- Base excess (actual)
- Base excess (standard)

Blood gas analyzers directly measure pH, PCO_2 and PO_2 . Bicarbonate is calculated from modified Henderson-Hasselbalch equation, while standardized HCO_3^- and base excess are derived from computerized nomograms.

The concepts of standard bicarbonate and standard base excess have been introduced to assist with quantifying the metabolic derangement. Standard bicarbonate is the calculated bicarbonate value that would be present if the blood sample was adjusted to a pCO_2 of 40 mm Hg and therefore removes the respiratory component of the acid-base abnormality to reveal any metabolic derangement. Standard base excess or deficit quantifies the amount of acid in mmol/liter that must be added or subtracted from the same blood sample to regain a normal pH at a pCO_2 of 40 mm Hg.

Normal Value of Blood Gas Parameters

pH = 7.35 to 7.45

pCO_2 = 40 mm

pO_2 = 50 to 80 mm

HCO_3^- = 24 mEq/L

Base excess = \pm 5 mEq/L

Acidosis = pH < 7.35

Alkalosis = pH > 7.45

Developmental Aspects of Acid-base Physiology

Maturation of renal functions continue during neonatal period and early infancy. The relative immaturity of the kidney, which is more pronounced in the preterm infant, affects acid-base status.¹

During initial 24 to 48 hour of life, acid-base balance is influenced by the degree of perinatal stress and environmental factors such as temperature and diet. These factors modify the blood gas parameters. Median umbilical artery values, with the 2.5th percentile value in parentheses, are pH 7.26 (7.10) and base excess -4 mmol/L (-12 mmol/L).²⁻⁴ Values for pH, PCO_2 , and base excess also vary with differences in sampling technique. Preanalytical error can be introduced if the cord is not clamped immediately, there is an excess quantity of heparin in relation to the amount of blood collected, air is present in the syringe, or the sample is kept at room temperature for longer than 15 minutes.⁵

Between 7 and 21 days of life, neonates are in a state of mild metabolic acidosis (pH 7.25-7.35, HCO_3^- 19-22 mEq/L). In some infants, blood pH drops below 7.25 or base deficit exceeds 8 mEq/L.⁶ Many factors cause metabolic acidosis in neonates. The threshold for bicarbonate reabsorption in proximal tubules is lower in neonates, especially preterm infants. In addition, low GFR, particularly in preterm neonates, decreases the availability of phosphates and other buffers. Tubular immaturity results in reduced tubular secretory surface for organic acid secretion. Renal control of acid-base homeostasis doesn't reach adult levels until approximately 2 years age.

CLASSIFICATION OF ACID-BASE DISORDERS

- *Metabolic acidosis*: Accumulation of abnormal acid in body or loss of buffer base.
- *Metabolic alkalosis*: Accumulation of abnormal base in body or loss of acid.
- *Respiratory acidosis*: Increase in pCO_2 in blood.
- *Respiratory alkalosis*: Decrease in pCO_2 in blood.

Steps in Interpreting Blood Gas

A blood gas report should be read and interpreted in following order:

- Look for primary disorder (acidosis/alkalosis) (Fig. 1)
- Look for possible explanation for the disorder (respiratory/metabolic)
- Look for compensation

Table 1: Compensatory responses to primary acid-base disorders

Primary disorder	Compensation	Rate of compensation
Metabolic acidosis	$\downarrow \text{PCO}_2$	For every 1 mEq fall in HCO_3^- , PCO_2 fall by 1-1.5
Metabolic alkalosis	$\uparrow \text{PCO}_2$	For every 1 mEq rise in HCO_3^- , PCO_2 rise by 0.5-1
Acute respiratory acidosis (<12-24 hour)	$\uparrow \text{HCO}_3^-$	For every 10 rise in PCO_2 , HCO_3^- rise by 1 mEq
Chronic respiratory acidosis (3-5 days)	$\uparrow \text{HCO}_3^-$	For every 10 rise in PCO_2 , HCO_3^- rise by 4 mEq
Acute respiratory alkalosis (<12 hours)	$\downarrow \text{HCO}_3^-$	For every 10 fall in PCO_2 , HCO_3^- fall by 1-3 mEq
Chronic respiratory alkalosis (1-2 days)	$\downarrow \text{HCO}_3^-$	For every 10 fall in PCO_2 , HCO_3^- fall by 2-5 mEq

Modified from Brewer ED: Disorder of acid-base balance. *Pediatr Clin North Am* 1990;37:430-47

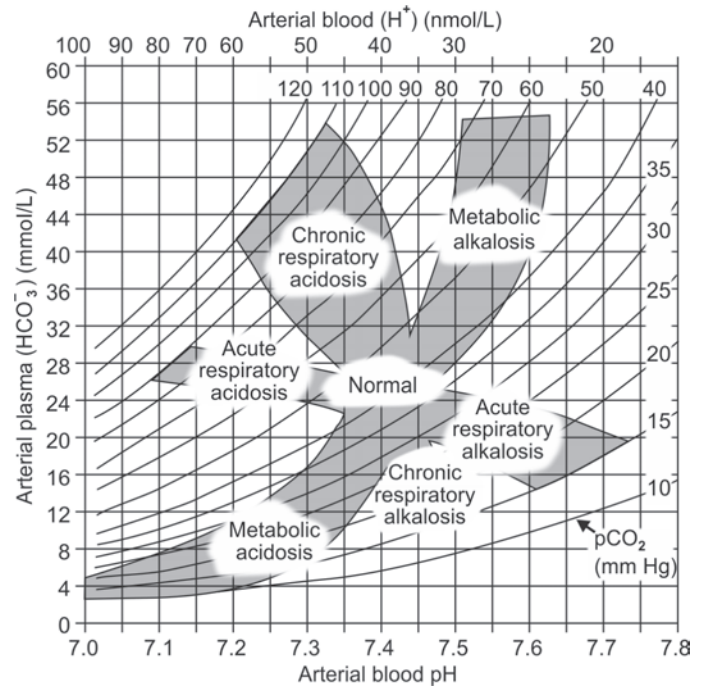


Fig. 1: Acid-base nomogram showing 95% confidence limits for compensatory responses to primary acid-base disorders. (From Cogan MG, Rector FC Jr' Acid-base disorders. In Brenner BM, Rector FC Jr [Eds]: *The Kidney*. Philadelphia, WB Saunders, 1986, p 462)

Step 1

Look for primary disorder. It can be acidosis (if $\text{pH} < 7.35$) or alkalosis (if $\text{pH} > 7.45$)

Step 2

Look for possible explanation for the disorder.

- If acidosis is there, then it could be either metabolic acidosis ($\text{HCO}_3^- < 24$) or respiratory acidosis ($\text{PCO}_2 > 40$) or both.
- If alkalosis is there, then it could be either metabolic alkalosis ($\text{HCO}_3^- > 24$) or respiratory alkalosis ($\text{PCO}_2 < 40$) or both.

Step 3

Look for compensation (Table 1):

- For primary metabolic acidosis, there will be compensatory respiratory alkalosis; for primary metabolic alkalosis, there will be compensatory respiratory acidosis.
- For primary respiratory acidosis, there will be compensatory metabolic alkalosis; and for primary respiratory alkalosis, there will be compensatory metabolic acidosis.
- Respiratory compensation of metabolic disturbances is fast and occurs within minutes to hours where as full

metabolic compensation of primary respiratory disorders takes days. Hence respiratory acidosis and alkalosis are subdivided into acute and chronic based on duration of illness and degree of compensation.

- Compensation is obligatory, not optional.
- Compensation is never complete. That means pH is near normal (close to 7.35) but never completely normalized or overshoot (7.4 or above) by compensatory mechanism itself.
- If expected compensation does not occur, then mixed disorder (respiratory + metabolic) should be suspected.
- Expected compensation can be derived from either by acid-base nomogram by Cogan (Fig. 1) or Table 1.

METABOLIC ACIDOSIS (FIG. 1)

Metabolic acidosis is a common problem, particularly in the critically ill neonate. Metabolic acidosis occurs when the drop in pH is caused by the accumulation of acid other than H_2CO_3 by ECF resulting in loss of available HCO_3^- or by direct loss of HCO_3^- from body fluids. Metabolic acidosis is categorized into normal anion gap or increased anion gap metabolic acidosis. Anion gap reflects the unmeasured anion in body. Anion gap is calculated by following equation:

Anion gap = $\text{Na} + \text{K} - \text{Cl} - \text{HCO}_3$ (Normal value 12 ± 4 mEq/L)

Causes of Metabolic Acidosis

Increased Anion Gap

- Secondary lactic acidosis (hypoxia, ischemia, shock, dehydration, hypothermia, sepsis, etc.)
- Primary lactic acidemia
- Organic acidemia
- Renal failure
- Late metabolic acidosis
- Adrenal insufficiency, CAH
- Toxins (benzyl alcohol)
- Diabetic ketoacidosis.

Normal Anion Gap

- Renal bicarb wasting due to immaturity
- Renal tubular acidosis
- Carbonic anhydrase inhibitors
- Gastrointestinal bicarb loss (diarrhea, ileostomy drainage, fistula)
- Dilutional (rapid ECF expansion with non- HCO_3 fluid in hypovolemic infant), excessive chloride in IV fluids, aldosterone deficiency.

Evaluation

The etiology of metabolic acidosis is often apparent from history and physical examination. Basic laboratory tests in an infant with metabolic acidosis include BUN, creatinine, serum electrolytes, blood sugar, and lactate and urine analysis. Blood gas report and serum electrolytes will differentiate normal and increased anion gap acidosis.

In acutely sick neonate who had incurred hypoxia or hypoperfusion, secondary lactic acidosis is most common differential diagnosis for increased anion gap acidosis. An elevated BUN, Creatinine are present in renal insufficiency, whereas elevated BUN/Cr ratio ($>20:1$) supports a diagnosis of prerenal azotemia and associated hypoperfusion induced lactic acidosis. Unexplained increased anion gap metabolic acidosis with or without hypoglycaemia should prompt a work-up for inborn errors of metabolism or endocrinopathy (adrenal insufficiency, CAH).

A metabolic acidosis with normal anion gap is usually due to intestinal content losses or renal abnormalities. If there is no history of GI losses, probable etiology of acidosis is renal. A urine pH >6.5 in presence of metabolic acidosis supports the diagnosis of RTA or prematurity associated bicarb wasting.

Further investigations can be done based on findings of initial work-up.

Management

Treatment of secondary lactic acidosis is usually supportive with correction of hypoxia/hypoperfusion, restoration

of hydration, and treatment of sepsis. Supportive therapy will rapidly correct the acidosis. Bicarb therapy is not advocated routinely. However, if pH is <7.2 , (particularly despite restoration of oxygenation/perfusion), bicarb administration can be considered along with other supportive measures.

Amount of bicarb is calculated by following formula:

Bicarb deficit (mEq) = $0.3 \times \text{Desired} - \text{standard bicarb}$

Give calculated bicarb as slow infusion (1:1 diluted) over 2-4 hours (no more than 1 mEq/kg/hr). Most clinicians would use half of the calculated dose for initial therapy to avoid overcorrection of metabolic acidosis. Subsequent doses of sodium bicarbonate are then based on the results of further blood gas measurements.

In case of unexpected/refractory increased anion gap metabolic acidosis, possibility of inborn errors should be considered and appropriate evaluation should be done. Do blood lactate, ammonia, urine ketone, blood sugars, urine reducing substance, plasma and urine organic acids, blood TMS, etc. to establish the cause. Restrict/modify dietary protein intake. Give bicarb correction if pH is <7.2 . As vitamins are cofactors in various enzymatic reactions, vitamin cocktail therapy is used empirically in suspected inborn errors of metabolism. In refractory conditions, peritoneal dialysis may be helpful.

Normal anion gap acidosis is usually due to renal immaturity or renal tubular acidosis. Treatment is bicarb supplementation as required to maintain pH in acceptable range (7.25–7.35). Requirement for bicarb supplementation may decrease gradually as renal functions improve, warranting periodic assessment.

METABOLIC ALKALOSIS

Metabolic alkalosis is characterized by alkalemia due to a primary increase in the extracellular HCO_3^- concentration. In newborn, metabolic alkalosis occurs when there is a loss of H^+ or due to gain of HCO_3^- or due to depletion of extracellular volume with the loss of more chloride than HCO_3^- .

Conventionally, etiology of metabolic alkalosis is divided into two categories: Chloride responsive (urinary chloride <15 mEq/L) or chloride resistant (urinary chloride >15 mEq/L).

Chloride responsive (urine Chloride <15 mEq/L):

- Gastric losses (nasogastric suction, persistent vomiting)
- Diuretic therapy
- Chloride losing diarrhea
- Cystic fibrosis
- Posthypercapnia

Chloride resistance (urine Chloride >15 mEq/L)

High Blood Pressure

- Hyperaldosteronism
- Congenital adrenal hyperplasia (17 α -hydroxylase def., 11 β -hydroxylase def, 11 β -HSD)

Normal Blood Pressure

- Bicarb administration, blood products
- Hypokalemia
- Bartter syndrome
- Gitelman syndrome

In loss of gastric content conditions, HCl loss is mechanism of generation of metabolic alkalosis, which is further maintained through volume depletion. Volume depletion interferes with urinary loss of bicarbonate through following mechanisms. First there is reduction of GFR so less bicarbonate is filtered. Second, volume depletion increases reabsorption of sodium and bicarbonate from proximal tubules mediated by angiotensin II. Third, increased aldosterone, in response to volume depletion, increases bicarbonate reabsorption and H^+ secretion in collecting ducts.

Chronic diuretic therapy, which may be a part of management of chronic lung disease, posthemorrhagic hydrocephalus or congestive cardiac failure, induces volume depletion and hence metabolic alkalosis through the same mechanisms.

Posthypercapnic metabolic alkalosis occurs after sudden correction of chronic respiratory acidosis. This is typically seen after placing infant with chronic respiratory acidosis on ventilator. During chronic respiratory acidosis, appropriate renal compensation is elevation of bicarbonate, which maintains pH close to 7.35. On sudden resolution of respiratory acidosis through ventilation of these infants, elevated bicarbonate leaves behind the metabolic alkalosis, which is spontaneously corrected gradually, unless patient in volume depleted in addition.

Chlorideresistant metabolic alkalosis is more often an iatrogenic condition, when there is chronic excessive administration of soda-bicarbonate, lactate, citrate or acetate in intravenous fluids or blood products. Metabolic alkalosis in these situations resolves readily, once HCO_3^- administration is discontinued, unless urine output is very low. Other causes of high urinary chloride metabolic alkalosis can be further differentiated based on normal or high blood pressure and confirmation can be done by appropriate laboratory tests.

Evaluation

A possible diagnosis can be ascertained by thorough history and clinical examination, supported by common laboratory tests, such as serum electrolytes and urine chloride. Assess for possibility of ECF contraction, diuretic therapy or bicarb administration as cause of metabolic alkalosis.

Management

Approach to therapy of metabolic alkalosis depends on the severity of alkalosis and underlying etiology.

In mild metabolic alkalosis induced by diuretic therapy, no intervention may be required, though in severe

alkalosis, dose may be reduced or drug discontinued. Adequate potassium supplementation or addition of potassium sparing diuretic is also helpful in diuretic induced metabolic alkalosis.

In settings of nasogastric suction, suctioning may be reduced or stopped. Alternatively, addition of proton pump inhibitor may be considered, where suctioning cannot be discontinued and alkalosis is severe.

Many infants with metabolic alkalosis have volume depletion as etiology for the disorder. In this situation, administration of sufficient sodium chloride and potassium to correct the volume deficit and potassium deficit is necessary for resolution of metabolic alkalosis. This option may not be appropriate in conditions where volume repletion is contraindicated (chronic lung disease, congestive cardiac failure, etc.).

In metabolic alkalosis due to hyperaldosteronism state, treatment focuses on eliminating the excess aldosterone effect. Glucocorticoid-remediable aldosteronism, 17α -hydroxylase deficiency and 11β -hydroxylase deficiency respond to administration of glucocorticoids. The mineralocorticoid effect of cortisol in 11β -HSD deficiency can be decreased by using spironolactone.

In children with Bartter syndrome and Gitelman syndrome, therapy includes oral potassium supplementation and potassium sparing diuretics.

In post hypercapnic metabolic alkalosis, management involves reducing ventilatory settings so as to keep pH in acceptable range. Metabolic alkalosis will resolve spontaneously over 3-4 days.

RESPIRATORY ACIDOSIS

Respiratory acidosis is fall in pH due to an inappropriate increase in blood CO_2 .

Causes

- CNS depression
 - HIE, IVH, PVL
 - Sepsis/meningitis/encephalitis
 - Structural brain malformations, brain stem dysfunction
 - Central apnea, Ondine curse
 - *Drugs*: Phenobarb, morphine, midazolam, etc.
- Disorders of spinal cord, peripheral nerve, neuromuscular junction, muscle
 - Diaphragmatic paralysis
 - Spinal cord injury
 - Spinal muscular atrophies
 - Myasthenia
 - Botulism
 - Muscular dystrophies
 - Drugs/hypokalemia
- Upper airways diseases
 - Obstructive apneas

- Micrognathia
- Vocal cord paralysis
- Extrinsic compression
- Pulmonary disease
 - Pneumonia, sepsis
 - Pneumothorax, effusions, pulmonary edema
 - MAS, pulmonary hemorrhage, HMD, BPD
 - Pulmonary hypoplasia

Diagnosis

Diagnosis of respiratory acidosis is straight forward by looking at gas parameters. Establishing cause of respiratory acidosis requires thorough history and physical examination, chest X-ray and other investigation.

Treatment

Treatment is directed to the underlying cause and providing adequate ventilatory support, if required. Care should be exercised in ventilator management of respiratory acidosis, as overenthusiastic ventilation will lead to lung injury. A blood PCO_2 up to 60 mm may be acceptable as long as pH remains above 7.2 to 7.25 (permissive hypercapnia) and work of breathing is not very high. Gradually metabolic compensation will take place, with restoration of pH.

Particular attention should be paid in management of chronic respiratory acidosis. In chronic respiratory acidosis, there might have been appropriate metabolic compensation. Overenthusiastic ventilation of such patient will lead to rapid lowering of pCO_2 with residual metabolic alkalosis. This condition should be anticipated and ventilatory support should be appropriate so as to avoid post hypercapnic metabolic alkalosis.

RESPIRATORY ALKALOSIS

When a primary decrease in an increase in arterial pH beyond 7.45, respiratory alkalosis develops.

Causes

- Central nervous system disorders (asphyxia, hyperammonia, etc.)
- Pain, fever, sepsis
- Retained lung fluid, mild aspiration pneumonia
- Iatrogenic: Excessive ventilatory support
- Erroneous: contamination with air bubble in blood sample

Diagnosis

Diagnosis of cause is ascertained by history and physical examination. A common scenario is contamination of blood gas sample with air bubble. In this situation, pCO_2 is unexpectedly low and pO_2 is unexpectedly high (usually >100). In normal circumstances, $\text{pO}_2 >80$ is unusual in a neonate breathing at room air. Even in ventilated neonate, pO_2 above 100 is unusual, if SPO_2 is in target range (88–92%). Hence, we find pCO_2 too low and pO_2 too high (which is not explainable by clinical settings), consider possibility of contamination by air bubble and repeat the blood gas.

Management

Management is conservative. Treat underlying disorder (pain, fever). Decrease ventilatory settings if ventilated. Mild sedation can be attempted in case of severe central hyperventilation

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CHAPTER 7

Hemodynamic Assessment in the Newborn

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INTRODUCTION

Cardiorespiratory assessment and management of the newborn is essential for the provision of neonatal intensive care. Over the last decade, with the advances in the microprocessor technology there are now a variety of modalities available for respiratory support of the newborn. Additionally, clinicians have realised the usefulness of hemodynamic assessment in the management of sick and very premature newborn infants. As oxygenation and carbon dioxide removal depends on adequate ventilation and perfusion, changes in ventilation can affect perfusion and vice versa. Lung and organ perfusion depends on intact cardiac function and hemodynamics, hence understanding of the later is crucial for appropriate management of sick newborns. Traditionally hemodynamic assessment utilized clinical signs with limited objectivity but the technological advances have provided new tools to compliment clinical assessment and quantify the measurements.

This chapter focuses on hemodynamic assessment techniques utilized on the Neonatal Intensive Care Unit with a special emphasis on the use of point of care echocardiography.

CHARACTERISTICS OF HEMODYNAMICS IN THE NEWBORN

The neonatal cardiovascular system differs from those of fetal, pediatric and adult patients. At term a neonate must successfully transition through abrupt changes in the cardiorespiratory system including changes in the lung volume and compliance and changes in the left and right heart preload and afterload. Intracardiac and extracardiac shunts via the foramen ovale and ductus arteriosus have varying effects on immediate postnatal hemodynamics. The neonatal heart may also have

to cope with structural heart disease and extracardiac congenital and acquired conditions such as congenital diaphragmatic hernia, sepsis, or pulmonary hypotension. A premature birth has to cope with the immaturity of the cardiovascular system and other organ systems, which makes it even more difficult for the neonate to appropriately respond to the challenges of postnatal transition and extrauterine existence.

TRANSITION FROM FETUS TO NEONATE

An understanding of perinatal cardiovascular physiology is essential if subsequent interventions are to be logical rather than merely treating figures. One also needs to understand the characteristics of the fetus and the premature infant which is different from a child or an adult. In the fetus myocytes are smaller and typically have a single nucleus compared with the multinucleated myocytes that are prevalent in later life. Although the fetus has a higher indexed myocardial mass, the fetal myocardium is less organized at the cellular level with fewer sarcomeres per unit mass, different isoforms of contractile proteins, a developing sarcoplasmic reticulum, an overall higher water content and a decreased number of mitochondria. In addition, the heart is enclosed within a poorly compliant thorax. As a result of these factors, the fetal heart is less compliant and less contractile than a term newborn or adult heart. These differences are manifested in the developmentally regulated limited fetal cardiac response to changes in preload or afterload, with changes in the heart rate to alter fetal cardiac output although some response to preload occurs if afterload remains constant. The fetal right and left ventricles also differ in myofibril architecture throughout gestation, with the right ventricle less tolerant to increases in afterload despite its contributing slightly more to the combined ventricular output than

the left ventricle during fetal life. The fetal pulmonary vasculature also exhibits significant differences from the adult pulmonary circulation. In the fetus, the pulmonary arteries are larger, preacinar vessels demonstrate significant elastin in their medial layer with a relative paucity of pulmonary smooth muscle in contrast to the more distal preacinar and acinar vessels which have a predominance of pulmonary smooth muscle in the media and the most distal inter acinar vessels with no smooth muscle medial layer. These differences all result in the fetal pulmonary vasculature limiting fetal pulmonary blood flow to 11 to 22 percent of the combined cardiac output from early-to-late gestation, respectively.

After birth, there is a decrease in pulmonary vascular resistance secondary to ventilation and lung expansion, increasing the arterial pO_2 . The exact mechanism of oxygen induced pulmonary vasodilation during the transition remains unclear. The increase in pulmonary arterial oxygen tension occurs with decreased pulmonary vascular resistance, either directly by dilating the small pulmonary arteries or indirectly by stimulating the production of vasodilator substances, such as phosphoglucose isomerase (PGI), bradykinin, or more importantly nitric oxide.

After birth, the preload to the right heart increases because of cessation of umbilical venous return and also a decrease in pulmonary vascular resistance increases the blood flow to the left side of the heart which allows the flap of the foramen ovale to close functionally soon after birth in term babies, but it can take longer to close in very premature babies. Additionally, the ductus venosus is functionally closed immediately with cessation of the umbilical venous flow. The functional closure of ductus arteriosus however happens slowly over the first several hours or days in term babies under the effect of circulating prostaglandin E_2 and other vasoactive factors and its fully developed muscular medial layer closes it structurally in a few days time. In premature babies, however, it lacks the muscle in the medial layer and allows the ductus to be patent causing the changes in the circulation affecting cardiorespiratory adaptation. Myocardial contractility is also affected by increased levels of thyroid hormone, corticosteroids and catecholamine surge that occurs with labor and delivery.

HEMODYNAMIC ASSESSMENT ON THE NEONATAL UNIT

Traditionally hemodynamic assessment of the sick and premature newborns on the neonatal intensive care unit utilize the clinical assessment tools, such as blood pressure monitoring, capillary filling time, core temperature peripheral difference and the investigations such as blood lactate and base deficit to assess perfusion. These are however limited by low sensitivity and specificity and have poor correlation with cardiac output. Newer modalities such as echocardiography, near infrared spectroscopy

and other noninvasive methods of assessing hemodynamics allow quantification of flows and oxygen extraction. When such advanced modalities are used alongside clinical assessment, they could allow better understanding of the cardiopulmonary interaction and could aid clinician in targeting therapy to the underlying problem.

Clinical Assessment

Assessing clinical signs is part of any medical or nursing training. Heart rate, skin temperature and blood pressure are standard nursing observations. However in the critical ventilated neonate it is desirable to identify cardiovascular dysfunction before it becomes irreversible. Capillary refill time is a poor predictor of cardiovascular function in adults, children and neonates and cannot be recommended as a dependable sign. An increase in heart rate was once thought to be the major mechanism for increasing cardiac output but this is now known to be incorrect in human neonates. Increasing heart rate will still often increase cardiac output but tachycardia has a low specificity for predicting cardiovascular compromise. Similarly evidence of reduced urine output and a baby's decrease in spontaneous activity may be important elements of overall evaluation but are not individually predictive. Moreover base deficit on blood gas are nonspecific indicators of problems in which cardiovascular dysfunction may be primarily or secondarily involved. Lactate can predict poor outcome but as yet is not useful in directing any intervention although future research incorporating other parameters with serial lactate measurements may be more helpful.

Blood Pressure

Blood pressure is regularly monitored in preterm and term babies receiving intensive or high dependency care. Initial normative ranges were reported for small selected groups of babies in the first 12 hours of life with no long-term outcome data. There have been variations in the way blood pressure values are monitored and interpreted. The common ways of monitoring blood pressure include intra-arterial blood pressure using umbilical arterial catheter or peripheral arterial line, oscillometric methods utilizing the Dynamap and the Doppler measurements of blood pressure. It has been shown that the correlation between the Dynamap blood pressures and intra-arterial blood pressure is poor, however the Doppler measurements of systolic blood pressure are comparable to intra-arterial monitored blood pressures.

There have been various practices utilizing different blood pressure references for taking clinical action such as use of gestation equivalent mean blood pressures, mean blood pressures below 30 mm of mercury in premature babies and systolic blood pressure values. Initial normative ranges for mean blood pressure were reported for a

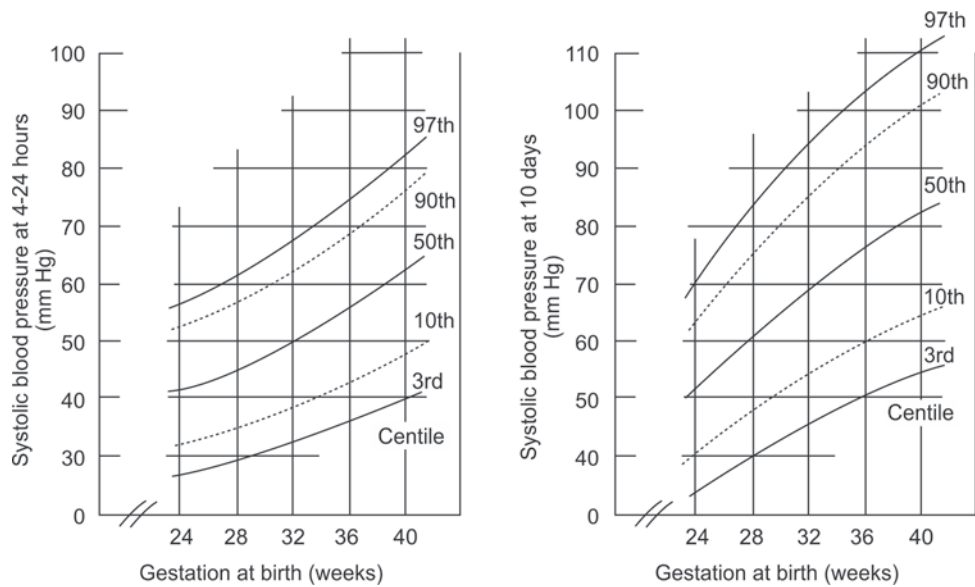


Fig. 1: Systolic blood pressure nomogram (Tin W. Northern Neonatal Nursing Initiative. 1999)

small selected group of babies in the first 12 hours of life with no long-term outcome data. The Northern Neonatal Nursing Initiative in the North of England published population-based normative data for systolic blood pressure for the first 12 days of life.¹ This data was obtained from 398 babies of less than 32 weeks gestation at birth who were free from severe disability at two years of age and is the best normative population data available with known outcomes (Fig. 1).

Subsequent work has demonstrated that blood pressure values can be affected by the presence of the fetal shunt such as patent ductus arteriosus. In the presence of PDA the mean blood pressure values have been found to have no correlation with the cardiac output. However, systolic blood pressures were reported to have moderate correlation with the left ventricular cardiac output.² The timing of the measurement of blood pressure is also important and the values in the first four to six hours of life while the physiological adaptation is taking place results in wide variations and such values are difficult to interpret.

ECHOCARDIOGRAPHY FOR HEMODYNAMIC ASSESSMENT

Functional echocardiography or point of care echocardiography has rapidly evolved in the last decade. Clinicians now recognize its value in the assessment of the sick or premature infants requiring intensive care for assessment and guiding management.³ The reasons for this are essentially pragmatic. Ultrasound evolved as a clinical tool during the 1970s and early 1980s. The provision of real time

information on cardiovascular performance and systemic hemodynamics, noninvasive nature of the technique, rapidity of data acquisition and report generation emulated to perform longitudinal functional assessments have all contributed to the increased use of functional echocardiography by the neonatologists in the neonatal intensive care unit.⁴

Imaging the Newborn

Echocardiographic evaluation of the newborn is complicated by the issues related to patient size and the acoustic window. Ideally care should be taken to maintain the temperature, prevent infection and to minimize duration of contact with the patient. As far as possible the serial scan should be performed by the same examiner as this would reduced the interobserver variability. There are however now efforts to standardize the echocardiographic assessment for hemodynamics and recommendations suggested for a common approach (Fig. 2).

To interpret and assess the cardiac function high quality imaging is essential particularly when Doppler interrogation of vessels is being performed to evaluate blood flow. In preterm babies image quality may be compromised in the presence of hyperinflated lungs. Imaging neonates with bronchopulmonary dysplasia often poses a particular challenge as the hyperinflated lungs shields the areas of interest and may obstruct the views of heart.

Two-dimensional Echocardiography Methods

Two-dimensional imaging is the most common modality to study the structure and anatomy of the heart. Using



Fig. 2: Functional echo basic views

the sector view the frame rate of the probe is the number of sweeps per second. In order to generate seamless images of the moving myocardium the frame rate needs to be faster than the heart rate of the infant. The two important parameters to consider while acquiring images using the frequency of ultrasound waves is image quality and resolution. Higher frequencies provide enhanced image resolution but a lower power admissible for infants limits the depth of the image. Conversely, lower frequencies can reach deeper into the tissue but with poor image resolution. Ideally 7.5 to 10 megahertz of probe frequency rates provide excellent resolution with adequate tissue penetration.

M-mode Echocardiography

The M-mode scanning interrogates moving tissue along a single line with respect to time. In M-mode, the time base is displayed in a sideways fashion but perpendicular to the line of interrogation. The clinical applications of M-mode echocardiography include the estimation of the chamber size, valve thickness, valvular motion and quantification of the myocardial contractility. This requires clear signals, precise measurements and appropriate cuts. Again the standardized measurement techniques have been described which should be utilized while reporting the results.

Doppler Imaging

The Doppler effect of physical principles is a term given to the change in frequency of a wave experienced by an object when there is relative movement between the object and the wave transmitter. In echocardiography, the probe

is the stationary object and the red cells are the moving objects. The difference in frequencies is expressed as an audible pitch and velocity on the screen. The clinical applications of Doppler include continuous wave Doppler, pulse wave Doppler and color flow Doppler methods.

Continuous Wave Doppler

Using continuous wave Doppler, the transducer generates continuous waves with simultaneous wave reception. The main advantage of this modality is the ability to accurately measure blood flow at high velocity. This is particularly important when assessing infants with a restrictive ductus arteriosus, pulmonary hypertension, tricuspid regurgitation and valvular abnormalities and septal valve defects. These lesions usually have valve velocities of more than 2 meters per second and require continuous wave Doppler for ideal examination and assessing the flow pattern and calculation of the velocity. The velocities are also utilized in calculating the pressure gradient. The calculation of peak velocity of the regurgitant jets using continuous wave Doppler such as in tricuspid regurgitation can give the right ventricular pressure estimation. This is calculated using the Bernoulli's equation:

$$\text{Pressure (mm of Hg)} = 4 \times (\text{velocity})^2$$

Continuous wave Doppler is however limited by the lack of selectivity and depth recognition and it would calculate and take into account the velocities of all the flows in its line.

Pulse Wave Doppler

The main advantage of pulse Wave Doppler is its ability to provide a Doppler-shaped data specifically from a small segment along the ultrasound beam, referred as a sample volume or pulse gate. The angle of insonation for a pulse gate is important so that the angle of Doppler beam to the blood flow is less than 15 percent otherwise it would add to the error in calculated value. Pulse gate Doppler has a limitation that it is unable to accurately measure velocities more than 1.5 to 2 meters per second due to a phenomena called aliasing. Aliasing on the screen shows as an abnormal velocity exceeding the rate at which the Pulse gate system can record it properly and gives the illusion that the examined flow is traveling backwards.

Color Flow Doppler

Color flow Doppler is used routinely and commonly utilized to assess the direction of flow of blood. Traditionally, the blood flow occurring towards the probe is taken as red and away from the flow is taken as blue. It is very useful in identifying the areas of flow acceleration or flow regurgitation across valves, septal defects of transseptal shunts.

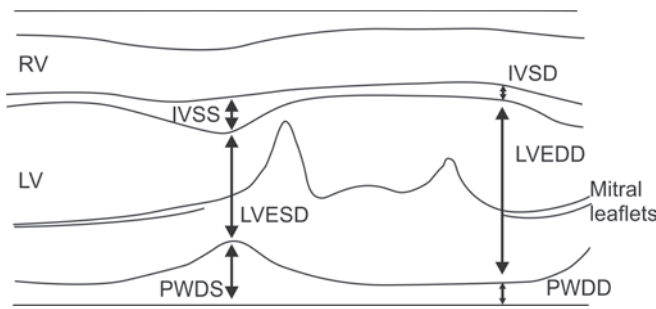


Fig. 3: Calculation of fractional shortening

Echocardiography for Hemodynamic Assessment in Clinical Practice

Ventricular Function

It is important to remember that ventricular function (or myocardial fiber shortening) and ventricular output are not the same although they are clearly related. Ventricular function and cardiac output need to be measured and considered separately while also assessing preload and after load to gain a more complete hemodynamic picture.

Fractional Shortening

Fractional Shortening (FS) is the most reproducible and commonly used assessment of left ventricular contractility. It is assessed in the long axis parasternal view using a M-mode echocardiography (Fig. 3). It is calculated using Left ventricular end diastolic diameter (LVEDD) and Left ventricular end systolic diameter (LVESD) as:

$$FS (\%) = \frac{LVEDD - LVESD}{LVEDD} \times 100$$

The normal range of fractional shortening for pre-term neonates is 25 to 40 percent. However, this measurement is affected by both preload and afterload. The errors may also occur because of the distortion of the left ventricle in the pre-term infant and the paradoxical septal valve motion associated with right ventricular dominance. The other parameter used is the mean velocity of fiber shortening (velocity of circumferential fiber) which is an alternative measurement of contractility and is less sensitive to minor damage and discrepancies and involves no assumption about ventricular shape. However, it is also influenced by volume loading of the left ventricle which tends to increase both measurements.

Tissue Doppler Imaging

Tissue Doppler imaging (TDI) is a relatively new ultrasound technology that derives measurements of contraction and relaxation velocities directly from the myocardium. As it is a direct measurement it is affected less by preload and afterload and normal values have been documented. However, as yet it can only be seen in an area for further

promising research as there is wide intraobserver and interobserver variability.

Measurement of Cardiac Output

Doppler assessment of left and right ventricular output provides the hemodynamic information regarding the adequacy of blood flow. Assessment of LVO involves measuring the mean velocity of blood flow across the ascending aorta from an apical five chamber view using pulse gate Doppler and determining the diameter of the aortic root from the parasternal long axis view. The maximum ascending and descending aortic velocity in pre-term infant is usually less than 2 meters per second in the absence of valvular disease and hence pulse gate Doppler is better suited for this analysis.

The left ventricular output (LVO) is calculated using the formula:

$$LVO (\text{ml/min}) = \text{Stroke volume} \times \text{heart rate}$$

$$\text{Stroke volume (ml/cycle)} = \text{VTI} \times \text{Cross-sectional area of vessel} (\pi r^2)$$

The VTI (velocity time integral) is calculated from the Doppler trace at the aortic outlet in apical 5 chamber view. It is the area under one cardiac cycle and denotes the measure of a distance traveled by blood during a given beat. The stroke volume depicts the volume of blood ejected in one cardiac cycle. If we multiply the stroke volume by the heart rate it gives the total left ventricular output. When the left ventricular output is divided by the weight of the child it gives the cardiac index which allows it to compare across the patients and is used as a reference data. The normal values for the left ventricular output range from 170 to 320 ml per kg per minute.

One needs to be careful while interrogating the values of the left ventricular output particularly in the presence of the left to right shunt such as patent ductus arteriosus commonly seen in preterm infants. In the presence of a PDA, the left ventricular output overestimates the LV cardiac output and in these situations it has been suggested that right ventricular outflow measurement (Right ventricular output, RVO) would have better correlation with the systemic flow as it is less compounded by the presence of a PDA.⁵ However, RVO measurements can also be affected by the presence of shunts such as patent foramen ovale.

The measurement of right ventricular output can also be done utilizing the same approach as described above. The pulmonary artery diameter is assessed from the oblique parasternal long axis view and the right ventricular velocity time integral is obtained from the Doppler interrogation in the same view in line with the flow in the pulmonary artery. The pulmonary artery diameter calculated in this view of parasternal short axis view is used to compute the cross-sectional area of the vessel.

Superior Vena Cava Flow

As already mentioned the right ventricular output is less affected by the presence of a PDA however the turbulence in the pulmonary artery from the ductal flow can disturb the flow pattern making accurate determination of the RVO difficult. In these situations, superior vena cava flow has been proposed to be a better echocardiographic measure of systemic blood flow as it reflects exclusive venous return from brain and upper body and is unaffected by the shunt. For measurement of the superior vena cava flow a subcostal approach is utilized to gain the SVC Doppler signals and using the pulse gate Doppler interrogate the flow pattern utilizing the technique described above. The SVC diameter is calculated using the modified high suprasternal view and the diameter of the SVC is calculated at a point where it starts funneling. Recently with the availability of the MRI data SVC flow measurements have been challenged due to the crescent shape of SVC in cross-section pressed by pulsating aorta.⁶ It is said to have wide variations in the calculated values and dependent on point of measurement of vessel diameter and calculating VTI in SVC in a baby spontaneously breathing at high rates. The SVC flows of less than 40 ml per kg per minute in the first 24 hours of life have been shown to be associated with the late interventricular hemorrhage which tended to occur as perfusion improved⁷. For objective intervention of hypotension, SVC flows are utilized in proposed trials to selectively identify the babies to target treatment using the normative values.

Diastolic Performance of Myocardium

The diastolic performance is altered in the newborn but its relevance to clinical decision-making is not well appreciated. The diastolic filling is influenced by the compliance of the ventricular wall. As the transmitral flow occurs in two phases, i.e. an early phase of passive flow during which the majority of the filling occurs, and a late period of the late atrial contraction phase during which the remaining third of the venous return to the ventricle is delivered. In patients with diastolic dysfunction the majority of filling occurs during the atrial phase as the stiff ventricular wall prevents passive early flow across the mitral valve. The immature fetal and preterm myocardium is characterized by the impaired diastolic function. Utilizing the pulse wave Doppler and the tissue Doppler imaging, the first phase of early wave (E wave) reflects the passive blood flow across the atrial ventricular valve in early diastole. The second phase is the atrial contraction wave (A wave) and is the result of atrial contraction at the end of diastole. The maximum E and A wave velocities are compared as ratios. The E/A ratio of less than one indicates diastolic dysfunction (indicating a noncompliant ventricle).

The TEI Index (or myocardial performance index) has been found to be a valuable quantitative echocardiography

index of ventricular function by incorporating both systolic and diastolic performance of the right and left ventricles.⁸ It is defined as the sum of iso-volumetric contraction and relaxation times divided by the ejection time, which requires measurement of the time interval between the end and onset of the mitral or tricuspid inflow (the A interval) and the ejection time of the left ventricular or right ventricular outflow (the B interval).

$$\text{TEI Index} = A - B/B.$$

The TEI index is easy to calculate, reproducible and independent of heart rate and blood pressure. Normal values in the healthy neonates range from 0.25 to 0.38. It is also relatively independent of age and has a low degree of inter- and intraobserver variability.

Pulmonary Pressure Measurements

Pulmonary pressure measurements are usually required to assess pulmonary hypertension at birth, persistent ventilatory support with suspected cor pulmonale or after cardiac surgery. This particularly poses a significant problem in the immediate postnatal period as differentiation from an underlying structural heart disease is important.

Once structural heart disease is ruled out there are various functional echocardiography techniques to ascertain right sided pressures. Serial echo can also be utilized to assess response to nitric oxide therapy or for progression of PPHN. The evaluation of pulmonary hypertension may be divided into 1. Evaluation of severity of pulmonary hypertension, 2. Evaluation of the impact on RV performance and pulmonary hemodynamics, and 3. Evaluation of the impact on LV performance and systemic blood flow.

Evaluation of Severity of Pulmonary Hypertension

The RV systolic pressures (RVSP) are calculated using indirect method and utilizing Bernoulli's equation.

$$\text{RVSP} = 4 V^2 + \text{Right atrial pressure}$$

The maximum velocity of tricuspid regurgitation jet is calculated in apical 4 chamber view using CW Doppler. This method has a limitation of inability to calculate the RV systolic pressures in the presence of RV dysfunction.

Patent ductus arteriosus with unrestricted flow can also be utilized to estimate the pulmonary pressures. The peak velocity of right to left transductal flow can be utilized using Bernoulli's equation to calculate pressure difference between systemic and pulmonary circulations. Additionally direction of ductal shunt can be used to evaluate the severity of pulmonary hypertension.

In absence of these shunts such as chronic lung disease direct assessment of pulmonary pressures is difficult to calculate. By utilizing PW Doppler in the main pulmonary artery, right ventricular pre-ejection period (RPEP), time to peak velocity (TPV) and right ventricular ejection time (RVET) can be calculated. The normative data of the

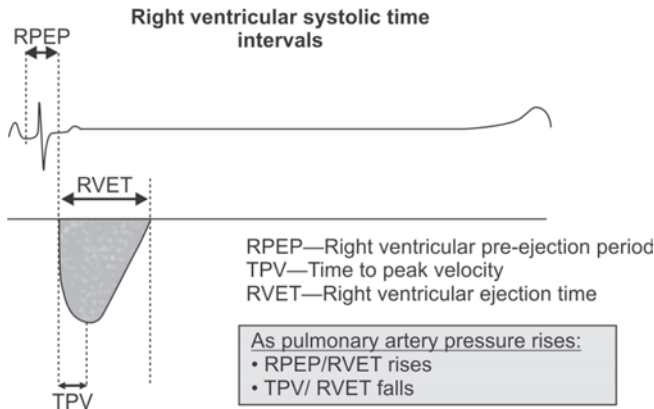


Fig. 4: Right ventricular systolic time intervals

indices RPEP/RVET and TPV/RVET are available. If pulmonary pressures rise, RPEP/RVET rises and TPV/RVET falls (Fig. 4).

Evaluation of right ventricular performance and pulmonary hemodynamics

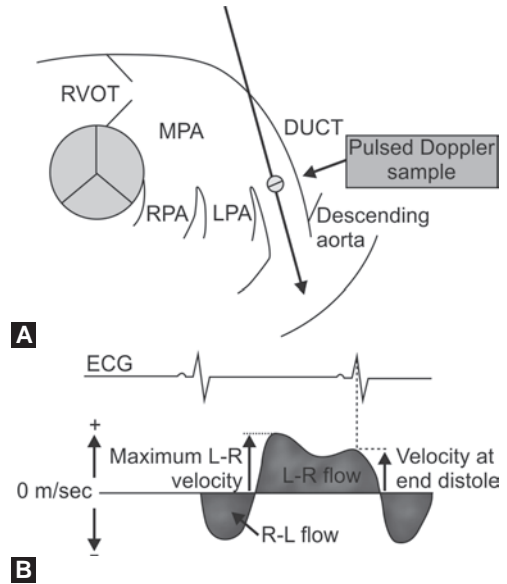
Moderate-to-severe RV systolic dysfunction is obvious by visual inspection. Low RV output (<150 ml/kg/min) may also support a diagnosis of impaired RV performance. Fractional shortening of RV is difficult to measure and interpret as RV is wrapped around LV. In PPHN, RV appears larger and stiffer than the LV, with a dilated out-flow tract and contractility may appear subjectively diminished. The interventricular septum may become flattened due to the rising RV pressure and septal wall motion may be reversed in severe cases.

Assessment of a Patent Ductus Arteriosus (PDA)

Functional assessment of a PDA incorporates; Is the duct patent (Figs 5A and B)? What is its diameter? What is the direction of shunting? Is PDA likely to be hemodynamically important? To evaluate this functional echo is targeted at studying ductal characteristics, evaluate pulmonary hyperperfusion and evaluation of systemic hypoperfusion.

Ductal Characteristics

This includes size of the PDA and ductal flow pattern (Fig. 6). The size of the PDA is calculated at the narrowest point near the pulmonary end with appropriate gain settings. A PDA dimension of >1.5 mm is traditionally taken as significant.⁹ This however varies when treatment is considered for closure in first 72 hours or later when it is symptomatic. The ductal flow pattern is classified into pure right to left as in PPHN, growing pattern with bidirectional flow, pulsatile pattern with high systolic and low diastolic peak velocity and closing pattern with minimal variation in peak velocity between systole and diastole.



Figs 5A and B: Ductal view with PW Doppler

Evaluation of Pulmonary Hyperperfusion

This is assessed using left heart size and LV function. The left heart size is calculated using left atrial to aortic root ratio (LA:AO ratio).¹⁰ A value of 1.5 mm or more is considered to be significant. However in presence of a patent foramen ovale left atrium may be decompressed allowing LA:AO ratio to stay normal even in presence of a large PDA. Left ventricular end diastolic diameter to aortic root ratio of >2.1 is also considered symptomatic. The LV output in presence of a PDA of more than 300 ml/kg/min reflects hyperdynamic circulation. Similarly left pulmonary artery peak velocity of >4.2 m/s is also considered significant.

Evaluation of Systemic Hypoperfusion

This is evaluated using preductal aortic flow pattern, mesenteric or descending aorta diastolic steal and SVC flow. Absent or reversal of diastolic flow in celiac, mesenteric artery or descending aorta reflects ductal steal.¹¹ A low SVC flow (<40 ml/kg/min) in first 24-48 hours and IVO/SVC flow ratio of >4 is also sign of systemic hypoperfusion.

There are various combinations of echo criteria suggested to predict the severity of PDA while defining its significance and grading into small, moderate or large size PDA.¹²

Training and Accreditation

There is a growing acceptance that neonatologist-performed functional echocardiography is a useful tool in the NICU, with increasing evidence of improved patient

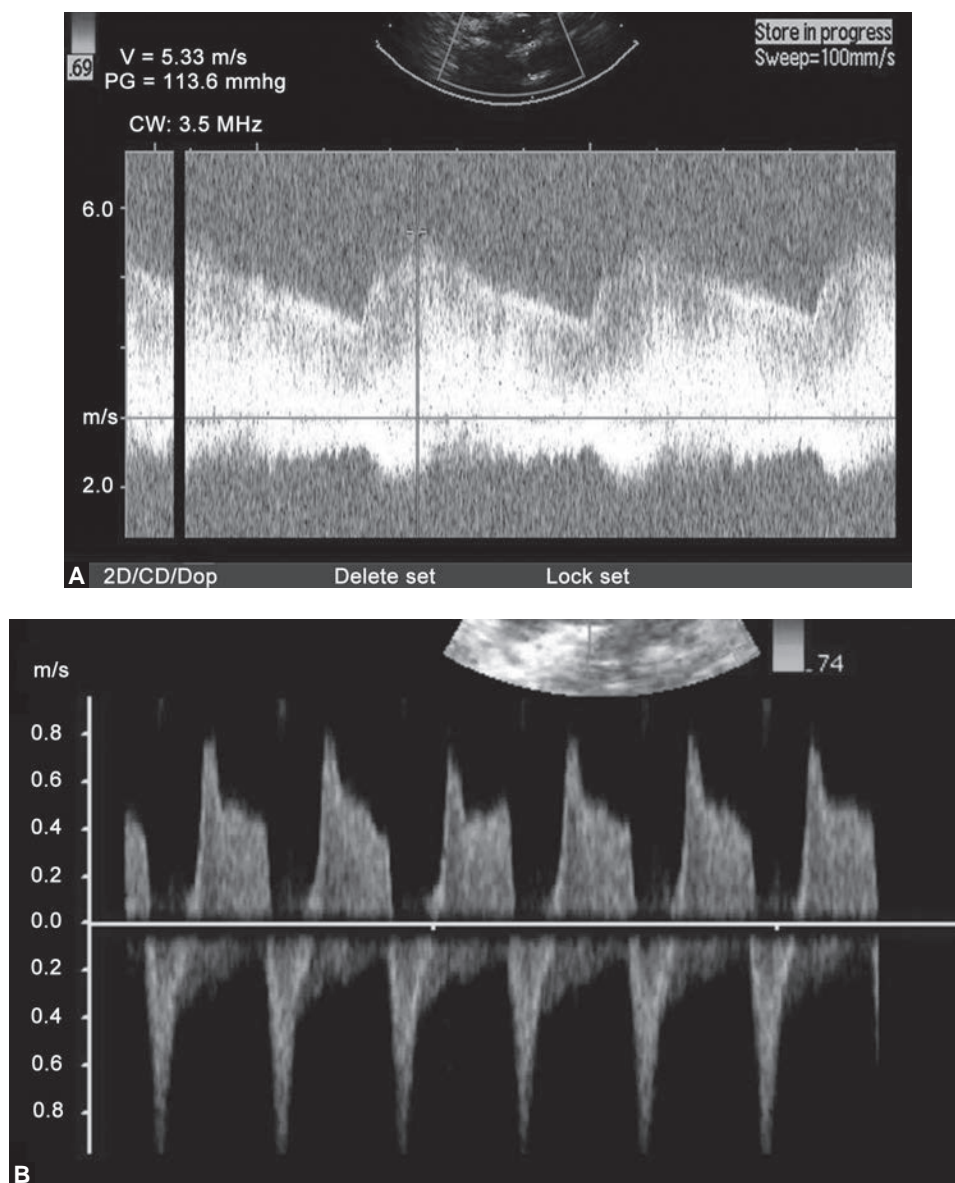


Fig. 6: Patent ductus arteriosus flow patterns

outcomes.¹³ What is lacking at present is a formalized training and accreditation program necessary for the development of echocardiography skills. The potential risks of introducing this skill set without formal training include a divergence from clinical assessments and misdiagnosis of congenital heart disease (CHD).¹⁴ This may result in inadvertent withholding of treatments or instituting incorrect therapies. Collaboration with the pediatric cardiology service is essential in developing standards for practice. It is essential that standards are set to ensure that competence is achieved and maintained with ongoing quality assurance. There are now first guidelines and recommendations published for targeted neonatal echocardiography in NICU.¹⁵

Near Infrared Spectroscopy (NIRS) for Hemodynamic Assessment

NIRS has drawn attention because it provides continuous bedside reading, is easy to apply and is noninvasive. It can monitor the brain and other organs simultaneously, is validated, accurate and precise and has good inter and intra-patient repeatability. It can be used to measure cerebral blood flow, cerebral blood volume and cerebral venous saturation. Various indices can be extracted from NIRS application such as cerebral fractional oxygen extraction (CFOE), cerebral oxygen delivery (CDO_2) and cerebral metabolic rate for oxygen (CMRO_2).

The new generation NIRS monitors have overcome some of the problems of older models such as having more

than one receiving optode, allowing subtraction of contribution from scalp/skull, calculations of estimated distance traveled by scattered light and allowing quantification of measurements of Hb and HbO.

The uses of NIRS include early detection of cerebral autoregulation even in babies who are apparently clinically well but are associated with a higher mortality. Its use is still limited to some neonatal units and outside those units is considered as a research tool as interobserver variability is high and is dependant on the position of application of optode. The concept and advances in this field are promising as it provides direct measure of perfusion of target organ with a potential of allowing early intervention and management.

Other Hemodynamic Assessment Modalities

There are other techniques being tested at point of care such as noninvasive continuous cardiac output monitoring using CW Doppler (US COM) and machines using impedance methods. Volumetric echo using 4D image acquisition and reconstruction looks promising but are limited by the nonavailability of neonatal probes. Same applies for transesophageal echo limited by the size of the probes. Functional MRI is also being researched which allows precise understanding but is limited by the fact that these can be one off examinations rather than point of care serial assessments. Until further validated techniques are available bedside, functional echocardiography remains the gold standard for bedside assessment of hemodynamics. Further efforts are however required to achieve common standards of measurement and special emphasis on training and accreditation is required utilizing telemedicine linked with pediatric cardiology centers.

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CHAPTER 8

Apnea

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Apnea or cessation of breathing is common in preterm babies born before 34 weeks gestation and almost universal in babies born before 26 weeks. Despite being such a common problem, we are *neither sure of the impact apnea has on the neurodevelopmental outcome of neonates nor are we sure that treatment of apnea by different modalities improves neurodevelopment.*

DEFINITION

Apnea of prematurity (AOP) is found in >50 percent of premature infants and is almost universal in infants who are <1000 g at birth. Most of the available literature defines apnea in infants as breathing pauses which last more than 20 seconds, or a shorter duration if associated with bradycardia or oxygen desaturation.¹ However, there is no consensus about the duration of apnea, the degree of change in oxygen desaturation, or severity of bradycardia that should be considered pathologic, i.e. we don't have an answer as of now whether an apnea which last 20 seconds will have the same connotation as a pause for 40 seconds and whether apnea which leads to desaturation to a value of 30 percent will differ in neurodevelopmental outcome from an apnea which results in a oxygen saturation levels of 80 percent. Apnea events exceeding 30 seconds are occasionally seen in both healthy term and preterm infants.² This suggests that apnea duration *per se* may not be the critical feature of altered breathing and its relation to circulatory consequences. Lack of standardization of this data is the most important reasons for ambiguity in outcome measure in neonatal apnea.

CLASSIFICATION

- *Central apnea (40%):* Both the inspiratory effort and airflow cease simultaneously in this type of apnea (Absence of chest wall movement and airflow).

- *Obstructive apnea (10%):* This type is characterized by absence of airflow in the presence of inspiratory efforts (Presence of chest wall movement but no airflow).
- *Mixed apnea (50%):* Central apnea is either preceded or followed by airway obstruction. Central apneas tend to be shorter, whereas the obstructions tend to prolong the episodes and accelerate the onset of bradycardia.

PATHOPHYSIOLOGY

Although pathogenesis of apnea of prematurity has not been fully elucidated, it is probably related to both the overall neurological and cardiorespiratory immaturity of preterm babies. Apnea of prematurity results from immaturity of brainstem respiratory control centers. As immaturity is more pronounced with decreasing gestational age and hence there is more chance of apnea at lesser gestational age. In normal individuals, the respiratory center (situated in the medullary region of brainstem) responds to the various signals like increase in carbon dioxide, decrease in oxygen and decrease in pH by increasing the firing of respiratory neurons. This increased firing results in increased impulses to respiratory muscles and hence results in increased ventilation. These responses are impaired in newborns and this result in apneas.³

Respiratory responses to increased carbon dioxide are decreased in preterm babies and slope of response continues to increase from 26 weeks onwards till 33 weeks and hence in face of hypoventilation due to any reason, babies are not able to increase their respiratory drive and land in apnea.

Responses to hypoxia are also altered in preterm babies. In contrast to events in older infants where hypoxia results in sustained hyperventilation, preterm babies are characterized by a very brief period of hyperventilation followed by depressed ventilation despite continued

hypoxia. Initial hyperventilation may be completely blunted in preterm babies.

Negative pressure in the upper airways in preterm babies can result in inhibition of diaphragmatic contraction. In cases of mixed apneas, the lack of airflow due to obstruction, e.g. due to passive neck flexion, results in generation of a negative pressure in airways and as a result cause decrease in central respiratory drive. One of the mechanism by which CPAP helps in apnea is by splinting the upper airways and hence obviating this reflex inhibition. Also neonates are obligate nose breather and cannot make an immediate switch to oral breathing when nose is obstructed.

Active or REM sleep is marked by irregularity of tidal volume and REM sleep predominates in preterm infants. Coupled to this fact is that chest wall compliance of premature infants is poor and hence they have more episodes of hypoventilation.

APNEA AND NEURODEVELOPMENT

Since apnea is associated with desaturation and bradycardia, it is plausible to think that significant episodes of apneas may have a significant impact on neurodevelopment. However, this information at present is not clear. Earlier reports found little evidence of any neurodevelopmental risk directly attributed to a history of apnea of prematurity or ALTE.^{4,5} Studies are few due to non-standardized criteria for diagnosis and for quantifying severity of apnea related events in NICU and also due to variable treatment strategies. Also separating the consequences of conditions associated with premature births like sepsis, intraventricular hemorrhage from effects of apnea of prematurity has proven difficult.

Cheung et al⁶ followed 124 very low-birth-weight babies to 24 months of age to evaluate the relationship between precisely measured pre-discharge apnea that persisted beyond 35 weeks and the neurodevelopmental outcome. They found that duration of artificial ventilation and the grade of IVH were independent predictors of neurodevelopmental outcome and the mean oximetry desaturation and frequency of pre-discharge apnea correlated with mental and motor developmental scores. Mean oximetry desaturation during apnea was an independent predictor for both mental and motor scores in infants with grade 3 or 4 intraventricular hemorrhage. Authors suggested that pre-discharge respiratory recordings may be useful in predicting subsequent neurodevelopment of high-risk preterm infants, especially those with severe intraventricular hemorrhage. Increasing number of days on which at least one apnea occurred also has been associated with impaired neurodevelopmental outcome.⁷ In the same study number of days, ventilation was required for apnea was also associated with poor neurodevelopmental outcome. Even delay in resolution of apnea beyond the

36 weeks postconceptional age has been associated with impaired neurodevelopmental outcome.⁸ Apnea of prematurity has been shown to be an independent predictor of poor early school age outcome like cognitive functions and other neuropsychological rating.⁹ These events are probably related to hypoxemia/blood flow during the episodes of apnea. CHIME study¹⁰ also provides some insights regarding risk of neurodevelopmental sequel in infants with events documented using home memory monitoring. Of the infants included in the study, there was an inverse relation between number of conventional events detected by home monitoring and neurodevelopmental outcome. This association was seen both in term and preterm babies. The adjusted difference in mean MDI scores with at least five events compared to no events was 5.6 points lower in full term babies and 4.9 points lower in preterm babies. A dose effect was also suggested by tendency for mean BSID-II values with 1 to 4 events to be intermediate between 0 and at least 5 events. Changes in cerebral blood flow velocity have been documented to decrease to the level of no or minimal diastolic blood flow during prolonged apnea.¹¹

Although no authoritative statements can be made based on sparse data, it may be worthwhile keeping a close check on neurodevelopment in newborn *with recurrent apneas and in whom the apneas persist beyond term gestation*. Validity of pre-discharge apnea event recording still has to be confirmed in larger trials before it can be used as a predictive tool for neurodevelopment in newborns.

MONITORING AND EVALUATION OF APNEA

Who all to Monitor

All infants less than 35 weeks of gestation should be monitored for apneic spells for at least the first week of life because of high risk of apneas in this group of babies. Apneic spells generally begin after 24 hours although it can begin on the first postnatal day of life also. Progesterone (which is a known respiratory stimulant) transferred from the mother before delivery has been suggested as the reason for the delayed presentation of apnea. In addition *term babies who have any central nervous system disorder, systemic illness or has received drugs which depress respiration like narcotics, etc. should be monitored for apnea*.

Routine monitoring for apnea includes monitoring of heart and respiratory rates as well as oxygen saturations since impedance monitors cannot detect obstructive apneas. Polysomnogram which measures cardiorespiratory patterns, muscular activity, ET_{CO}₂, Tc_{CO}₂, oral and nasal flow and chest and abdominal movements is ideal but is not routinely used in clinical practice.

How Long to Monitor

Both term and preterm babies show a progressive decline in apneic episodes over time. In a old citation involving

249 term and preterm infants, 92 percent had no further apnea beyond 37 weeks and by 40 weeks 98 percent of the babies were apnea free.¹² That study involved larger preterm babies. In a recent study involving preterm babies between 24 to 28 weeks, apnea frequently persisted beyond 36 weeks and continued beyond 40 weeks post-conceptual age in some.¹³ CHIME study data showed that cardiorespiratory events in preterm babies return to baseline normal level at 43 to 44 weeks postconceptional age. Only one study till date has attempted to answer the question of what constitutes a safe period and it concluded 8 days as a safe period but again there is paucity of data in extremely premature babies.¹⁴

Hence based on available literature, one should monitor for apnea till at least 37 weeks gestation, but in extremely premature babies one may have to monitor for a longer time. *Apnea free period of 8 days* seems to be a reasonable period to address recurrence.

Role of Home Monitoring

Home monitoring has not shown to decrease the incidence of sudden infant death syndromes (SIDS). Home monitor could be used as an alternative to prolonged hospital stay in babies who are otherwise well but continue to have non-life-threatening apneas at the time of discharge. Such monitoring should continue for a maximum of 44 weeks postconceptional age as suggested by the CHIME study. Infants with frequent events at home should be rehospitalized and have further studies. Additional diagnoses have been diagnosed after admission in such babies.¹⁵

MANAGEMENT OF APNEA

Once apnea is diagnosed, the clinician must investigate for a number of causes while continuing to monitor and provide supportive care (Table 1). In term babies, most cases are likely to have secondary causes of apnea, where as in extremely premature babies, although investigations for secondary causes must be completed, 80 percent of the infants would have no identifiable cause and diagnosis is of apnea of prematurity.

Physical examination should include observation of the infants breathing pattern and careful neurological and respiratory examination. One should look for presence of secretions in the oropharynx which may have resulted in occlusion of the airway. It is particularly important to *rule out systemic conditions like seizures, gastroesophageal reflux as pharmacotherapy with methylxanthines is known to decrease the threshold for seizures and reflux.* Among the first tests to be done is blood sugar, as symptomatic hypoglycemia is independently associated with neurodevelopmental poor outcome. Infants should be evaluated for stability of thermal environment. Other blood tests include complete blood counts for sepsis, electrolytes including calcium. Other test

Table 1: Secondary causes of apnea in a newborn

Central nervous system

Intraventricular hemorrhage, drugs, seizures, hypoxic injury, herniation, neuromuscular disorders, Leigh syndrome, brainstem infarction or anomalies (e.g. olivopontocerebellar atrophy) and effect of general anesthesia

Respiratory

Pneumonia, obstructive airway lesions, upper airway collapse, atelectasis, extreme prematurity (<1,000 g), laryngeal reflex, phrenic nerve paralysis, severe hyaline membrane disease, pneumothorax, hypoxia, malformations of the chest

Infectious

Sepsis, necrotizing enterocolitis, meningitis (bacterial, fungal, viral), respiratory syncytial virus

Gastrointestinal

Necrotizing enterocolitis, GERD (questionable)

Metabolic

↓ Glucose, ↓ calcium, ↓/↑ sodium, ↑ ammonia, ↓ organic acids, ↑ ambient temperature, hypothermia

Cardiovascular

Hypotension, hypertension, heart failure, PDA, anemia, hypovolemia, vagal tone

Other

Immaturity of respiratory center, sleep state, maternal drug

like ECG, chest radiograph, spinal fluid analysis should be carried out based on circumstances.

Best Practice Guidelines for the Prevention and Treatment of Apnea

Prevention of Prematurity

Since the incidence of apneas is directly related to the gestational age at birth, decrease in incidence of premature births may offer the simplest solution to decrease the incidence of apneas. However, this is most difficult to achieve.

Tocolysis

Tocolysis has not been able to prolong a preterm birth for long-time in preterm labor. In fact, magnesium sulphate used for pre-eclampsia and tocolysis in mother has been associated with increased risk of apneas in neonates.¹⁶ Hypermagnesemia during parenteral nutrition has also been a cause of apnea.¹⁷

Antenatal Steroids

Although antenatal steroids do not directly affect the maturation of respiratory centers, it does decrease the incidence of respiratory distress syndrome which can present as apnea in extremely premature babies.

Noxious Stimuli

Like deep suctioning, painful procedure should be avoided or done gently as these promote a vagal inhibition of respiration.

Kangaroo Mother Care

Skin-to-skin contact or kangaroo care for preterm infants has been associated with an increased occurrence of apnea, bradycardia and desaturation and irregular breathing;¹⁸ this appears to be unrelated to hyperthermia.¹⁹ The observation suggests that obstructive events may occur during skin-to-skin contact. Recent investigators however found no adverse events during kangaroo care.²⁰ The disparity among the reported studies may be related to the specific practice of skin-to-skin care in a particular NICU or the validity of monitoring during skin-to-skin contact. Till further data is available, given the benefits of KMC in reducing serious infections and preventing hypothermia in preterm babies (which independently increase the risk of apneas), KMC does hold promise in care of premature babies.

Blood Transfusions

Classical teaching recommends red blood cell transfusions, if apnea coexisted with anemia. However, data available at present in preterm babies with both mild (Hb 8-12 mg/dl)²¹ and moderate anemia (<8 mg/dl)²² have shown that giving transfusion to such babies does not decrease the episodes of hypoxia/bradycardia. Given all the hazards associated with blood transfusions in neonates, apnea of prematurity alone should not be an indication for transfusions.

Sensory Stimulation

Introduction of pleasant odor in the incubator in preterm babies who continued to have apneas despite pharmacological therapy has been shown to decrease the incidence of apneas by almost 30 percent.²³ Presence of a pleasant odor in the environment may help the infant to regulate his physiological state, however it is possible that vanillin used in the study possesses pharmacological properties and therefore has direct or indirect effects on the respiratory centers. Since, some of the odors can have negative influence on the respiration use of this modality *should wait further trials*.

CO₂ Inhalation

Although one of the pathophysiological mechanisms of apnea is decreased respiratory drive to increased CO₂ in the blood, inhalation of low concentration of CO₂ has also been proposed as an effective treatment. In one study involving 10 preterm babies with gestational age between 31 to 33 weeks exposure to 1 hour of CO₂ concentration

ranging from 0.5 to 1.5 percent was associated with significant decrease in the episodes of apnea and improved oxygenation. This data *however is too limited to recommend this therapy at this time*.²⁴

Oxygen Supplementation

Oxygen may decrease the frequency of apneas by replacing functional residual capacity gases by oxygen and ensuring that during brief episodes of apnea there is enough oxygen in the lungs to diffuse into the blood and avert hypoxemia. However, oxygen therapy in the neonates is fraught with dangers of oxygen mediated free radical injury like BPD, ROP, etc. *Hence, oxygen should be used to keep the pulse oximeter values in the 88 to 93 percent range*. If a newborn requires oxygen supplementation to keep oxygen saturation in that range, then one must search for secondary causes of apnea like sepsis, PDA, etc. and not label as apnea of prematurity.

Temperature

Hypothermia is a known risk factor for apnea and should be avoided or corrected before considering any further therapy. Increase in ambient temperature to 30°C has been shown to increase the incidence of apneas in preterm babies reaching term as compared to the keeping the babies at 24°C.²⁵ Even a slight increase in body temperature of 0.8°C increased the indices of periodic breathing with apneic oscillations.²⁶ Air temperature in an incubator *should be kept near the lower end of the thermoneutral zone to lessen the episodes of apnea*.

Position

Extremes of flexion and extension should be avoided to decrease the likelihood of airway obstruction. Although physiologically ventilation is better in prone position, central apneas tend to be more in prone position²⁷ with less arousals emphasizing the importance of recommending supine sleeping after neonatal unit discharge for prematurely born infants.

Kinesthetic Stimulation

Physical stimulation by nursing staff is commonly used to arouse the apneic infant and stimulate breathing. This led people to speculate whether frequent physical stimuli by means of oscillating mattress to provide kinesthetic stimulate breathing and might reduce the number of apneic events. Kinesthetic stimulation has not been shown to prevent occurrence of apnea.²⁸ Cochrane review²⁹ on kinesthetic stimulation to treat established apneas has shown decreased frequency of apnea of short duration but had no impact on the clinically significant apneas (those more than 20 secs in duration or those with hypoxia and bradycardia). The studies included in the review all used a different

method of providing stimulation and because of the cross-over design later outcomes on neurodevelopment could not be studied. *Further research with larger trials is needed with focus on neurodevelopment before recommending this modality.*

Carnitine Supplementation

Preterm infants have lower muscle carnitine reserves compared to term infants. This is probably related to poor tissue uptake due to immaturity of the carnitine biosynthetic pathways, reduced placental transfer and reduced intakes from breast milk. Treatment with carnitine has shown benefit in the respiratory status of ventilator dependent adults, as well as stabilization of respiratory parameters and increased physical performance in adult patients with chronic respiratory insufficiency. Cochrane review³⁰ on carnitine for apnea has shown no benefit and *hence its use at present is not recommended.*

Immunization

There is an increase in adverse cardiorespiratory events following the first dose of DTP-IPV-Hib in preterm infants. The increase in apnea has been attributed to the whole-cell pertussis component.³¹ Investigators have observed reduced morbidity with newer vaccines that contain acellular pertussis.³² However, one recent study showed no difference between those who received whole cell as compared to the acellular variant.³³ Chronic diseases in preterm babies at the time of immunization greatly increased the risk of apneas.³⁴ If the neonate is in the NICU for chronic diseases at 2 months post-birth, *monitoring for apnea, bradycardia and desaturation is recommended after vaccination.* Healthy preterm infants without chronic disease and therapy seem to be less vulnerable to such adverse effects *but still should be vaccinated in hospital settings.* Acellular pertussis should be used for immunization in preterm babies if cost is not a factor.

Pharmacological Treatment

There are no definite guidelines as when to start pharmacological therapy but most would start treatment when apneic spells continue despite supportive measures or if one apneic episode was severe enough require bag and mask ventilation.

METHYLYXANTHINES

Most commonly prescribed drug therapy for AOP.

- Caffeine
- Aminophylline and its oral substitute theophylline.

Mechanisms of action of methylxanthines

- Increased response to CO₂ and decreased hypoxic depression of central respiratory drive
- Increased diaphragmatic activity
- Increased minute ventilation.

Pharmacokinetics

Theophylline

Mean half-life of theophylline is approximately 30 hours in infants. Oral theophylline is given with a loading dose of 5 mg/kg followed by a maintenance dose of 1 to 2 mg/kg every 8 hours. A therapeutic effect is seen at a plasma concentration of at least 5 mg/L, although a target plasma concentration is around 10 mg/L. Plasma concentration of theophylline may vary widely at the same dosage levels, which necessitates frequent monitoring and dose adjustments.³⁵ Toxicity usually starts after 20 mg/L but can be seen at plasma concentration of more than 13 mg/L. Side effects include tachycardia, abdominal distention, feeding intolerance, seizures, hyperglycemia and electrolyte imbalances.

Caffeine citrate can be administered either orally or intravenously. The recommended loading dose of 10 mg/kg of caffeine (equivalent to 20 mg/kg of caffeine citrate) followed 24 to 48 hours later by a single daily maintenance dose of 2.5 mg/kg (5 mg/kg of caffeine citrate). Caffeine toxicity is rarely observed at plasma serum concentration below 50 mg/L, which is markedly higher than the serum therapeutic concentration of 5-20 mg/L. Side effects commonly seen with caffeine are jitteriness, tachycardia and occasionally GI intolerance is reported.

Choice of methylxanthine therapy: Evidence suggests that caffeine is equal in efficacy with fewer drawbacks.³⁵ Dosing regimens of caffeine are simpler and produce more predictable results. Moreover, caffeine has a wider therapeutic window and required very infrequent monitoring of plasma levels.

Reasons for Concern with Methylxanthines

Xanthines inhibit two (A1 and A2a) of the four known (A1, A2a, A2b and A3) adenosine receptors and experimental evidence suggests that *nonspecific adenosine receptor blockade in very preterm infants may have detrimental effects on growth, neurological and cognitive development and childhood behavior.*

Effect on Growth

Methylxanthines increase oxygen consumption³⁶ in preterm babies by 20 to 25 percent and it has been shown that even a single loading dose of theophylline 5 mg/kg can increase the energy expenditure by 15 kJ/kg/day. This data although not conclusive suggests that use of methylxanthines may increase energy consumption and hence effect growth of premature babies.

Effect on Neurological Development and Behavior

Adenosine is neuroprotective in many experimental models of hypoxia/ischemia.³⁷ However, the results are not consistent and Bona et al³⁸ found that theophylline reduced rather than increased brain injury after hypoxia-ischemia

in 7-day old rats. Efforts to manipulate adenosine receptors in neonatal and adult animal models of hypoxic-ischemic brain injury with specific agonists and antagonists for the adenosine A1 and A2a receptors have yielded complex and occasionally contradictory results. Furthermore, there is an evidence that chronic administration of adenosine receptor ligands has different effects on hypoxic-ischemic brain injury than acute ligand administration.³⁹ Mice with experimental deficiency of A1 and A2 receptors are more anxious and aggressive.⁴⁰

But the famous CAP trial (Caffeine in apnea of prematurity)⁴¹ which involved around 2006 preterm newborn in multiple study centers has demonstrated the safety of this silver bullet. Infants with a birth weight of 500 to 1250 g were eligible for enrolment if their clinicians considered them to be candidates for methylxanthine therapy during the first 10 days of life. The results of this trial showed that caffeine therapy decreased incidence of bronchopulmonary dysplasia and mean duration of mechanical ventilation by a week. Besides, caffeine did not increase the incidence of ultrasonic evidence of brain injury and necrotizing enterocolitis.

Long-term safety data on caffeine therapy for apnea of prematurity has shown that improves the rate of survival without neurodevelopmental disability at 18 to 21 months in infants with very low birth weight.⁴² Effect of caffeine on neonatal morbidities in the CAP trial.

Patent Ductus Arteriosus

That significant reduction in the number of neonates requiring pharmacologic closure of Patent Ductus Arteriosus (PDA) in the caffeine-treated group (293/1006 or 29.3%) compared to placebo (381/1000 or 38.1% $p < 0.001$).

Bronchopulmonary Dysplasia

Bronchopulmonary dysplasia (BPD) rates were significantly lower in the caffeine treated group (350/1006 or 36.3%) compared to the placebo control (447/1000 or 43.2%, $p < 0.001$).

Retinopathy of Prematurity

Caffeine significantly reduced the risk of severe ROP (stage 4 or 5 or had laser or cryotherapy in at least one eye). Severe ROP occurred in only 5.1 percent (49/965) in caffeine-treated infants and in 7.9 percent (75/955) in the placebo control group.

Necrotizing enterocolitis (NEC) and intraventricular hemorrhage (IVH): No protective effect of caffeine on these morbidities.

Long-term Outcome

Death or survival with disability was significantly lower in the caffeine-treated group (377/937, 40.2%) compared to

the placebo group (431/932, 46.2%, $p = 0.008$). Infants who had cerebral palsy was also lower in the caffeine-treated group (40/909, 4.4%) compared to the placebo group (66/901, 6.5%, $p = 0.009$). Those with cognitive impairment was also lower in the caffeine-treated group (293/867, 33.8%) compared to the placebo treated infants (329/858, 38.3%, $p = 0.04$).

Post-hoc subgroup analyses were performed on the basis of: (1) indication for commencement of study drug: treat apnea, prevent apnea or facilitate extubation; (2) positive pressure ventilation (PPV) at randomization: Endotracheal tube (ETT), noninvasive ventilation or none; and (3) timing of commencement of study drug: Early or late (≤ 3 versus > 3 days). Results of this post-hoc analysis showed that effects of caffeine was more in the group who were ventilated within 24 hours of birth and were given caffeine early.⁴³

Based on the above data, it is reasonable in current era to start caffeine treatment in all infants less than 1250 gm, however if one chooses to be a bit more selective then, at least those babies who have an endotracheal tube inserted for ventilation should be started on caffeine early.

Doxapram

Doxapram is a respiratory stimulant that acts on both peripheral chemoreceptors and the central nervous system. Dose: 3 mg/kg bolus followed by 1.5 mg/kg/hr as infusion. Cochrane review on doxapram (only one study) showed decreased apnea in the first 48 hours after starting the drug but the benefit was not sustained. No major side effects were reported. But number of subjects in the study was too small to make useful conclusions. Doxapram has been shown to decrease the cerebral blood flow in preterm babies⁴⁴ and even mental developmental delay has also been associated with prolonged days of doxapram therapy for apnea.⁴⁵ Other short-term side effects like hypertension, central nervous system stimulation, gastrointestinal disturbances and even heart block has been reported in some of the observational studies. Given that there are no substantial data available on the benefit/side effects, doxapram use *should be restricted* to scenarios where recurrent apneas are continuing despite use of methylxanthines and *facilities for ventilator support are not available*. Doxapram infusion could be used to transfer the baby to a NICU with such facilities.

VENTILATION

Continuous Positive Airway Pressure

CPAP delivered by a nasal interface is an effective treatment of apnea of prematurity.⁴⁶ Mechanisms proposed—patency of upper airways, stabilizing chest wall, maintaining functional residual capacity. Cochrane review⁴⁷ comparing CPAP with methylxanthines suggested higher failure rates with CPAP. The only trial included in the review, used mask CPAP—a modality which is no longer

being used. Masks require a complete seal and improper use might have resulted in a higher failure rates. Recent studies on VLBW babies show that early application of nCPAP and avoidance of mechanical ventilation resulted in no adverse neurodevelopment/growth.⁴⁸ A significantly higher developmental quotient was found in the nCPAP group at 18 months' corrected age. Several trends were also noted in the nCPAP group with a decrease of intraventricular hemorrhage and in "abnormal neurodevelopment" at 6 months corrected age. However, these studies were not in babies having apnea. *Prophylactic CPAP has no role in prevention of apnea.*

Nasal Intermittent Positive Pressure Ventilation

If apneas continue despite CPAP and methylxanthines, intubation and ventilation become necessary. Owing to the risks of invasive ventilation, nasal intermittent positive pressure ventilation is an alternative worth considering. NIPPV reduces asynchronous thoracoabdominal motion as a result of better stabilization of chest wall.⁴⁹ Two trials^{50,51} comparing the NCPAP to NIPPV have shown different results—one showing no difference where as the more recent one⁵¹ has shown NIPPV to be more effective in reducing apneas. Gastrointestinal perforation has been reported by some authors.⁵² Newer machines can synchronise ventilator breaths (SNIPP) with the infant's respiratory cycle. For practical purposes NIPPV may be a used if apneas continue despite NCPAP.

Intubation and Assisted Ventilation

If the infant continues to have clinically significant episodes of apnea despite maximum pharmacological and noninvasive positive airway pressure ventilation, intubation and assisted ventilation become necessary.

High-Flow Nasal Cannulae

Recently, it has been shown that NC can deliver positive distending pressure (PDP) to premature neonates if the flow is increased to 1 to 2 L/min (high-flow nasal cannulae [HFNC]). Only one study has compared nasal cannulae (with air oxygen blender) to nasal CPAP. NC was as effective as NCPAP in the management of apnea of prematurity with no difference in the number of apneas, bradycardias, or desaturation during a 6-hour period.⁵³ This is a small study with period of observation limited to 6 hours. The nasal cannulae being inexpensive and easier to use, *need to be studied in larger trials.*

SUMMARY

The treatment of AOP requires trials of multiple strategies. Both pharmacologic and nonpharmacologic interventions carry some risks. The risks of treatment should be

weighed against the risks and consequences of prolonged apnea before starting treatment. For those infants who do receive treatment, appropriate monitoring and a plan for home therapy should be in place. Periodic check-ups for improvements in apnea and a plan for discontinuation of treatment must also be developed to keep the treatment periods as short as possible.

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CHAPTER 9

Birth Asphyxia and Hypoxic-Ischemic Encephalopathy

Vikas Mahajan, Sanjay Wazir

Birth asphyxia refers to an impairment of the normal exchange of respiratory gases during parturition, and the ensuing adverse effects on the fetus. It is an important cause of fresh stillbirth and early neonatal death. The condition of a newborn infant is determined by a complex interaction of maternal, placental, uterine and fetal factors extending through pregnancy to delivery. At the core of the fetomaternal unit is the process of placental exchange where by oxygen from the maternal circulation and carbon dioxide from the fetal circulation passively diffuse across the placental membrane. During normal uterine contractions placental exchange is abolished when the uterine pressure exceeds 10 mm Hg. Studies using infrared spectroscopic techniques during normal labor show that many infants undergo intermittent hypoxia during the process of delivery. Despite this hypoxic stress most infants are born in good condition. The fetus who experience significant asphyxia episode is at risk of developing hypoxic ischemic encephalopathy or other end organ damage.

Certain terms are commonly used during evaluation of a baby at risk for brain injury in the perinatal period.

NEONATAL DEPRESSION

It is a general term used to describe infants who have a prolonged transition from intrauterine-to-extrauterine environment and usually have low APGAR scores.

NEONATAL ENCEPHALOPATHY

It is a clinical term used to describe an abnormal neurobehavioral state that consists of a decreased level of consciousness. It characteristically begins within the first postnatal day and may be associated with seizure like activity, hypoventilation or apnea, depressed primitive reflexes and the appearance of brainstem reflexes. It does

not imply a specific etiology, nor does it imply irreversible neurological injury.

HYPOXIC ISCHEMIA ENCEPHALOPATHY

It is an abnormal neurobehavioral state in which the predominant pathogenetic mechanism is impaired cerebral blood flow.

Definition

The major difficulty in collecting accurate epidemiological data on birth asphyxia is the lack of a common definition of the condition. The 1996 guidelines from the AAP (American Academy of Pediatrics) and ACOG (American College of Obstetricians and Gynecologists)¹ for hypoxic-ischemic encephalopathy (HIE) indicate that all of the following must be present for the designation of perinatal asphyxia severe enough to result in acute neurological injury:

- Profound metabolic or mixed acidemia (pH <7) in an umbilical artery blood sample, if obtained
- Persistence of an Apgar score of 0 to 3 for longer than 5 minutes
- Neonatal neurologic sequelae (e.g. seizures, coma, hypotonia)
- Multiple organ involvement (e.g. kidney, lungs, liver, heart, intestines).

However, the National Neonatology Forum of India has defined asphyxia as “gasping or ineffective breathing or lack of breathing at one minute of life”.

Apgar and Birth Asphyxia

Apgar score was devised by Virginia Apgar, an obstetric anesthesiologist in 1952 to express the early postnatal condition of the newborn. It was designed to be a guide to the resuscitation of the newborn. Over time the universality

of the Apgar score led many investigators to adopt it as a marker for birth asphyxia. Most commonly a one minute Apgar less than or equal to three, or a five minute Apgar less than seven have been taken to indicate birth asphyxia. The problems with using Apgar score as a marker of birth asphyxia are:

1. Apgar score may be low because of causes other than birth asphyxia, e.g. prematurity, maternal sedation, neuromuscular disorder, etc.
2. Apgar score has a poor correlation with the long-term outcome. However, the extended Apgar score recorded 20 minutes after birth has much better specificity for the prediction of both early death and disability.²

Cord Blood Gases and Birth Asphyxia

The normal cord blood gas values of the fetus are important to know to interpret gases after delivery. During the course of normal labor, the PaO_2 drops, the PaCO_2 rises, and the base deficit rises. Severe acidemia is when the pH is below 7 and there is a base deficit of more than 12 mmol/L. Metabolic acidosis in isolation also proved to be a poor predictor of significant perinatal brain injury. The sensitivity and positive predictive value of a low pH for adverse outcome are 21% and 8%, respectively.³

Incidence

Each year 4 million neonates in the world die due to asphyxia which represents 38% of all deaths under 5 years. The frequency of perinatal asphyxia is approximately 1 to 1.5% of live births in western hemisphere and is inversely related to gestational age and birth weight. It occurs in 0.5% of live born infants >36 weeks gestation and accounts for 20% of perinatal deaths. According to the National Neonatal Perinatal Database of India,⁴ 23% of all neonatal deaths in our country are related to asphyxia. Twenty-five to thirty percent of all stillbirths occur intrapartum. In absolute numbers, this translates into between 2,50,000 and 3,50,000 deaths due to asphyxia and contributes to as many as 300,000 to 400,000 stillbirths annually. To add to this, there is an accounted disability related to asphyxia in the developing countries. Because of the limited availability of data, and despite its enormous magnitude, available figures are likely to underestimate the real proportion of the problem.

Clinical Manifestations of HIE

There is multiorgan involvement in the birth asphyxia and neurological involvement is the hallmark of the birth asphyxia. Hypoxic-ischemic encephalopathy (HIE) is characterized by clinical and laboratory evidence of acute or subacute brain injury due to lack of blood supply and oxygen.

Birth to 12 hours: In the first hours after the insult, signs of presumed bilateral cerebral hemispherical disturbance predominate. The severely affected infant is either deeply stuporous or in coma. Periodic breathing or respiratory irregularity is prominent. Severely affected ones may exhibit marked hypoventilation or respiratory failure. Majority of infants at this stage are markedly hypotonic with minimal spontaneous or elicited movement. Less affected ones, have preserved tone and is more likely with prominent involvement of basal ganglia.

12 to 24 hours after insult: During this time the infants neurological status changes in a variable manner. Infants with severe disease remain stuporous and those with less severe disease often begin to exhibit some degree of improvement in alertness. Infants with injury to basal ganglia often exhibit an increase in their hypertonia, especially in response to their handling. Full term infants often exhibit weakness in the hip shoulder distribution, with more impressive involvement of proximal extremities. Seizures often occur during this time.

24 to 72 hours: During this time, the severely affected infant's level of consciousness often deteriorates further and deep stupor or coma ensues. Babies who die with HIE most often do so at this time. Preterm babies may have intraventricular hemorrhages, and term babies often demonstrate signs of major cerebral necrosis.

After 72 hours: Infants who survive to this extent usually improve over the next few days or weeks. Although the level of consciousness improves, mild-to-moderate stupor continues. Disturbances of feeding are common. Generalized hypotonia is common but hypertonia may be seen in babies who have had significant basal ganglia involvement.

Grading of HIE

In 1976, Sarnat and Sarnat (Table 1) published a combined clinical and EEG study of 21 term infants who displayed evidence of fetal distress.⁵ They described a syndrome of neurological and electroencephalogram (EEG) features that they labeled neonatal encephalopathy following fetal distress.

In their original study, the syndrome was divided into three stages, with severely affected infants typically progressing from grades 1 to 3.

This scheme was later modified by Fenichel et al⁶ (Table 2), who grouped the clinical features of what he termed *hypoxic ischemic encephalopathy* (HIE) into three different patterns (mild, moderate and severe). The asphyxiated infant was not considered to progress through the grades but rather to exhibit the characteristic features and time course (of either deterioration or resolution) consistent with a particular grade.

Table 1: Sarnat clinical stages of perinatal hypoxic-ischemic brain injury

	<i>Stage 1</i>	<i>Stage 2</i>	<i>Stage 3</i>
Level of consciousness	Hyperalert	Lethargic or obtunded	Stuporous
Neuromuscular control			
Muscle tone	Normal	Mild hypotonia	Flaccid
Posture	Mild distal flexion	Strong distal flexion	Intermittent decerebration
Stretch reflexes	Overactive	Overactive	Decreased or absent
Segmental myoclonus	Present	Present	Absent
Complex reflexes			
Suck	Weak	Weak or absent	Absent
Moro	Strong; low threshold	Weak; incomplete; high threshold	Absent
Oculovestibular	Normal	Overactive	Weak or absent
Tonic neck	Slight	Strong	Absent
Autonomic function	Generalized sympathetic	Generalized parasympathetic	Both systems depressed
Pupils	Mydriasis	Miosis	Variable; often unequal; poor light reflex
Heart rate	Tachycardia	Bradycardia	Variable
Bronchial and salivary secretions	Sparse	Profuse	Variable
GI motility	Normal or decreased	Increased; diarrhea	Variable
Seizures	None	Common; focal or multifocal	Uncommon (excluding decerebration)
EEG findings	Normal (awake)	Early: low-voltage continuous delta and theta Later: periodic pattern (awake) Seizures: focal 1-to 1-Hz spike-and-wave	Early: periodic pattern with isopotential phases Later: totally isopotential
Duration	1-3 days	2-14	Hours to weeks

Table 2: Fenichel grading for hypoxic-ischemic encephalopathy. The features in the bold are the main requirements for each grade. Features not in bold may be present but are essential for syndrome assignment. a/ b: either abnormal tone or abnormal suck should accompany altered conscious level to assign grade 1

<i>Features</i>	<i>Grade 1 (Mild)</i>	<i>Grade 2 (Moderate)</i>	<i>Grade 3 (Severe)</i>
Conscious level	Irritable/ Hyperalert	Lethargic	Comatose
Tone	Either^aMildly abnormal (hypo/hyper)	Moderately abnormal (Hypotonic or dissociated)	Severely abnormal (Hypotonia)
Suck	Or ^b abnormal	Poor	Absent
Primitive reflexes	Exaggerated	Depressed	Absent
Seizures	Absent	Present	Present
Brainstem reflexes	Normal	Normal	Impaired
Respiration	Tachypneic	Occasional apneas	Severe apnea

For usage in clinical studies and for well equipped centers, Sarnat and Sarnat staging is mostly used but Fenichel grading may be of use in resource constrained settings since it is based only on clinical criteria alone.

Other organ systems⁷ involved following a hypoxic-ischemic events include the following:

1. **Heart (43-78%):** May present as reduced myocardial contractility, severe hypotension, passive cardiac dilatation, and tricuspid regurgitation.
2. **Lungs (71-86%):** Patients may have severe pulmonary hypertension requiring assisted ventilation.
3. **Renal (46-72%):** Renal failure presents as oliguria and, during recovery, as high-output tubular failure, leading to significant water and electrolyte imbalances.
4. **Liver (80-85%):** Elevated liver function test results, hyperammonemia, and coagulopathy can be seen. This may suggest possible GI dysfunction. Poor peristalsis and delayed gastric emptying are common; necrotizing enterocolitis is rare. Intestinal injuries may not be apparent in the first few days of life or until feeds are initiated.
5. **Hematologic (32-54%):** Disturbances include increased nucleated RBC's, neutropenia or neutrophilia, thrombocytopenia, and coagulopathy.

Differential diagnosis of neonatal encephalopathy:

These include: i. perinatal hypoxia-ischemia; ii. hypoglycemia; iii. infection; iv. severe hyperbilirubinemia; v. cerebral trauma; vi. intracranial hemorrhage; vii. idiopathic cerebral infarction; viii. inherited metabolic disorders; ix. congenital neuromuscular disease; and x. congenital dysmorphic syndromes.

Pathophysiology^{8,9} (Fig. 1)

Brain hypoxia and ischemia due to systemic hypoxemia, reduced cerebral blood flow (CBF), or both are the primary physiological processes that lead to hypoxic-ischemic encephalopathy. The initial compensatory adjustment to an asphyxial event is an increase in CBF due to hypoxia and hypercapnia. This is accompanied by a redistribution of cardiac output to essential organs, including the brain, heart, and adrenal glands. With prolonged asphyxial insult and failure of compensatory mechanisms, cerebral blood flow falls, leading to ischemic brain injury. In adults, CBF is maintained at a constant level despite a wide range in systemic BP. This phenomenon is known as the cerebral autoregulation, which helps maintain cerebral perfusion. In human adults, the BP range at which CBF is maintained is 60 to 100 mm Hg.

Data in the human fetus and the newborn infant suggest that CBF is stable over much narrower range of BPs, CBF autoregulation is maintained may be only between 10 to 20 mm Hg (compared with the 40 mm Hg range in adults noted above). In the fetus and newborn suffering from acute asphyxia, after the early compensatory

adjustments fail, the CBF can become pressure-passive, at which time brain perfusion depends on systemic BP. As BP falls, CBF falls below critical levels, and the brain injury secondary to diminished blood supply and a lack of sufficient oxygen occurs. This leads to intracellular energy failure which is also known as *primary energy failure*.

Primary Energy Failure

During the early phases of brain injury, a large cascade of events follows hypoxic-ischemic encephalopathy injury which includes:

- Excitatory amino acid (EAA) receptor overactivation
- Impaired uptake of glutamate
- These result in high synaptic levels of glutamate and EAA receptor overactivation, including N-methyl-D-aspartate (NMDA), amino-3-hydroxy-5-methyl-4 isoxazole propionate (AMPA), and kainate receptors.
- NMDA receptors are permeable to Ca^{++} and Na^+ , whereas AMPA and kainate receptors are permeable to Na^+ . Accumulation of Na^+ coupled with the failure of energy dependent enzymes such as Na^+/K^+ -ATPase leads to rapid cytotoxic edema and necrotic cell death.
- Consequences of increases intracellular Ca^{++} concentration include activation of phospholipases, endonucleases, proteases, and, in select neurons, nitric oxide synthase (NOS). Activation of phospholipase A2 leads to release of Ca^{++} from the ER via activation of phospholipase C. Activation of proteases and endonucleases results in cytoskeletal and DNA damage.

Reperfusion Energy

During the reperfusion period, free radical production increases due to activation of enzymes such as cyclooxygenase, xanthine oxidase, and lipoxygenase. Free radical

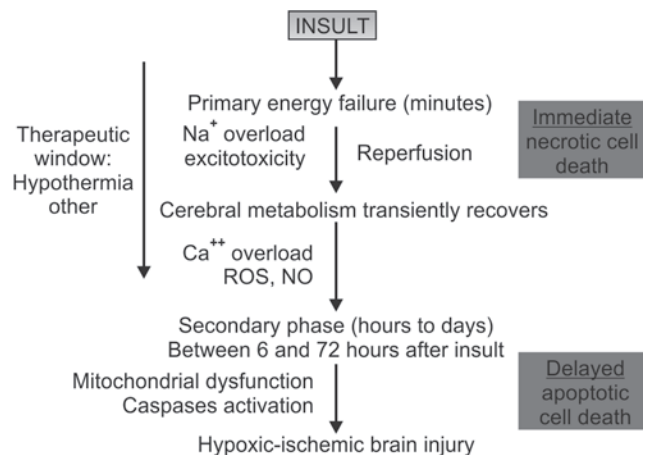


Fig. 1: Pathophysiology of hypoxic-ischemic brain injury in the developing brain. During the initial phase of energy failure, glutamate mediated excitotoxicity and Na^+/K^+ -ATPase failure lead to necrotic cell death. After transient recovery of cerebral energy metabolism, a secondary phase of apoptotic neuronal death occurs. ROS = Reactive oxygen species

damage is further exacerbated in the neonate because of immature antioxidant defenses. Free radicals can lead to lipid peroxidation as well as DNA and protein damage and can trigger apoptosis. Finally, free radicals can combine with nitric oxide (NO) to form peroxynitrite a highly toxic oxidant. NO production plays an important role in the pathophysiology of perinatal hypoxic-ischemic brain injury.

Secondary Energy Failure

Following the initial phase of energy failure from the asphyxial injury, cerebral metabolism may recover following reperfusion, only to deteriorate in a secondary energy failure phase. This new phase of neuronal damage, starting at about 6 to 24 hours after the initial injury, is characterized by mitochondrial dysfunction, and initiation of the apoptotic cascade. This phase has been called the “delayed phase of neuronal injury”. The duration of the delayed phase is not precisely known in the human fetus and newborn but appears to increase over the first 24 to 48 hours and then starts to resolve thereafter.

LABORATORY STUDIES

These are nonspecific tests to confirm or exclude a diagnosis of hypoxic-ischemic encephalopathy (HIE) because the diagnosis is made based on the history, physical and neurological examinations, and laboratory evidence. Many of the tests are performed to assess the severity of brain injury and to monitor the functional status of systemic organs. As always, the results of the tests should be interpreted in conjunction with the clinical history and the findings from physical examination.

Laboratory Studies should Include the Following

Serum Electrolyte Levels and Renal Function Test

In severe cases, daily assessment of serum electrolytes is valuable until the infant's status improves. Markedly low serum sodium, potassium, and chloride levels in the presence of reduced urine flow and excessive weight gain may indicate acute tubular damage or syndrome of inappropriate antidiuretic hormone (SIADH) secretion, particularly during the initial 2 to 3 days of life. Serum creatinine levels, creatinine clearance, and BUN levels suffice in most cases.

Cardiac and Liver Enzymes

These values are an adjunct to assess the degree of hypoxic-ischemic injury to these other organs. These findings may also provide some insight into injuries to other organs, such as the bowel.

Blood Gas Monitoring

Blood gas monitoring is used to assess acid-base status and to avoid hyperoxia and hypoxia as well as hypercapnia and hypocapnia.

Neuroimaging

Neuroimaging has become increasingly important in the evaluation of neonatal encephalopathy, and may provide information regarding the type and timing of brain injury. Various modalities have been used to evaluate infant brains with neonatal encephalopathy, including cranial sonography (CS), computed tomography (CT) and magnetic resonance imaging (MRI) with MR spectroscopy. Head MR imaging techniques yield the most useful information, though the resources necessary for transporting, monitoring, and supporting sick babies during this procedure are not always readily available.

Cranial sonography: Head sonography has a low sensitivity (50%) for the detection of anomalies associated with hypoxic-ischemic encephalopathy. Findings include global increase in cerebral echogenicity and obliteration of cerebrospinal fluid (CSF) containing spaces suggestive of cerebral edema. Increase in the echogenicity of deep gray matter structures may also be identified, typically when ultrasonography is performed after 7 days of life. Cranial sonography has a high sensitivity and specificity for locating hemorrhages and defining ventricular size.

Head CT: CT scan of the head can be useful to confirm cerebral edema (obliteration of cerebral ventricles, blurring of sulci), manifested as narrowness of the lateral ventricles and flattening of gyri. Areas of reduced density that indicate evolving zones of infarction may be present. Evidence of hemorrhage in the ventricles or in the cerebral parenchyma may also be seen.

Head MRI, MR spectroscopy and diffusion-weighted imaging (DWI) techniques: MRI¹⁰ is the imaging modality of choice for the diagnosis and follow-up of infants with moderate-to-severe hypoxic-ischemic encephalopathy (HIE). Early MRI (and particularly after day 4), conventional images may accurately demonstrate the injury pattern as area of hyperintensity. DWI allows earlier identification of injury patterns in the first 24 to 48 hours. The MRI sequence identifies areas of edema and, hence, injured areas. DWI changes peak at 3-5 day and pseudonormalizes by the end of the first week. MRS allows for quantification of intracellular molecules. Proton MRS allows identification of cerebral lactate, which persist for weeks following a significant hypoxic-ischemic injury.

Electroencephalography

Amplitude-integrated electroencephalography (aEEG): Several studies¹¹ have shown that a single-channel aEEG performed within a few hours of birth can help evaluate the severity of brain injury in the infant with hypoxic-ischemic encephalopathy. The abnormalities seen in infants with moderate-to-severe hypoxic-ischemic encephalopathy include the following:

- Discontinuous tracing characterized by a lower margin below 5 mV and an upper margin above 10 mV.
- Burst suppression pattern characterized by a background with minimum amplitude (0-2 mV) without variability and occasional high voltage bursts (>25 mV).
- Continuous low voltage pattern characterized by a continuous low voltage background (< 5 mV).
- Inactive pattern with no detectable cortical activity.
- Seizures, usually seen as an abrupt rise in both the lower and upper margin.

Note that considerable training is required for conducting and properly interpreting the aEEG findings. aEEG can accurately predict poor outcome with a sensitivity of 91% (95% CI, 87-95).

Standard EEG

Traditional, multichannel EEG is an integral part of the evaluation of infants diagnosed with hypoxic-ischemic encephalopathy. It is a valuable tool to assess the severity of the injury and evaluate for subclinical seizures.

Generalized depression of the background rhythm and voltage, with varying degrees of superimposed seizures, are early findings. EEG characteristics associated with abnormal outcomes include:

- Background amplitude of less than 30 mV.
- Interburst interval of more than 30 seconds.
- Electrographic seizures.
- Absence of sleep-wake cycle at 48 hours.

Serial EEGs should be obtained to assess seizure control and evolution of background abnormalities. Improvement in the EEG findings over the first week, in conjunction with improvement in the clinical condition, may help predict a better long-term outcome.

TREATMENT

Following initial resuscitation and stabilization, treatment of hypoxic-ischemic encephalopathy (HIE) is largely supportive. Delivery room management follows standard Neonatal Resuscitation Program (NRP) guidelines. Close attention should be paid to appropriate oxygen delivery, perfusion status, and avoidance of hyperthermia. All babies with neonatal asphyxia should be admitted in a neonatal intensive care unit. Major goals include:

- Maintenance of physiologic homeostasis
- Neuroprotective therapeutic measures.

Maintenance of Physiologic Homeostasis

Central aspects of supportive care include the following:

- Maintenance of adequate ventilation:* Avoidance of hypoxemia, hyperoxia, hypercapnia, and hypocapnia. Hypocapnia in particular may lead to severe brain hypoperfusion and cellular alkalosis and has

been associated with worse neurodevelopmental outcomes.

- Maintenance of sufficient brain and organ perfusion (avoidance of systemic hypotension or hypertension; avoidance of hyperviscosity):* Mean blood pressure (BP) above 35 to 40 mm Hg is necessary to avoid decreased cerebral perfusion. Hypotension is common in infants with severe hypoxic-ischemic encephalopathy and is due to myocardial dysfunction, capillary leak syndrome, and hypovolemia; hypotension should be promptly treated. Dopamine or dobutamine can be used to achieve adequate cardiac output in these patients.
- Fluid and electrolytes management:* Because of the concern for acute tubular necrosis (ATN) and syndrome of inappropriate antidiuretic hormone (SIADH) secretion, fluid restriction is typically recommended for these infants until renal function and urine output can be evaluated. Therefore, fluid and electrolyte management must be individualized on the basis of clinical course, changes in weight, urine output, and the results of serum electrolyte and renal function studies. Avoidance of fluid overload is critical to prevent brain edema.
- Maintenance of normal metabolic status (e.g. normoglycemia, nutritional status, pH):* Avoid hypoglycemia and hyperglycemia because both may accentuate brain damage. Initial hypoglycemia (<40 mg/dL) is significantly associated with adverse neurological outcomes. Arterial blood gases and serum calcium, magnesium, glucose, and electrolytes should be assessed early in the course and as needed.
- Avoid hyperthermia:* It has been shown to be associated with increased risk of adverse outcomes in neonates with moderate-to-severe hypoxic-ischemic encephalopathy. In one observational study,¹² the risk of death or moderate-to-severe disability was increased 3.6-fold to 4-fold for every 1°C increase in the mean of the highest quartile of skin or esophageal temperature.
- Control of seizures:* HIE is the most common cause of seizures in the neonatal period. Studies suggest that seizures, including asymptomatic electrographic seizures, may contribute to brain injury and increase the risk of subsequent epilepsy. Current therapies available to treat neonates with seizures include phenobarbital, phenytoin, and benzodiazepines. Phenobarbital has been shown to be effective in only 29 to 50% of cases. Phenytoin only offers an additional 15% efficacy. Benzodiazepines, particularly lorazepam, may offer some additional efficacy.

Neuroprotective Therapeutic Measures

Including therapeutic hypothermia or other potential neuroprotective measures.

Therapeutic Hypothermia

Extensive experimental data suggest that mild hypothermia (3-4°C below baseline temperature) applied within a few hours (no later than 6 h) of injury is neuroprotective. The neuroprotective mechanisms are not completely understood. Possible mechanisms include:

1. Reduced metabolic rate and energy depletion.
2. Decreased excitatory transmitter release.
3. Reduced alterations in ion flux.
4. Reduced apoptosis due to hypoxic-ischemic encephalopathy.
5. Reduced vascular permeability, edema, and disruptions of blood-brain barrier functions.

Therapeutic hypothermia compared with usual care was associated with a significant reduction in the combined primary endpoint of death or moderate to severe neurodevelopmental disability. Hypothermia is the only effective neuroprotective therapy currently available for treatment of HIE and is safe and easy to administer. The clinical efficacy of therapeutic hypothermia in neonates with moderate-to-severe hypoxic-ischemic encephalopathy has been evaluated in seven randomized controlled trials.¹³⁻²⁰ Inclusion criteria varied slightly. Criteria from the larger trials (NICHD, CoolCap, and TOBY) are summarized as follows:

- Near-term infants born at 36 weeks' gestation or more with birth weight of 1800 to 2000 g or more, younger than 6 hours at admission.
- Evidence of acute event around the time of birth:
 - Apgar score of 5 or less at 10 minutes after birth
 - Severe acidosis, defined as pH level of less than 7 or base deficit of 16 mmol/L or less (cord blood or any blood gas obtained within 1 h of birth)
 - Continued need for resuscitation at 10 minutes after birth.
- Evidence of moderate to severe encephalopathy at birth: At least two of the following:
 - Lethargy, stupor, or coma
 - Abnormal tone or posture
 - Abnormal reflexes [suck, grasp, Moro, gag, stretch reflexes]
 - Decreased or absent spontaneous activity
 - Autonomic dysfunction [including bradycardia, abnormal pupils, apneas]
 - Clinical evidence of seizures.
- Moderately or severely abnormal amplitude-integrated electroencephalography (aEEG) background or seizures (CoolCap and TOBY).

Many theoretical concerns surround hypothermia and its side effects, which include coagulation defects, leukocyte malfunctions, and pulmonary hypertension, worsening of metabolic acidosis, and abnormalities of cardiac rhythm, especially during rewarming. Although all these trials suggest, cooling is well tolerated and not associated with any increase in death or serious adverse events.

Several meta-analysis have been conducted and indicate that that therapeutic hypothermia is beneficial to term newborns with hypoxic-ischemic encephalopathy.

- In a Cochrane review,²¹ Jacobs et al found that therapeutic hypothermia results in significant reduction in the following: Combined outcome of mortality or major neurodevelopmental disability at age 18 months [relative risk (RR), 0.76; 95% confidence interval (CI), 0.65-0.89], with a number needed to treat (NNT) of 7 (95% CI, 4-14).
- Meta-analysis by Schulzke et al²² concluded that significant benefit of hypothermia on the composite outcome of death or disability (RR, 0.78; 95% CI, 0.66-0.92) with an NNT of 8 (95% CI: 5-20).

PROCEDURE OF HYPOTHERMIA

Indication: As above

Initiation time: Cooling must begin early, within 6 hours of injury. However, experimental evidence strongly suggest that the earlier the better.

Duration of hypothermia therapy: The optimal duration of brain cooling in the human newborn has not been established. In most of the clinical trials, it is for 72 hours.

Methods:

Two methods have been used in clinical trials:

- Selective head cooling
- Whole body cooling.

In selective head cooling, a cap (CoolCap) with channels for circulating cold water is placed over the infant's head, and a pumping device facilitates continuous circulation of cold water. Nasopharyngeal or rectal temperature is then maintained at 34 to 35°C for 72 hours.

In whole body hypothermia, a cooling blanket wrapped around the baby is necessary for keep the core temperature in the desired range.

The relative merits and limitations of these two methods have not been established.

In resource constrained setting like ours, few feasibility trials of achieving hypothermia with ice packs have been tried but those have to undergo rigorous safety studies to test their efficacy and safety.

Rewarming Method

Rewarming is a critical period. In clinical trials, rewarming was carried out gradually, over 6 to 8 hours.

PROGNOSIS

Clinical criteria which suggest bad prognosis are:

- *Urine output:* If an infant had good urine output, the chances of mortality and neurologic injury are 5% and 10%, respectively, whereas oliguria beyond 24 hours

resulted in rates of mortality and neurologic injury of 33% and 67%, respectively.²⁵ Acute tubular necrosis has not been shown to be of good prognostic value.

- *Severity and duration of encephalopathy:* Grading schemes for the severity of HIE have been used as predictors of long-term neurological function. Almost all infants with mild encephalopathy have a good outcome. The outcome of infants with moderate encephalopathy is less predictable and up to 75% of infants may make a normal recovery. Persistence of stage 2 for more than 7 days or stage 3 at any time is associated with later neurologic impairment or death.²⁶ When the neurologic syndrome was severe, 80% of infants died and the remaining 20% had significant sequel.
- *Persistent seizures:* If the seizures are persistent or recalcitrant to anticonvulsant medications, they are nearly uniformly associated with death or significant neurologic deficits.
- *Discharge neurological examination:* If a newborn's neurologic examination returns to normal by 1 to 2 weeks, the infant likely will be normal at follow-up.

Laboratory finding which suggest poor prognosis:

- *EEG:* EEG has proved to be a more reliable predictor of outcome than the early neurological examination. Conventional and amplitude integrated EEG has been used to predict long-term neurological outcome in asphyxiated infants. At any time, a burst-suppression (especially when it is unresponsive to stimuli) or an isoelectric pattern is associated with poor outcome. If there is only mild depression early, there can be normal outcome. If there is depression after 12 days, poor outcome is expected. A normal EEG at 7 days predicts normal outcome.
- *CT scan:* Presence of cystic encephalomalacia on follow-up at 3 to 4 weeks on CT scan is suggestive of a very poor outcome.
- *MRI imaging:* The optimal timing of MRI scans for maximal prognostic power remains unresolved. This is in large part because of the natural evolution of brain tissue injury and its changing appearance on MRI studies. Because cerebral edema usually peaks around 3 days after birth and gradually resolved over the subsequent week, some authors have favored MRI studies at 72 hours for prognostic purposes. Specifically, a normal MRI scan at 72 hours is predictive of a favorable outcome where as diffuse edema with impaired cortical gray white differentiation or lesions in the dorsolateral thalamus or dorsal putamen are reliable predictors of poor outcome. When deep nuclear lesions occur in combination with brainstem injury, the outcome is particularly poor, with prominent disturbances in speech, sucking and swallowing.

Follow-up: Close physical therapy and developmental evaluations are needed prior to discharge in patients with birth asphyxia. The goal of follow-up is to detect impairments and promote early intervention for those infants who require it.

CONCLUSION

Hypothermia therapy should be conducted under strict protocols and reserved to regional referral centers offering comprehensive multidisciplinary care and planning to conduct long-term neurodevelopmental follow-up. Therapeutic hypothermia compared with usual care was associated with a significant reduction in the combined primary endpoint of death or moderate to severe neurodevelopmental disability. Hypothermia is the only effective neuroprotective therapy currently available for treatment of HIE and is safe and easy to administer.

Future prospects—A variety of potential neuroprotective treatments are being studied both to prevent the cascade of injurious effects after hypoxia-ischemia.

- *Erythropoietin:* In a recent study,²³ low-dose erythropoietin (300-500 U/kg) administered for 2 weeks starting in the first 48 hours of life decreased the incidence of death or moderate and severe disability at age 18 months (43.8% vs 24.6%; $P < 0.05$) in infants with moderate-to-severe hypoxic-ischemic encephalopathy.
- *Prophylactic barbiturates:* In a small randomized trial,²⁴ high-dose phenobarbital (40 mg/kg) was given over 1 hour to infants with severe hypoxic-ischemic encephalopathy. Treated infants had fewer seizures (9 of 15) than untreated control infants (14 of 16). Treated infants also had fewer neurological deficits at age 3 years (4 of 15) than untreated infants (13 of 16). Meta analysis on the use of anticonvulsants in perinatal asphyxia did not show any significant benefit of using prophylactic phenobarbitone and also in experimental animals phenobarbitone has been shown to causes apoptosis of brain cells during asphyxia. Hence at the current moment, phenobarbitone should be used for prophylactic reasons.
- *Allopurinol:* Slight improvements in survival and cerebral blood flow (CBF) were noted in a small group of infants tested with this free-radical scavenger in one clinical trial. Currently a multicentric trial called the ALLO-Trial is going on to document the efficacy of allopurinol in decreasing birth asphyxia when given to the mother.
- *Excitatory amino acid (EAA) antagonists:* MK-801, an EAA antagonist, has shown promising results in experimental animals and in a limited number of adult trials.
- Administration of growth factors (monosialo-gangliosides, brain derived growth factor), nitric oxide synthase inhibitors, and blockers of apoptosis.

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CHAPTER 10

Neonatal Seizures

RG Holla

INTRODUCTION

A seizure is defined clinically as a paroxysmal alteration in neurologic function, i.e. motor, behavior and/or autonomic function. Neonatal seizures constitute a medical emergency and clinicians caring for neonates with seizures are inevitably faced with questions regarding diagnosis, evaluation, management and outcome. Although, controversies exist in the diagnosis of neonatal seizures, once the diagnosis is made, these babies have significant mortality and risk for major neurodevelopmental disability. The immature neonatal brain has a limited repertoire of clinical manifestations. This developmental characteristic has bearing on the etiology, clinical, electrographic features and management of neonatal seizures. Since, EEG correlation of seizures is not always available and clinical features are often atypical and dependant on individual interpretation, management options need to be carefully considered before they are instituted. Most neonatal seizures occur over only a few days, and fewer than half of affected infants develop seizures later in life.

BIOCHEMICAL BASIS OF SEIZURES

Seizures occur when a large group of neurons undergo excessive, synchronized depolarization. The arborization of axons and dendritic processes as well as myelination are incomplete in the neonatal brain, resulting in weakly propagated, fragmentary seizures, whose electrical activity may not spread to surface EEG electrodes. Seizure threshold is determined by the interplay of excitatory vs. inhibitory neurotransmitter systems. The immature brain is more prone to seizures than the mature brain because of a developmental mismatch between excitation and inhibition. GABA (gamma-amino-butyric acid) is the principal inhibitory neurotransmitter and glutamate is the excitatory neurotransmitter.

RECEPTORS IN THE BRAIN

GABA(A) receptor is a transmembrane receptor located at the neuronal membrane which causes chloride ions to move down an electrochemical gradient, leading to hyperpolarization of the neuron, increase in the firing threshold and reduction in the action potential initiation. Increased chloride permeability can, however, depolarize the neuron under conditions of high intracellular chloride, a situation that exists in the neonatal period. This, in turn, can potentially excite the cell to fire or to activate calcium entry via voltage gated channels, leading to persistent depolarization. Certain ligands interact with the GABA(A) receptor to mimic GABA or to potentiate its response. These include benzodiazepines (increase pore opening frequency), barbiturates (increased pore opening duration), and certain steroids. Other compounds which interact with the GABA(A) receptor to attenuate the effects of GABA are flumazenil (a competitive benzodiazepine antagonist) and picrotoxin, which blocks the channel directly.

The GABA(B) receptor is metabotropic, coupled indirectly to potassium channels and causes an efflux of potassium from the neuron and suppresses action potential. GABA(B) receptors can mediate both post- and presynaptic inhibition.

In the newborn, the GABA system is functionally immature and characterized by decreased binding and uptake of GABA by receptors.¹ Interestingly, it has been found that the response to GABA(A) can be excitatory or inhibitory depending on the age, region of the brain studied and also upon the sex of the newborn animal.² In newborn rats, GABA has been found to have excitatory effects as immature neurons have high chloride content. The other major postsynaptic inhibitory system, the postsynaptic GABA(B), adenosine, and 5 hydroxytryptamine-G

protein coupled potassium channels, also have a delayed maturation.

The excitatory neurotransmitter, glutamate acts through the n-methyl-d- aspartate (NMDA), alpha-amino-3-hydroxy-5-methylisoxazole-4-proiponic acid (AMPA) and kainite (KA) receptors. In adults, the sequence of events for neuronal transmission consists of AMPA stimulation (leading to sodium entry), activation of NMDA channels and subsequent calcium entry into the cell, followed by postsynaptic inhibition by GABA. In the neonate, AMPA and postsynaptic GABA receptors are underdeveloped. This, coupled with the excitatory nature of presynaptic GABA receptors leads to a situation in which there is poor transmitter-gated inhibition, creating a milieu in which seizures are easily elicited.

EFFECTS OF SEIZURES ON THE NEONATAL BRAIN

The immature brain is more susceptible to epileptiform activity than its more mature counterpart. Although the immature brain is less vulnerable than the mature brain to seizure induced cell death, seizures in the developing brain can result in irreversible alterations in neuronal connectivity.

Seizures, particularly those that are prolonged, stress the neurons ability to generate energy necessary for cell function. Mitochondria which subserve this metabolic function produce reactive oxygen species during seizures, which then initiate excitotoxic injury by altering calcium homeostasis and energy production.

Seizures also affect the brain in other ways. Both electroclinical and electrographic (without overt clinical features) neonatal seizures produce an increase in cerebral blood flow velocity which is not related to an increase in blood pressure associated with the seizure.³ Regional hyperperfusion during clinical or EEG seizures has been reported on SPECT in neonates.⁴ This can adversely affect cerebral autoregulation in sick neonates. Experimental evidence also suggests that enhanced neuronal firing by itself, even without clinical seizures inhibits protein synthesis and causes cell damage. In newborn rats, seizures inhibit brain protein synthesis, reduced brain size and delayed developmental milestones.⁵ It is known that brain growth continues postnatally and mitotic activity continues in the human cerebellum during the first year of life, lending a unique vulnerability to the neonatal brain.

Alongside the increased vulnerability of the immature brain to seizures is the relative resistance to seizure induced excitotoxic damage when compared with adult counterparts. Although several hypotheses have been proposed, no consensus exists as to the mechanism of this neuroprotection. A family of mitochondrial uncoupling proteins (UCPs) which dissociate ATP production from oxygen consumption by reducing the membrane potential across the mitochondrial membrane, reducing the production of free oxygen reactive species has been proposed.

Higher levels of UCP have been reported in the neonatal brain.⁶

ETIOLOGY

Perinatal Asphyxia

Perinatal asphyxia is the single most important cause of neonatal seizures.⁷ Asphyxia insult may occur before, during or after the intrapartum period, the last accounting for about 10 percent of the cases. Seizures frequently present within the first 72 hours of life and may include subtle, clonic or generalized seizures. Intrauterine risk factors for asphyxia are related to poor placental transfer of oxygen and/or glucose due to pre-eclampsia, uteroplacental abnormalities such as abruption placentae, cord compression or placental insufficiency. Vascular insufficiency may also occur due to chorioamnionitis, antepartum trauma and meconium passage *in utero*. Using logistic regression analysis, Patterson et al identified antepartum anemia, antepartum bleeding, asthma, meconium-stained amniotic fluid, malpresentation, fetal distress and shoulder dystocia as risk factors for seizures in the first 72 hours in term neonates.⁸ Other risk factors include failure to use prophylactic antibiotics for antepartum infection, non-reassuring fetal heart rate patterns and lack of antepartum monitoring.⁹ It should be stressed that normal Apgar scores do not eliminate the possibility of severe intrauterine brain injury from asphyxia or other causes. As many as two-thirds of neonates who exhibit cerebral palsy at older ages had normal apgars at birth.¹⁰ Features of antenatal asphyxia injury in the form of joint contractures, persistent early cortical thumb, intrauterine growth restriction, etc. should be looked for.

Severe hypoxic insults can result in frequent seizures in the first week of life despite multiple medications at supratherapeutic dosages.

Hypocalcemia and Hypomagnesemia

Hypocalcemia may be associated with seizures, and may manifest at two distinct stages of the neonate's life as early or late hypocalcaemia. Early hypocalcemia (generally presents within 48 to 72 h after birth) may be accompanied by other epileptogenic situations such as hypoxic ischemic encephalopathy which may contribute to the seizure.¹¹ The outlook for neonates with seizures due to late onset hypocalcemia is generally good. Apart from the use of phosphate rich formula feeds, maternal hypovitaminosis D is an important cause of hypocalcemia in the neonate.

Hypoglycemia

Defined as a blood sugar level less than 45 mg/dl, hypoglycemia may cause seizures by itself, or in association with other comorbid conditions, e.g. hypocalcemia, hypoxic ischemic encephalopathy, and cranial trauma, which may

lower the threshold for seizures. Inborn errors of metabolism should be sought for in cases of persistent hypoglycemia. Low blood glucose substrate for neuronal metabolism and altered membrane excitability may both contribute to seizures in hypoglycemia. Jitteriness, apnea and altered tone are clinical may be the only clinical sign of hypoglycemia. Defect in glucose transport can also cause hypoglycorrachia and seizures in the absence of low blood glucose levels.

Sodium Disturbances

Hyponatremia (serum sodium less than 135 mmol/L) can occur in a variety of clinical situations in the neonatal intensive care unit. Increased losses, inadequate intake, diuretic use and clinical conditions like necrotizing enterocolitis can be associated with hyponatremia. Hypernatremia or its rapid correction may also be associated with seizures.

Cerebrovascular Lesions

Hemorrhagic and ischemic cerebral lesions are usually associated with seizures. In the preterm neonate, intraventricular hemorrhage is associated with seizures in about half the cases. Subtle seizures are seen frequently with this type of hemorrhage. Other hemorrhagic lesions include subarachnoid, subdural and intracerebral hemorrhages. Subarachnoid hemorrhage is more common in full term infants. The early appearance of neonatal jaundice in a neonate with seizures and abnormal sensorium should alert the clinician to the possibility of intracranial hemorrhage.

Cerebral infarction may occur in the antepartum or postnatal period. Venous infarcts due to lateral or sagittal sinus thrombosis may occur secondary to sepsis, polycythemia and dehydration. Deep white matter infarctions may follow intraventricular hemorrhage or hypocarbia in the preterm neonate.

Infection

Encephalopathy associated with TORCH, enterovirus or parvoviral infections may manifest with seizures. Seizures due to neonatal herpes simplex infection are associated with severe EEG abnormalities. Leptomenigeal inflammation, abscess or cerebrovascular occlusion associated with sepsis may be responsible for seizures.

Malformations

Neonates with lissencephaly, pachygyria and polymicrogyria may manifest seizures in the neonatal period.

Inborn Errors of Metabolism

Neonatal seizures may accompany nonketotic hyperglycinemia, sulfite oxidase deficiency, multiple carboxylase

deficiency and urea cycle disorders. Diagnostic work-up should include blood gas analysis, serum ammonia and blood sugar estimation. Zellweger syndrome and neonatal adrenoleukodystrophy are associated with high levels of very long chain fatty acids and characteristic findings on MRI. In pyridoxine dependency, low levels of pyridoxal phosphate, the active form of pyridoxine lead to inadequate synthesis of GABA, resulting in severe, resistant, early neonatal (and often fetal) seizures. The diagnosis is established by the administration of 50 to 100 mg of pyridoxine intravenously.

Drug Induced Seizures

Drugs such as barbiturates, alcohol, heroin, cocaine and methadone can cause irritability and seizures during withdrawal, as occurs in infants of mothers addicted to these substances. Inadvertent injection of local anesthetic agent into the fetal scalp during par cervical block can cause refractory seizures.

Epileptic Syndromes

Primary epileptic syndromes such as Ohtahara syndrome generally present beyond the neonatal period and are associated with myoclonic seizures and cerebral malformations (e.g. Aicardi syndrome or porencephaly). Other disorders to be excluded are neurocutaneous syndromes, including incontinentia pigmenti and tuberous sclerosis.

Familial Neonatal Seizures

Benign familial neonatal convulsions constitute a rare disorder with autosomal dominant inheritance of abnormality in the voltage gated potassium channel genes located at *20q13.3* and *8q24*. Seizures generally occur on the second or third day of life in otherwise healthy neonates and tend to persist. They are mainly clonic, sometimes with apneic spells; tonic seizures have rarely been described, the outcome is favorable, but secondary epilepsy may occur in 10 to 15 percent. Diagnosis is by exclusion of other etiologies and should include a work-up for infectious, metabolic and structural abnormalities.

Benign Neonatal Seizures

Benign idiopathic neonatal convulsions occur around the fifth day of life (day 1 to day 7, with 90% between day 4 and 6) in otherwise healthy neonates. Seizures are often multifocal clonic. The diagnosis is one of exclusion. Seizures usually resolve by 24 hours. The outcome is good, but increased risk of minor neurological impairment has been reported.

CLINICAL FEATURES AND CLASSIFICATION

Normal neonatal behavior can at times consist of stereotypic movements under normal circumstances or when

the neonate is under the effect of medications. Ideally, therefore, all suspected seizures should be confirmed by electroencephalography (EEG), keeping in mind, subcortical seizures may not have typical findings on the EEG.

The rarity of generalized tonic-clonic seizures in the neonate are related to the anatomical and physiological immaturity of the neonatal nervous system such as incomplete myelination which prevents highly organized, synchronous seizure activity.

The clinical classification of neonatal seizures has traditionally subdivided seizures into subtle, clonic, tonic and myoclonic.

Clonic seizures are characterized by rhythmic, repetitive movements of isolated parts of the body.

Focal clonic seizures involve one body part.

Multifocal clonic seizures involve several parts of the body simultaneously or in sequence with migration in a random fashion.

Myoclonic seizures represent very brief isolated jerks of parts of the body.

Tonic seizures involve stiffening of parts of the body and may be generalized or focal.

Subtle seizures consist of eye deviation, oral-buccal movements or patterned movements of the extremities like bicycling.

Mizrahi and Kellaway¹² showed that not all such clinical spells in neonates represented seizures. Using video-EEG, it was shown that most clonic seizures, myoclonic seizures and focal tonic seizures had definite epileptiform EEG correlates and thus had a definite epileptic pathogenesis. Generalized tonic seizures, and most forms of subtle seizures, except for isolated eye deviation, did not have any EEG correlate and thus were not felt to be true epileptic seizures. Seizures with no relationship or an inconsistent relationship to EEG seizure activity were correlated to diffuse processes such as hypoxic-ischemic encephalopathy and a poor short-term outcome. The authors proposed that these nonepileptic spells represented abnormal brainstem release reflexes, possibly due to loss of cortical inhibition from cortical damage. The classification proposed by Mizrahi and Kellaway is shown in Table 1.

INVESTIGATIONS

The sizeable differential diagnosis of a neonatal seizure demands that the initial investigations concentrate on the common etiologies requiring prompt treatment. Certain clues to the etiology may be present, such as a history of perinatal asphyxia, but other causes such as hypoglycemia, hypocalcemia and CNS infection may coexist and initial sampling should include a search for these. Laboratory samples to be collected before starting treatment should include blood glucose and serum electrolytes including calcium and magnesium. CSF examination should include a search for xanthochromia, pleocytosis, glucose

Table 1: Etiology of neonatal seizures

S.No	Cause
1.	Hypoxic-ischemic encephalopathy
2.	Intracranial hemorrhage
3.	Cerebral infarction
4.	Cerebral malformations
5.	Meningitis/septicemia
6.	Metabolic
7.	Hypoglycemia
8.	Hypocalcemia, hypomagnesemia
9.	Hypo/hyponatremia
10.	Inborn errors of metabolism
11.	Pyridoxine dependency
12.	Kernicterus
13.	Maternal drug withdrawal
14.	Idiopathic
15.	Benign idiopathic neonatal seizures
16.	Neonatal epileptic syndromes
17.	Congenital infections
18.	Injection of local anesthetic into scalp

and culture. TORCH titers, PCR for herpes virus, lactate, pyruvate and metabolic screen should be performed in the CSF where such conditions are suspected. In the absence of meningitis, a persistently low CSF glucose suggests a glucose transporter defect. Other disorders that require exclusion are inborn errors of metabolism for which arterial blood gas analysis, serum ammonia, amino acid profile, and assessment for organic acidurias. Indirect markers of hypoxia such as azotemia, abnormal liver function tests, and nucleated red blood cells on peripheral smear should be looked for.

Imaging

Each imaging modality available for neonates with seizures vary in terms of level of expertise to perform and interpret, convenience and interpretative quality. Neuroimaging in a case of neonatal seizures may help in diagnosing the etiology of the seizures and measuring the extent of severity of the cerebral insult.

Cranial sonography is a good bedside modality and helps to rule out intracranial hemorrhage, major malformations and abscesses and cerebral edema and should be performed in all sick neonates with seizures. Limitations of neurosonography include its inability to detect subarachnoid and subdural hemorrhage. Serial ultrasound studies are of greater value than a single examination, in both the preterm and term population.

In term infants with seizures with a history of neonatal encephalopathy, significant birth trauma, and evidence of low hematocrit and/or coagulopathy, a noncontrast CT should be performed to look for hemorrhage. In other newborns with encephalopathy or if CT findings are inconclusive, MRI should be performed between days 2 and 8 to assess the location and extent of injury.

In newborns with encephalopathy, CT scans are useful to identify the major pattern of injury on the third day of life while diffusion-weighted MRI is best able to identify cortical abnormalities, stroke or white matter injury. Subsequently (in the second week of life) the extent of cortical injury should be discernible by T₁- and T₂-weighted scans.

Electroencephalography

An electroencephalography may be useful to detect suspect seizures, to prognosticate the outcome, assess the severity of brain dysfunction and to decide the duration of antiepileptic medications.

Neonatal EEG patterns change with postnatal and gestational age and interpretation requires experience. While the EEG is of value in the diagnosis of electrical seizure, pathognomonic features are rarely present. Abnormal patterns include burst suppression, electrocerebral inactivity, low voltage invariant patterns, persistently slow background and multifocal sharp waves on the interictal EEG. Cerebrovascular disease is generally associated with persistent lateralized epileptiform discharges (PLEDs). Ictal patterns include abnormalities of background and focal abnormalities lasting for 10 sec or more.¹³ The duration of seizure patterns varies; status epilepticus in the neonatal period is defined as continuous seizure activity lasting for more than 30 min or 50 percent of the recording time.

Amplitude integrated EEG and cerebral function monitoring: The term amplitude integrated EEG is a method for electrocortical monitoring in which the EEG signal is recorded from one pair of biparietally placed electrodes. The signal is amplified and passed through a filter, which attenuates activity between 2 to 15 Hz in order to minimize artifactual activity from sources such as sweating, muscle activity and electrical interference. The band width in the output reflects variations in minimum and maximum electrical amplitudes, both of which depend on the maturity and severity of the illness. Cerebral function monitor (CFM) is the equipment used to monitor aEEG at the bedside. The normal background pattern consists of a continuous trace with a voltage of 10-25 μ V. Discontinuous traces, bursts and periods of inactivity suggest underlying abnormality. Seizures are recognized as a rapid rise in both upper and lower margins of the trace. Status epilepticus is associated with a "saw toothed" pattern.¹⁴ The advantage of 'aEEG' is its immediate availability, appropriate for bedside long-term monitoring, ease of application and interpretation. While it is not as sensitive in the detection

of seizures as conventional EEG, it is an excellent bedside monitoring tool, particularly in the pharmacologically paralyzed neonate to detect cerebral (and seizure) activity that would be missed clinically and for the prediction of outcome in the neurologically compromised neonate.

DIFFERENTIAL DIAGNOSIS

The most common mimic of seizures is jitteriness, which is a stimulus sensitive tremulousness not associated with gaze abnormalities or autonomic dysfunction and can be suppressed by passive flexion of the limb. Benign neonatal sleep myoclonus is bilateral or unilateral, synchronous or asynchronous myoclonus that occurs during active sleep and is often confused with seizures. Other non-seizure movement disorders seen in neurologically affected newborns include stimulus induced myoclonus and hyper-reflexia (Table 2).

Neonatal seizures may result from a variety of causes, some transient, not associated with structural abnormalities and are to an extent reversible in terms of neurological outcome. The age of the neonate at the onset of neonatal seizures gives a clue to the underlying disorders shown in Table 3 and Flow chart 1.

MANAGEMENT

The general principles of management of neonatal seizures are similar to that in older children, i.e. treatment of the underlying cause and specific management of

Flow chart 1: Management protocol for neonatal seizures

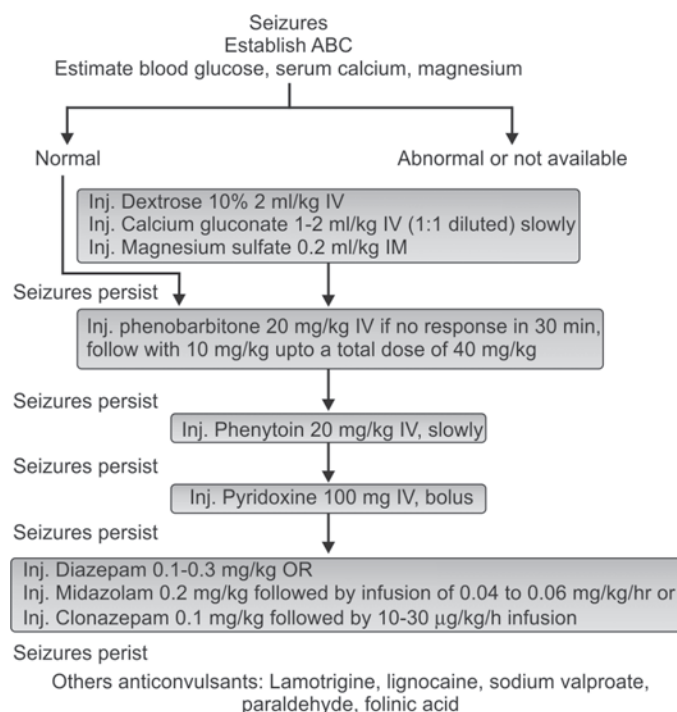


Table 2: Classification and characteristics of neonatal seizures (Modified from scher)

<i>Seizure class</i>		<i>Characterization</i>	<i>Provocation/suppression</i>	<i>Etiology</i>
Focal clonic		Repetitive rhythmic contraction of muscle groups, multi- or unifocal, synchronous or asynchronous	Cannot be suppressed by restraint	Epileptic
Focal tonic		Sustained posturing of single limbs, asymmetric posturing of trunk, sustained eye deviation	Cannot be provoked by stimulation/suppressed by restraint	
Generalized tonic		Sustained symmetrical posturing of trunk, neck, limbs	Provoked/intensified by stimulation, suppressed by restraint/repositioning	Epileptic or nonepileptic
Myoclonic		Random, single, rapid contractions of muscle groups, generalized, focal, fragmentary	Provoked by stimulation	
Spasms		Flexor, extensor, mixed	Cannot be provoked by stimulation/suppressed by restraint	Nonepileptic
Motor automatisms (nonepileptic behavior)	Ocular signs	Random roving eye movements, nystagmus	Provoked/intensified by tactile stimulation	
	Oral-buccal-lingual movements	Sucking, chewing, tongue protrusion	Provoked/intensified by tactile stimulation	Nonepileptic
	Progression movements	Rowing, swimming, bicycling, pedaling	Provoked/intensified by tactile stimulation, suppressed by repositioning/restraint	
	Complex purposeless movements	Sudden arousal, transient increase in random limb activity	Provoked/intensified by stimulation	

Table 3: Differential diagnosis of neonatal seizures by day of presentation (Modified from Ferreiro)

<i>Day</i>	<i>Etiology</i>	<i>Example</i>
Day 1	Traumatic brain injury	Subdural, subarachnoid
	Hypoxia-ischemia	Intraparenchymal
	Stroke	Arterial more than venous
	Infection	Bacterial or viral
	Severe inborn error of metabolism	Nonketotic hyperglycinemia
	Hypoglycemia	Hypocalcemia,
Day 2	Electrolyte imbalance	hyponatremia
	Drug withdrawal	Maternal substance abuse
Day 3	Stroke	Venous thrombosis
	Traumatic brain injury	
	Inborn error of metabolism	Glucose transporter defect
Day 3	Partial inborn error of metabolism	Organic acidemia
	Benign neonatal seizures	aminoacidopathy
	Stroke	
	Drug withdrawal	Arterial or venous
	Traumatic brain injury	Maternal substance abuse

seizures. Certain limitations in the use of antiepileptic drugs in neonates include the following:

- Electrographic seizures do not always correlate with clinical seizure phenomena
- If electrographic criteria were used in the recognition and management of seizures, complete suppression is often not possible
- Few drugs have been formally tested in the neonatal population
- Oral preparations often cannot be used in neonates
- Complicated metabolism and pharmacokinetics of drugs in neonates limits their use in this population.

Phenobarbitone

Currently, this is the most commonly used first line drug in the management of neonatal seizures.

Mechanism of Action

Phenobarbitone acts by inhibition of GABA, particularly the chloride permeable GABA_A receptors. Phenobarbitone also inhibits glutamate mediated neuroexcitation.

Pharmacokinetics and Pharmacodynamics

Phenobarbitone is absorbed from the oral route although the absorption is erratic. After a single intramuscular dose, phenobarbitone has a volume of distribution of 0.81 to 0.97L/kg, the half-life is 103.4 hours and the rate of clearance is 6.4 ml/kg/hour.¹⁵ The half life is variably longer in sick newborns, being up to 400 hours in preterms and approximately 150 hours in the asphyxiated term newborn.¹⁶ The drug is metabolized in the liver and excreted through the kidneys and higher blood levels and toxicity are to be expected in hepatic and renal dysfunction. The drug circulates predominantly in the protein bound form and may be displaced by bilirubin to result in higher free levels in hyperbilirubinemia.

Usage

Phenobarbitone is used as the first line drug in the control of seizures. It is administered intravenously at a loading dose of 20 mg/kg. The drug should be infused at a rate no faster than 1 to 2 mg/kg per minute (to avoid cardiopulmonary depression). The dose with intramuscular administration should be 10 to 15 percent higher than the intravenous dose.¹⁷ Oral administration should not be used for patients who suffer frequent seizures or who are compromised. The refractory seizures characteristic of postasphyxial neurological injury is amenable to higher loading doses of 30 mg/kg given intravenously over a 15 minute period.¹⁸ Gal and colleagues used phenobarbitone as a single anticonvulsant in 71 cases of neonatal seizures. They reported 85 percent seizure control with effective therapeutic levels between 10.1 and 46.4 mg/L, with dose related incremental responses from 20 to 30 mg/kg when administered as a loading dose.¹⁹ A study comparing phenobarbitone with phenytoin showed that 13 out of 30 babies (43%) responded to phenobarbitone in a dose sufficient to achieve a plasma concentration of free drug of 25 µg/ml. The therapeutic range is generally considered to be 20 to 40 µg/ml (88-160 µmol/l).²⁰ The use of video EEG telemetry has opened new insights into the mechanism and treatability of seizures. Boylan et al²¹ studied fourteen neonates who were treated with a loading dose of 20 to 40 mg/kg of phenobarbitone. Four responded clinically as well as electrographically. In the remaining 10 neonates, electrographic seizures increased after treatment, whereas clinical seizures reduced, a phenomenon known as 'electroclinical uncoupling'. Three of these neonates were treated with second line anticonvulsants, of whom two responded. One of these had a normal neurodevelopmental score at one year, but the outcome for the remainder of the whole group was poor.

Adverse Effects and Precautions while Using

Phenobarbitone, still the most widely used first line anticonvulsant in the neonatal period, has long been known

to have long-term effects on brain growth. Newer studies have added to these concerns, with the demonstration of increased apoptotic neurodegeneration in the developing rat brain after exposure to phenobarbitone, phenytoin, and benzodiazepines.²² Apnea and hypotension may occur, especially with concomitant use of benzodiazepines.

The latent period between asphyxial injury and onset of seizure activity may provide a "therapeutic window" for prophylactic intervention. The seizures that follow hypoxic-ischemic brain injury occur 6 to 12 hours later in about half of the cases. In many instances, they are refractory to treatment and require higher doses of phenobarbital or additional anticonvulsants. It is possible that treatment during the latent period might be more effective and prevent or control seizure activity with less doses of the drug. Barbiturates administered in high doses reduce cerebral metabolic rate and cerebral edema and remove harmful free radicals.²³ Phenobarbitone was found to have adverse hemodynamic effects, limiting its use initially. However, the study by Hall et al using phenobarbitone in the dose of 40 mg/kg in severe birth asphyxia reported an improvement in long-term neurological outcome in 31 severely asphyxiated infants, is encouraging and practice guidelines to this effect are awaited.²⁴

Phenytoin

Phenytoin is used as an adjuvant to phenobarbitone therapy.

Pharmacology of Drugs

Phenytoin possesses antiseizure properties without causing significant sedation or depression of the central nervous system. In toxic doses, it may produce excitatory signs and at lethal levels, a type of decerebrate rigidity.²⁵

Mechanism of Action

Phenytoin acts by blocking voltage dependant sodium channels. By slowing the rate of recovery of these channels from inactivation, it limits repetitive firing of action potentials evoked by a sustained depolarization. Being highly lipid soluble, it enters the brain rapidly. The drug is poorly water soluble and has a high pH, a characteristic that precludes intramuscular administration. It is highly protein bound, and small variations of the proportion of free drug dramatically affect its actions. Protein binding is lower in neonates and is related to serum albumin, protein, and bilirubin concentrations.²⁵ Excretion of phenytoin is predominantly renal, the drug exhibiting first-order kinetics, and clearance is related inversely to the serum level. The elimination rate of the drug is concentration-dependent, and the half-life decreases after the first postnatal week. The half-life in neonates varies from 40 to 200 hours with a mean of 100 hours. Achievement of therapeutic levels

requires a loading dose. The drug precipitates in dextrose and this should not be used as a vehicle.

Painter et al²⁰ compared the relative efficacies of phenobarbitone and phenytoin and found that of 29 neonates given phenytoin at a dose of 15 mg/kg as first-line treatment, 13 (45%) responded. Fifteen babies, who failed to respond to phenobarbitone as a first line treatment, were given phenytoin; only four of these babies responded. Overall, the success of a combination of both drugs in controlling seizures was 60 percent. Similarly, Laroia reported that 30 percent of neonates who had received full loading doses of phenobarbitone and phenytoin continued to have seizures, suggesting that the severity of the seizures was a better predictor of the success of treatment than was the assigned agent.²⁶ Neonates with mild seizures or with a low seizures burden are more likely to have their seizures controlled regardless of the treatment assignment.

Perhaps the best known side effect of phenytoin is its propensity to cause cardiac arrhythmias and hypotension. Phenytoin should probably be avoided in neonates requiring inotropic support. The drug should be administered slowly, under cardiac monitoring at a rate not exceeding 1 mg/kg/minute. Long-term effects of phenytoin usage in neonates have not been systematically studied. Cerebellar growth and development occurs principally postnatally and the effects of phenytoin on the cerebellum raise concerns regarding its prolonged use. Ohmori et al reported pyknotic cells in the external granular layer (EGL), reduced size and weight of the cerebellum and poorly developed walking reflex and negative geotaxis on postnatal day 14 in mice following prolonged, early, exposure to phenytoin.²⁷

Valproate competes with phenytoin for binding sites on plasma proteins, leading to a marked increase in levels of free phenytoin when a combination is used. Concurrent administration of any drug which is metabolized by the cytochrome P450 pathway can increase plasma concentration by decreasing its rate of metabolism. Carbamazepine, which may enhance the metabolism of phenytoin, causes a well documented decrease in phenytoin concentrations. Interaction between phenytoin and phenobarbitone is variable.

Sodium Valproate

Sodium valproate is a simple branched chain carboxylic acid derivative. Valproate acts in a fashion similar to carbamazepine and phenytoin and appears to be mediated by a prolonged recovery of voltage activated sodium channels from inactivation. Valproate also influences GABA synthesis and breakdown, leading to an increase in GABA concentrations in the brain. There is also evidence that Valproate interferes with glutamate-mediated excitation and limits sustained repetitive neuronal firing through voltage- and use-dependent blockade of sodium channels. It is rapidly absorbed after oral administration with a

volume of distribution of 0.2 L/kg. Approximately 90 percent of the drug is protein bound and metabolism is predominantly through hepatic glucuronidation. In adults, the half-life is approximately 15 hours.²⁵ Valproate has been used in the neonatal period in cases of refractoriness to traditional anticonvulsants. Gal and colleagues²⁸ used it in six neonates who had ongoing seizures despite full doses of phenobarbitone, five of whom had been given at least two other anticonvulsants. Seizures were controlled in 5/6 (83%), and in four cases, other anticonvulsants were withdrawn and seizures were controlled with valproate monotherapy.

The plasma concentration required for therapeutic effect is 30 to 100 µg/ml. Dosages used in children typically start at 15 mg/kg/day and stepped up in increments of 5 to 10 mg/kg/day to 60 mg/kg/day.

Dosages in neonates have not been established. Following a loading dose of 10 mg/kg, one neonate studied by Alfonso et al had a 45 minutes serum level of 41 µg/ml and a three hour level of 33 µg/ml. In another neonate a dose of 25 mg/kg increased the 45 minutes level to 100 µg/ml and the 3 hours level to 78 µg/ml. Each 1 mg/kg dose increased the 45 minutes level and the subsequent 3-hour level by 4 µg/ml and 3 µg/ml, respectively. Hypotension occurred in an older child at an infusion rate of 30 mg/kg per hour (0.5 mg/kg per minute).²⁹ The maintenance dose of valproate is started at 20 mg/kg/day.

Valproate primarily inhibits drugs metabolized by CYP2C9 including phenytoin and phenobarbitone and those metabolized by UGT, thus inhibiting metabolism of lamotrigine and lorazepam. The drug occupies binding sites on albumin and displaces drugs and other metabolites from it. Hyperammonemia has been reported following the use of valproate in newborns.²⁸ Its long-term use has been found to be associated with apoptotic neurodegeneration in the developing brain.

Carbamazepine

Carbamazepine is structurally related to the tricyclic antidepressants. It is highly lipophilic and no intravenous preparation exists. The pharmacokinetic properties of carbamazepine are influenced by its limited aqueous solubility. Absorption following an oral dose is slow and erratic, with peak plasma concentrations being achieved after 4 to 8 hours. It is bound to plasma proteins to the extent of 75 percent and only free drug crosses over to the CSF. It is metabolized to the 10,11 epoxide, a compound as active as the parent drug. This is then further metabolized to inactive glucuronide products, which are excreted in the urine. The half-life is 7 to 15 hours.³⁰ Carbamazepine inhibits repetitive firing of action potentials by causing slowing of voltage activated sodium channels.

The use of carbamazepine in neonatal seizures is mainly anecdotal. Hoppen et al investigated the use of carbamazepine in ten preterm neonates weighing 630 to

3080 gram (gestation 23-34 weeks) in oral daily doses of 7 to 23 mg/kg/day in 2 to 3 divided doses. Seizures were controlled in nine out of 10 patients.³¹ Rapid loading using the oral preparation has been achieved in critically ill infants.

Phenobarbitone, phenytoin and valproate may increase the metabolism of carbamazepine by hepatic enzyme induction, while erythromycin may inhibit its metabolism.

Acute intoxication may lead to hyperirritability, seizures and respiratory depression. Long-term therapy may be associated with bone marrow depression.

Benzodiazepines

The benzodiazepines are a group of drugs which include diazepam, lorazepam, midazolam and clonazepam. They are generally used when seizures are refractory to first line anticonvulsants and act by increasing GABA-mediated inhibition through activation of the GABA_A receptor.

Although diazepam has a rapid onset of action, there also is very rapid brain clearance, and seizures are likely to recur. This property also makes maintenance therapy difficult. Diazepam has a half-life of 31 to 54 hours. Onset of action of lorazepam is 2 to 3 minutes after a loading dose and lasts for up to 24 hours. Pharmacokinetic studies by McDermott³² revealed a decreased volume of distribution and clearance, and a prolonged half-life in comparison with data from older children and adults. Lorazepam has the following advantages over diazepam: a less rapid redistribution (with longer anticonvulsant activity) and less sedation and respiratory depression.

Maytal and colleagues³³ administered IV lorazepam at 0.05 mg/kg in seven patients unresponsive to phenobarbitone and repeated it up to a total dose of 0.15 mg/kg. Lorazepam controlled seizures completely in six patients and decreased them in one child. Two patients needed only one dose, three patients received two doses, and two patients received three doses.

Midazolam, a short-acting benzodiazepine, is used to treat status epilepticus in older patients. It is associated with less sedation and respiratory depression than diazepam and lorazepam. Sheth and associates³⁴ studied its use in six neonates, in whom seizures persisted for more than 12 hours despite high-dose phenobarbitone therapy, at an initial infusion of 0.1 to 0.4 mg/kg per hour for 1 to 3 days. Clinical seizures were controlled within 1 hour in all six infants, and EEG seizures were controlled in four. Deshmukh³⁵ reported cessation of seizures in seven infants to whom they administered lorazepam at 0.05 mg/kg over 2 to 5 minutes. They noted no adverse events.

Overall, benzodiazepines are safe for newborns. In one study, 10/63 (16%) newborns had 14 documented adverse events: seizures in six, hypotension in five, and respiratory depression in three.³⁶ Sedation and hypotonia have been reported with lorazepam use, probably aggravated in the

preterm infant due to limited excretion through the normal pathway of glucuronidation. Stereotypic movements may occur, especially myoclonus, perhaps related to benzyl alcohol.

Hypotension, apnea, and lethargy may occur and are potentiated by the concomitant use of phenobarbitone. There may be prolonged effects from diazepam because of the long half-life of its metabolite, N-desmethyldiazepam, especially in the preterm infant, so it may not be appropriate for sedation or even seizure therapy. It also is possible that sodium benzoate, contained in the IV preparation, may displace bilirubin from albumin.

Topiramate

Topiramate is a sulfamate substituted monosaccharide, used principally for partial seizures in older children and adults. It reduces voltage gated sodium currents in a manner similar to phenytoin, enhances postsynaptic GABA_A receptor currents and limits activation of the AMPA-kainate subtype of glutamate receptors.³⁷ Topiramate is rapidly absorbed from the gut and excreted predominantly unchanged. The half-life is approximately 24 hours.

There are no published reports of the clinical use of topiramate in neonatal seizures. However, it holds potential as a neuroprotective agent in hypoxic ischemic encephalopathy due to its action on the glutamate AMPA-kainate receptors, activation of which is thought to result in neuronal injury.

Lignocaine

Lignocaine has been used in refractory seizures. A 2 mg/kg loading dose, followed by infusion of 6 mg/kg per hour, produced an immediate effect in 18 infants, with control achieved within 30 minutes in another five. Ultimate control was obtained in 92 percent. No serious adverse events were seen.³⁸ Drug accumulation tends to be a problem with lignocaine. Rey and colleagues³⁹ administered lignocaine to 13 neonates, using decremental doses from 4 mg/kg/d to 1 mg/kg/d over four days. Seizures were controlled in 11 of the infants, with effective plasma concentrations between 3 and 6 mg/L. Clearance is decreased in the preterm infant.

Other Drugs

There are only anecdotal reports of the use of newer anticonvulsants like lamotrigine, vigabatrin, zonisamide and levetiracetam. Lamotrigine⁴⁰ was used in the dose of 4.4 mg/kg/day in one neonate who had refractory seizures that were not controlled with several anticonvulsants. Vigabatrin⁴¹ and zonisamide⁴² have been used for refractory seizures due to the Ohtahara and Aicardi syndromes, both associated with neonatal-onset seizures. The dose for vigabatrin initially was 50 mg/kg and increased up to 200

mg/kg. The zonisamide starting dose was 2.5 mg/kg and increased to 20 mg/kg.

Pyridoxine dependency is associated with refractory seizures, 1 to 4 Hz sharp and slow wave activity and responsiveness to 50 to 100 mg of intravenous pyridoxine.⁴³ The seizures may have a prenatal onset and other associated features include hypotonia, jitteriness, irritability, and exaggerated startle reflex.

The glucose transporter deficiency (De Vivo syndrome), should be considered when CSF glucose concentrations are low and other causes of hypoglycorrhachia have been excluded, such as systemic hypoglycemia or bacterial or fungal meningitis. If not treated, microcephaly and mental retardation occur. The condition is amenable to a ketogenic diet.

DURATION OF ANTICONVULSANTS

The duration of therapy depends on the etiology and the neurological status of the infant. Transient metabolic derangements causing seizures, which have been identified and corrected, do not require anticonvulsants beyond 3 to 4 days. Phenytoin is discontinued once intravenous therapy is stopped as it is difficult to maintain reliable levels orally. Phenobarbitone is stopped if the neonate has become neurologically normal prior to discharge. If the neurological examination is abnormal at discharge, the infant is closely followed up and the phenobarbitone continued. On follow-up, the neurological examination and EEG guide therapy. If the neurological examination and EEG are normal, anticonvulsants may be stopped.

PROGNOSIS

The long-term prognosis after neonatal seizures is directly related to the cause. Newborns with seizures related to

subarachnoid hemorrhage, transient metabolic disturbance like hypocalcemia and those with a normal background EEG generally do well, whereas those with a grade III or IV intraventricular hemorrhage have a high morbidity. Early onset of seizures is associated with the highest morbidity and mortality. The longer the seizure activity continues, the more likely the neonate is to have later neurological impairment. Table 4 outlines some poor prognostic features of neonatal seizures.

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Table 4: Poor prognostic factors in neonatal seizures

S. No.	Parameter	Findings
1.	Clinical	Prematurity Early onset of seizures (< 24 h) Three or more days with uncontrolled seizures Seizures lasting more than 30 minutes Need for multiple anticonvulsants for seizure control
2.	Underlying disease	Developmental defect, intraventricular hemorrhage, HIE, meningitis, persistent hypoglycemia
3.	Interictal EEG	Major background disturbances, burst suppression pattern, electrocerebral silence Status epilepticus PLED (Periodic lateralized epileptiform discharges)

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Respiratory Distress in Newborns

AK Dutta

Respiratory distress in newborn accounts for significant morbidity and mortality. It occurs in 5 to 12 percent of neonates. It may denote a significant life-threatening emergency. A working diagnosis should be made within few minutes of seeing the baby and treatment initiated. Then a detailed plan of history and management can be made and carried out.

At the time of birth, the fluid in the fetal lung is rapidly replaced by air. Associated with the lung inflation and increased oxygenation there is marked reduction in the pulmonary vascular resistance, with consequent increased pulmonary blood flow and closure of ductus arteriosus, foramen ovale and ductus venosus. As a result, the lungs take over the respiratory function previously carried out by the placenta. Many pathological processes can interfere with this normal sequence of events and give rise to respiratory distress in the newborn period.

DEFINITION

Respiratory distress is characterized by the following signs:

- *Tachypnea*: A respiratory rate great than 60/ minute.
- *Expiratory Grunt*: A physiological mechanism of preventing alveolar collapse by expiring against a partially closed glottis.
- *Chest recessions*: Which may be intercostals, subcostal, sternal, substernal or suprasternal.
- Central cyanosis.
- Working of accessory muscle of respiration especially flaring of alae nasi.

Presence of two or more signs persisting for four hours or more suggest respiratory distress.

CAUSES OF RESPIRATORY DISTRESS

It can be broadly classified into most common causes and less common but significant causes (Table 1). The causes

Table 1: Causes of respiratory distress in order of frequency

*Most common causes**

- Transient tachypnea of the newborn
- Respiratory distress syndrome (hyaline membrane disease)
- Meconium aspiration syndrome

Less common but significant causes

- Delayed transition
- Infection (e.g. pneumonia, sepsis)
- Nonpulmonary causes (e.g. anemia, congenital heart disease, congenital malformation, medications, neurologic or metabolic abnormalities, polycythemia, upper airway obstruction)
- Persistent pulmonary hypertension of the newborn
- Pneumothorax

** Listed in order of incidence*

of respiratory distress can also be broadly classified as per etiology that is non-respiratory and respiratory and in the respiratory causes as medical and surgical (Table 2). Accurate diagnosis is important for appropriate care. Rare causes should be considered when no cause is suggested by the initial history and examination.

TRANSIENT TACHYPNEA OF NEWBORN

Transient tachypnea of newborn (TTNB) is the most common cause of neonatal respiratory distress. A benign condition, it occurs when residual pulmonary fluid remains in the fetal lung tissue after delivery. Risk factors include male sex, macrosomia, maternal diabetes and cesarean delivery. The clinical presentation includes signs of respiratory distress immediately after birth or within two hours after birth. Symptoms can last for few hours to two days. Chest radiograph shows diffuse parenchymal infiltrates, a "wet silhouette" around the heart or interlobar fluid accumulation (Fig. 1).

Table 2: Causes of respiratory distress

<i>Nonrespiratory</i>	
<i>Congenital heart disease:</i> Hypoplastic left heart syndrome, obstructed total anomalous pulmonary venous drainage, critical coarctation of aorta	
Anemia	
Polycythemia	
Birth asphyxia	
Persistent pulmonary hypertension	
Sepsis	
Neuromuscular disorders	
Musculoskeletal disorders	
Metabolic disorders	
<i>Respiratory</i>	
<i>Medical:</i>	
Transient tachypnea of newborn	
Respiratory distress syndrome	
Congenital pneumonia	
Meconium aspiration syndrome	
<i>Air leaks:</i> Pneumothorax and pulmonary interstitial pneumonia	
Pulmonary hypoplasia	
Pulmonary hemorrhage	
<i>Surgical:</i>	
Choanal atresia, Pierre Robin sequence, diaphragmatic hernia, esophageal atresia with tracheoesophageal fistula, congenital lobar emphysema, cystic adenomatoid malformation	

RESPIRATORY DISTRESS SYNDROME

Respiratory distress syndrome (RDS) is the most common cause of respiratory distress in the premature infants correlating with the structural and functional lung immaturity. It is most common in infants born before 28 weeks gestation. Prevalence without antenatal steroids at <28 weeks GA is 60 percent, 28 to 31 weeks GA is 40 percent, 30 to 34 weeks is 15 percent and ≥34 weeks GA is 5 percent. Antenatal steroid therapy reduces this prevalence by 50 percent. The condition is more common in male infants. Incidence is approximately six times higher in infants of diabetic mothers.

The diagnosis of respiratory distress should be suspected when grunting, tachypnea and retractions occur in a premature infant immediately after birth. Chest radiograph shows homogeneous infiltrates and air bronchograms, indicating contrast in airless lung tissue seen against air-filled bronchi (Fig. 2).

MECONIUM ASPIRATION SYNDROME

Meconium-stained amniotic fluid occurs in approximately 15 percent of the deliveries. Ten to fifteen percent of these babies have meconium aspiration syndrome (MAS). MAS

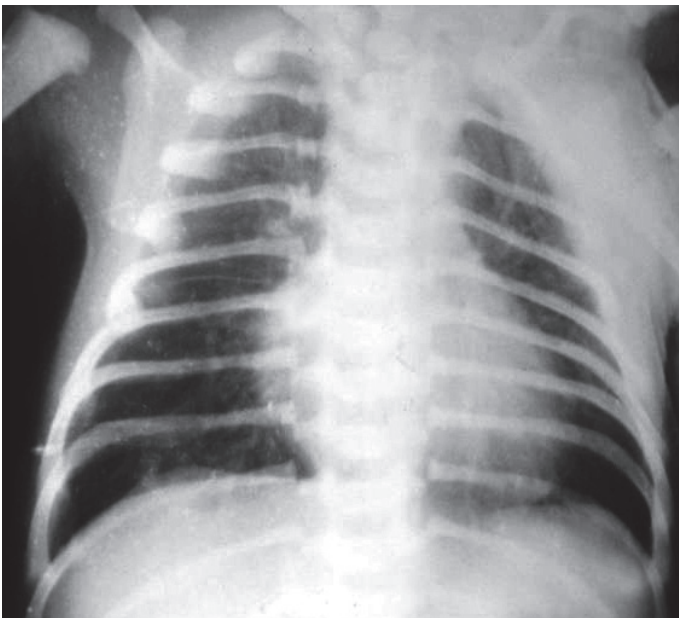


Fig. 1: Chest radiograph of newborn with transient tachypnea of newborn

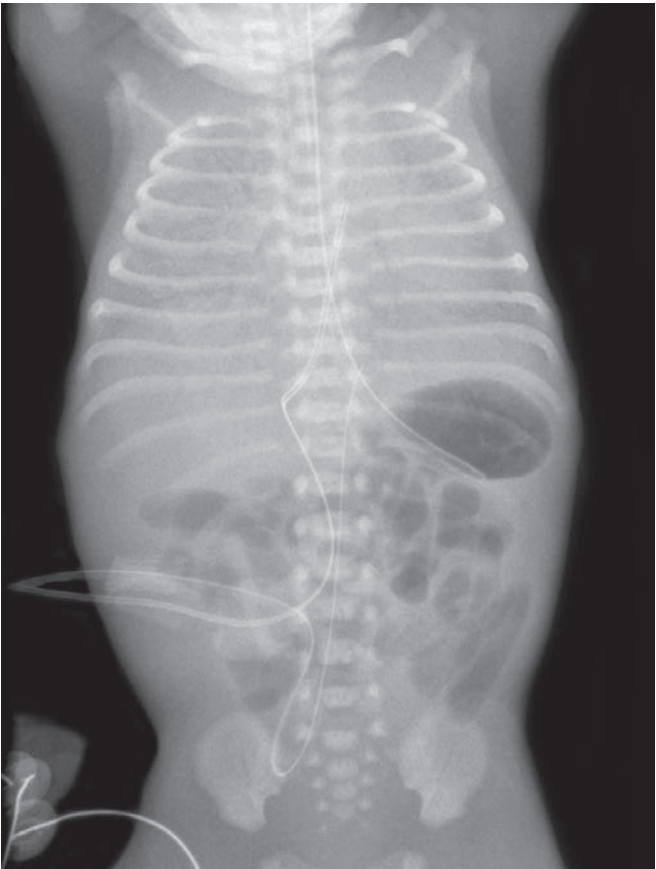


Fig. 2: Chest radiograph of newborn with respiratory distress syndrome

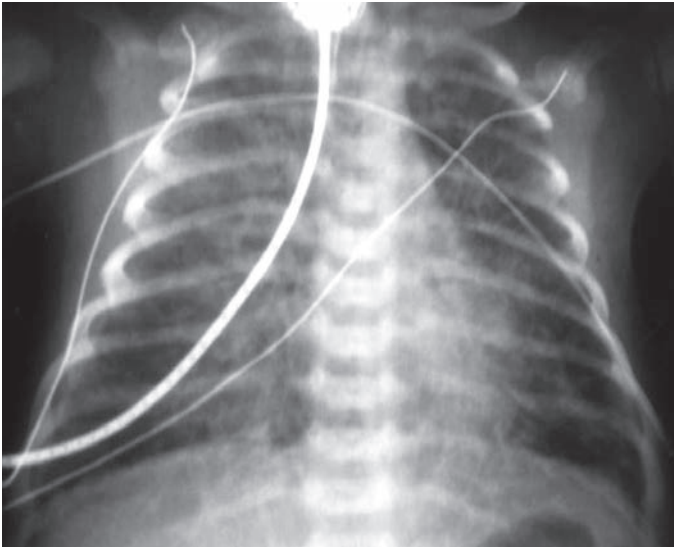


Fig. 3: Chest radiograph of newborn with meconium aspiration syndrome

causes significant respiratory distress because meconium is locally irritative, obstructive and a medium for bacterial growth. Chest radiographs show patchy atelectasis or consolidation (Fig. 3). There may be air leaks.

CONGENITAL PNEUMONIA

Risk factors for pneumonia include prolonged rupture of membrane, prematurity and maternal fever. Common pathogens include GBS, *Staphylococcus aureus*, *Streptococcus pneumoniae*, and gram-negative enteric bacilli. Unlike TTNB and RDS, bacterial infection takes time to develop, with respiratory consequences occurring hours to days after birth. Chest radiograph shows bilateral infiltrates. (Fig. 4). Pleural effusion may be present.

PERSISTENT PULMONARY HYPERTENSION OF NEWBORN

It is a condition characterized by marked pulmonary hypertension resulting from elevated pulmonary vascular resistance and altered pulmonary vasoreactivity, leading to right to left extrapulmonary shunting of blood across the foramen ovale and PDA. Persistent pulmonary hypertension of newborn (PPHN) may result from underdevelopment of lung together with vascular bed (CDH, hypoplastic lungs) and maladaptation of the pulmonary vascular bed to the transition occurring at the time of birth (perinatal stress, hemorrhage, aspiration, hypoxia, and hypoglycemia). The primary finding is respiratory distress with cyanosis. This may occur despite adequate ventilation. In an infant with pulmonary disease PPHN should be suspected when there is marked lability in oxygenation. Cardiac signs may include a prominent right ventricular impulse, a single second heart sound, and a murmur of tricuspid insufficiency.

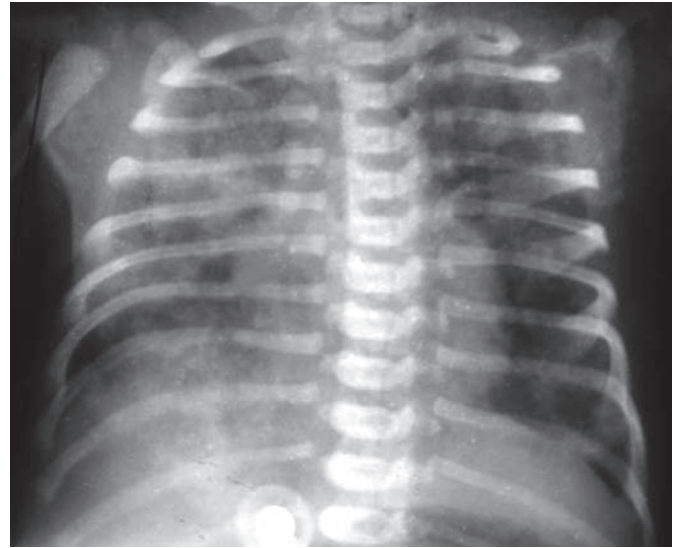


Fig. 4: Chest radiograph of newborn with congenital pneumonia

The chest X-ray may show normal sized heart or cardiomegaly. If there is no associated pulmonary pathology, vascularity may be normal or decreased. Echocardiography is essential in distinguishing PPHN from congenital heart disease. It may show flattened or septum bowed to the left suggestive of pulmonary hypertension. Color Doppler may reveal evidence of tricuspid regurgitation.

PNEUMOTHORAX

It is defined as air in the pleural space, can be cause of neonatal respiratory distress. It can occur spontaneously or as a result of infection, meconium aspiration, lung malformation or ventilator barotraumas. The incidence of spontaneous is one to two percent in term and 6 percent in preterm babies. Presence of cyanosis, sudden increase in tachypnea, bradycardia and shock may suggest that there is tension pneumothorax. There may be asymmetric chest with a bulge on the affected side, decreased breath sounds on the affected side and shift of the cardiac apical impulse away from the affected side. In an emergency transillumination can help in making a decision about doing an urgent needle decompression. Chest radiograph is diagnostic. It may show displacement of the lung on the affected side away from the chest wall by a radiolucent band of air, a shift of mediastinum away from the affected side and depression of the diaphragm on the affected side (Fig. 5).

CONGENITAL DIAPHRAGMATIC HERNIA

Herniation of abdominal visceral contents through the posterolateral foramen of Bochdalek or the anterior foramen of Morgagni leads to Congenital diaphragmatic hernia (CDH). Presence of abdominal viscera in the chest during the fetal life prevents normal development of the

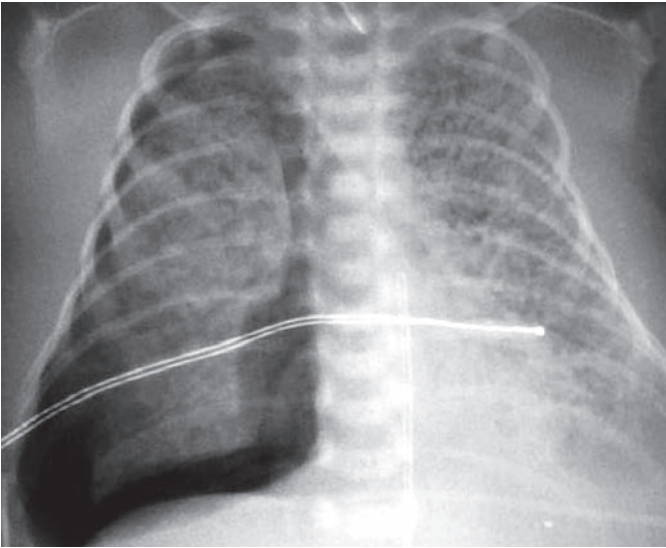


Fig. 5: Chest radiograph of newborn with right pneumothorax

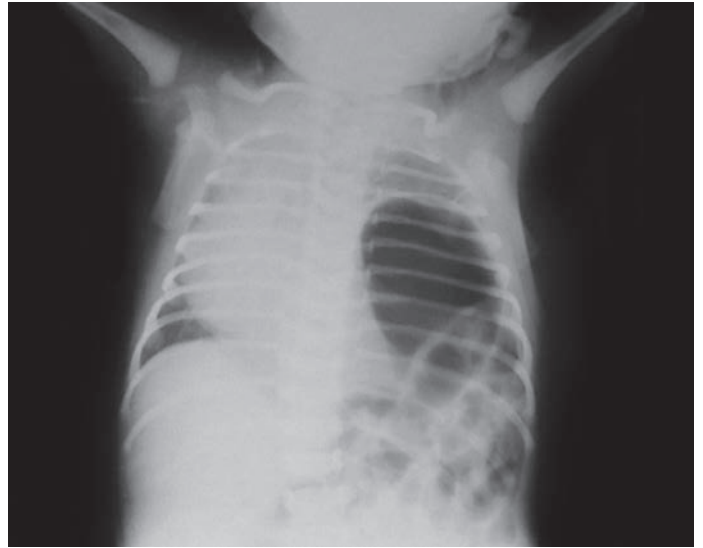


Fig. 6: Chest radiograph of newborn with congenital diaphragmatic hernia

lungs. A history of polyhydramnios is commonly present. Postnatally cyanosis, retraction tachypnea and grunting are commonly seen. On examination abdomen is scaphoid, the anteroposterior diameter of the chest is increased, mediastinum is shifted, and bowel sounds may be heard in the chest. Presentation may be delayed in the less severely affected babies. The diagnosis is made on chest radiograph which shows air filled bowel loops in the chest cavity with nonvisualization of diaphragmatic margin, mediastinal shift and relative paucity of abdominal gas (Fig. 6).

Congenital Cystic Adenomatoid Malformation

Congenital cystic adenomatoid malformation (CCAM) is characterized by a mass of cysts that may or may not intercommunicate. The primary defect is segmental bronchial atresia. Cysts may vary in size from few large cysts to a large number of microcysts. Symptoms of respiratory distress may develop soon after birth. Recurrent respiratory infection is common mode of presentation. Plain chest X-ray may show multiple air filled spaces (macrocyts) or a solid area within the lung (microcysts) (Fig. 7). CT of the chest is diagnostic (Fig. 8).

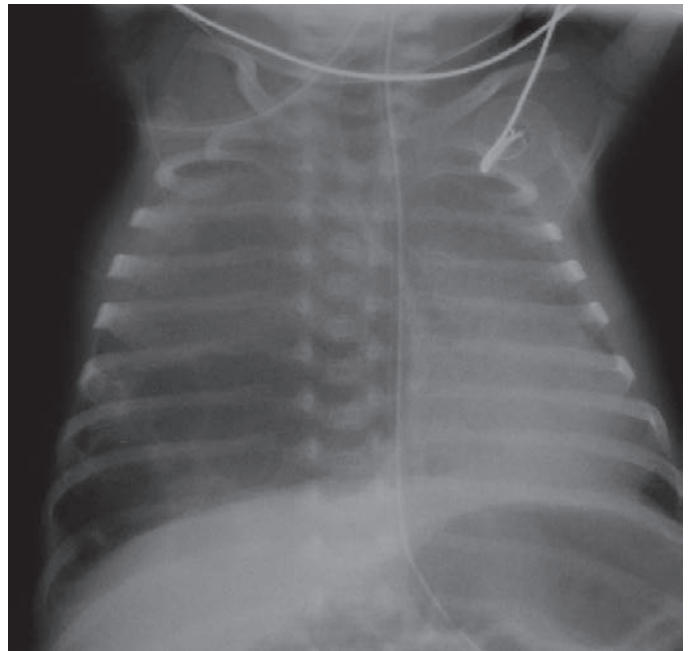


Fig. 7: Chest radiograph of newborn with CCAM

CONGENITAL LOBAR EMPHYSEMA

It is defined as postnatal over distention of one or more segments or lobes of the lungs. This over distended portion of the lung compresses the adjacent lung and compromises ventilation. Left upper lobe is involved most commonly. Males are affected three times as compared to females. The presentation is with respiratory distress. Physical examination reveals hyperresonance with decreased air entry on the affected side. Chest X-ray shows hyperlucent hyperexpanded area of the lung with compression or atelectasis

of the adjacent lobes of the lungs, depression of the diaphragm and mediastinal shift to the opposite side.

ESOPHAGEAL ATRESIA WITH OR WITHOUT TRACHEOESOPHAGEAL FISTULA

It is the most common surgical condition leading to respiratory distress. Neonates present soon after birth with frothing at the mouth or choking with attempted feeds or with manifestations of aspiration pneumonitis. An obstruction to the

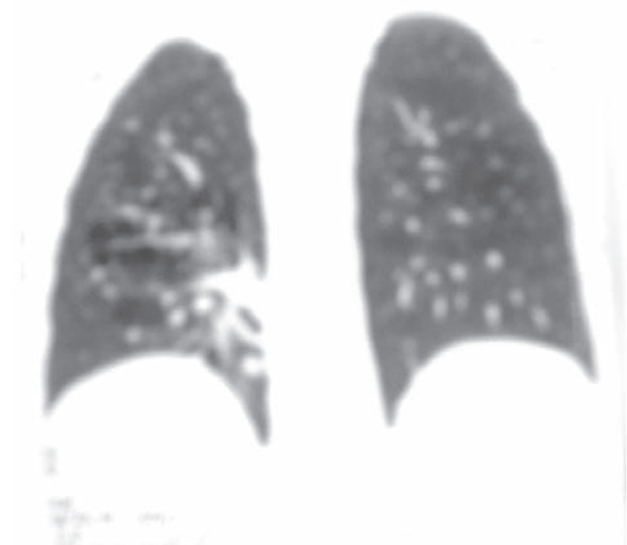


Fig. 8: CT chest of newborn with CCAM

passage of an orogastric tube at about 10 cm from mouth is usually diagnostic and dye studies are not required for confirmation. A chest X-ray showing coiling of an orogastric tube in upper pouch is fairly diagnostic (Figs 9A to C).

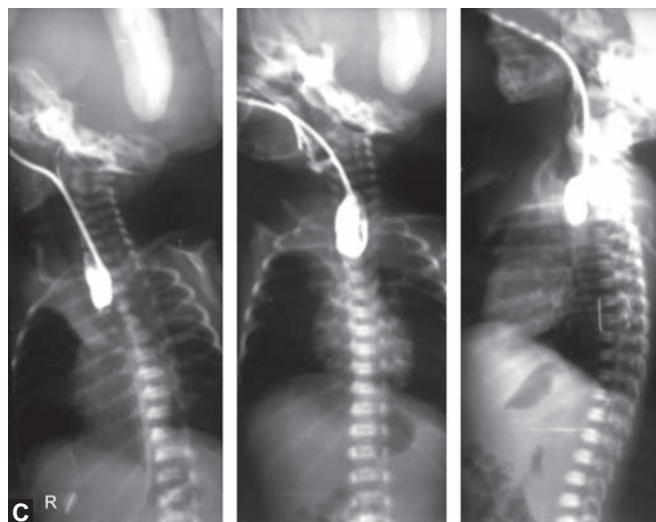
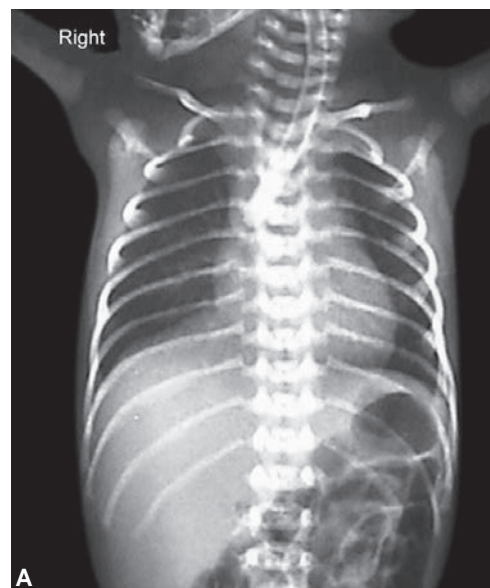
CHOANAL ATRESIA

It is a congenital blockage of the posterior nares caused by persistence of bony septum (90%) or a soft tissue membrane (10%). Choanal atresia which is bilateral and complete causes respiratory distress immediately after birth because neonates are obligate nose breathers. Diagnosis is suspected by inability to pass a catheter into the nasopharynx via either side of nose. CT nasopharynx is diagnostic (Fig. 10).

EVALUATION OF RESPIRATORY DISTRESS

History

A detailed history is critical to proper evaluation. The differential diagnosis changes with gestational age: respiratory distress syndrome typically affects preterm infants, whereas meconium aspiration syndrome affects term and post-term neonates. Antepartum infection status is important. Information about duration of rupture of membranes, color of amniotic fluid, maternal temperature, maternal tachycardia and fetal heart tracings status is vital to detect meconium aspiration and chorioamnionitis. Family history assists in identifying inheritable congenital defects. The onset and duration of respiratory symptoms also provides clues. Transient tachypnea of newborns begins early and improves with time. Conversely sepsis and pneumonia may have no early signs but may develop hours to days later. Respiratory distress syndrome begins early in premature infants without signs of spontaneous improvement.



Figs 9A to C: Chest radiograph of newborn showing esophageal atresia

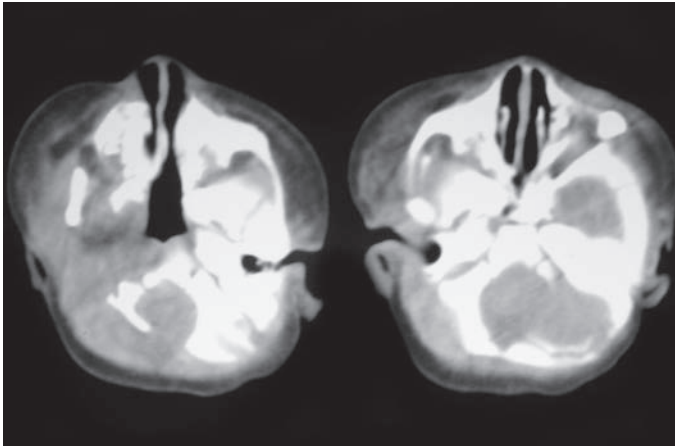


Fig. 10: CT nasopharynx of a newborn showing right sided choanal atresia

Examination

The severity of distress should be estimated with initial assessment. Mild distress may warrant observation and pulse oximetry. Severe distress, especially with a complicated birth history, requires immediate resuscitation, chest radiography and lab tests (Flow chart 1).

Severity of Respiratory Distress

Silverman-Anderson and Downes' scores (Tables 3 and 4) are used to grade the severity of respiratory distress. While the Silverman-Anderson score is more suited for preterm with respiratory distress, the Downes' score is more comprehensive and can be applied to any gestational age and condition. Scoring should be at hourly intervals and chart maintained to determine progress. A progressively increasing FiO_2 requirement to maintain saturation of 90

Flow chart 1: Management of respiratory distress

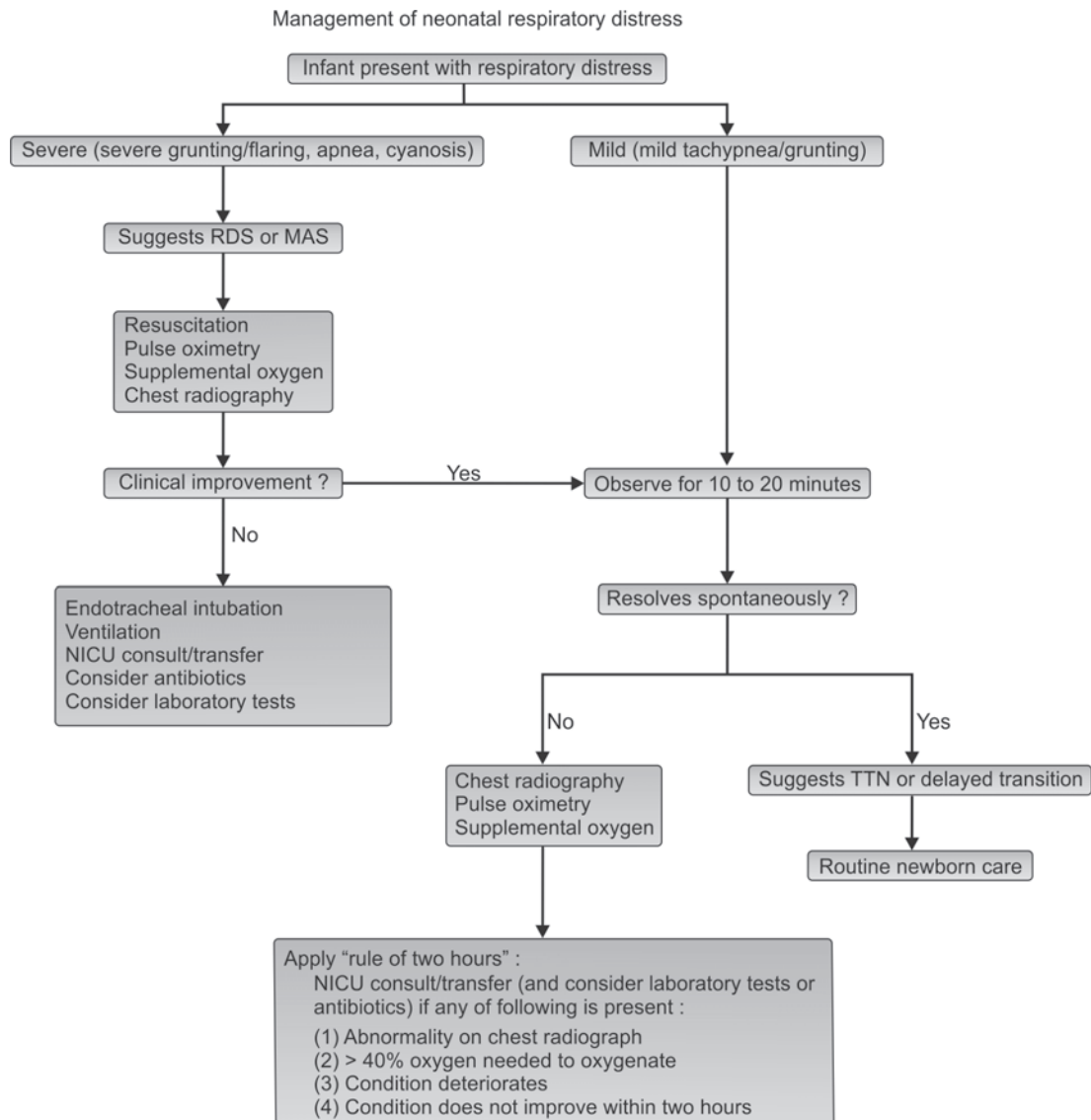


Table 3: Silverman Anderson retraction score

Score	Upper chest retraction	Lower chest retraction	Xiphoid retraction	Nasal dilatation	Grunt
0	Synch	None	None	None	None
1	Lag on inspiration	Just visible	Just visible	Minimal	Stethoscope only
2	See-saw	Marked	Marked	Marked	Naked ear

A score of >6 is indicative of impending respiratory failure

Table 4: Downes' score

Score	Respiratory rate	Cyanosis	Air entry	Grunt	Retraction
0	<60/min	Nil	Normal	None	Nil
1	60-80/min	In room air	Mild ?	Ausc with stethoscope	Mild
2	>80/min	In $\geq 40\%$	Marked ?	Audible with naked ear	Moderate

A score of >6 is indicative of impending respiratory failure

to 92 percent in preterm and 94 to 96 percent in a term baby is also a sensitive indicator of the severity and progress of distress.

Clues to likely diagnosis can be picked up on examination of the neonate. A preterm baby weighing <1500 grams with retractions and grunt is likely to have RDS. A term or post-term baby born through meconium stained amniotic fluid with increase in the anteroposterior diameter of the chest is likely to have MAS. A near term baby with no risk factors and mild distress most probably has TTNB. A growth retarded baby who looks plethoric might be having respiratory distress due to polycythemia.

An obstruction to the passage of an orogastric tube at about 10 cm from mouth is suggestive of esophageal atresia and TEF. Inability to pass 5F catheter through the nostril of a term baby is suggestive of choanal atresia. A baby with respiratory distress should be checked by placing a cold light over the chest light source over the chest wall in a darkened room. Transillumination is suggestive of air leak.

Investigations

Essential investigations for all cases of respiratory distress include chest radiograph, arterial blood gas, sepsis screen, blood culture, and blood glucose and serum calcium (Table 5).

The distinguishing features of TTNB, RDS and MAS three of the most common causes of respiratory distress presenting in a NICU have been summarized in the Table 6.

TREATMENT

General Supportive Treatment

Clearing of airway, ensuring adequate breathing and circulation are the first line of management. A baby in obvious respiratory distress needs to be on continuous pulse oximeter monitoring to decide when intubation and ventilation is

Table 5: Lab evaluation for respiratory distress

Test	Indication
Blood culture	May indicate bacteremia Not helpful initially because results may take 48 hours
Blood gas	Used to assess degree of hypoxemia if arterial sampling, or acid/base status if capillary sampling (capillary sample usually used unless high oxygen requirement)
Blood glucose	Hypoglycemia can cause or aggravate tachypnea
Chest radiography	Used to differentiate various types of respiratory distress
Complete blood count with differential diagnosis	Leukocytosis or bandemia indicates stress or infection Neutropenia correlates with bacterial infection Low hemoglobin level shows anemia High hemoglobin level occurs in polycythemia Low platelet level occurs in sepsis
Lumbar puncture	If meningitis is suspected
Pulse oximetry	Used to detect hypoxia and need for oxygen supplementation

required. Warm humidified oxygen is given with a head box preferably with a FiO₂ meter and pulse oximeter monitoring to determine the amount of oxygen required. Soft nasal cannula may also be used to give oxygen. Maintenance of correct temperature is essential. RDS and PPHN get

Table 6: Distinguishing features of TTNB, RDS and MAS

<i>Cause</i>	<i>Etiology</i>	<i>Timing of delivery</i>	<i>Risk factors</i>	<i>Clinical features</i>	<i>Chest radiography findings</i>
TTN	Persistent lung fluid	Any	Cesarean delivery Macrosomia Male sex Maternal asthma Maternal diabetes	Tachypnea Often no hypoxia or cyanosis	Parenchymal infiltrates “Wet silhouette” around the heart Intralobar fluid accumulation
RDS	Surfactant deficiency	Preterm	Male sex Maternal diabetes Preterm delivery	Tachypnea Hypoxia Cyanosis	Homogenous infiltrates Air bronchograms Decreased lung volumes
MAS	Lung irritation and obstruction	Term or post-term	Meconium stained amniotic fluid Post-term delivery	Tachypnea Hypoxia	Patchy atelectasis Consolidation

worsened if the baby is hypothermic. Electrolyte balance, fluid, calcium and glucose homeostasis are equally important. Fluids are usually started at a minimum of 60 ml/kg/day of 10 percent Dextrose. A minimum glucose infusion rate of 4 mg/kg/min should be ensured. Calcium in the dose of 6 to 8 ml/kg/day of calcium gluconate should be added to the fluid in all babies with respiratory distress. Packed cell volume should be maintained above 40 percent. All preterm babies with respiratory distress may be started on broad-spectrum antibiotics. In term babies, decision to start antibiotics would depend upon the clinical situation.

Respiratory Support

It is given in the form of continuous positive airway pressure (CPAP) or intermittent mandatory ventilation (IMV). CPAP should be started early in preterm with RDS. Indication for starting CPAP are Downe's score of >6 at birth or FiO_2 requirement of >0.4 to maintain an acceptable saturation on pulse oximeter. For best outcomes SIMV should be given to babies in impending respiratory failure or failed CPAP rather than in complete respiratory failure. CPAP is said to have failed when the FiO_2 requirement is >0.6 or the pressure required to maintain oxygenation exceeds 7 to 8 cm of H_2O . Respiratory failure is defined as $\text{PCO}_2 > 60$ mm or $\text{PO}_2 < 50$ mm or saturation <85 percent in 100 percent O_2 with or without a pH <7.25.

Specific Treatment

Pneumothorax

Tension pneumothorax must be drained immediately. A 21- or 23-gauge needle or 22- or 24-gauge angiocath is attached to a 20 ml syringe. The needle is inserted above the third rib at midclavicular line and advanced until air is withdrawn from the syringe. It may be left in place for continuous drainage till the time a chest tube is placed.

Respiratory Distress Syndrome

Babies with or at high risk of RDS should be given a natural surfactant preparation. Prophylaxis (within 15

minutes) should be given to almost all babies of <26 weeks gestation. Prophylaxis should also be given to all preterm babies with RDS who require intubation for stabilization. Early rescue surfactant should be administered to previously untreated babies if there is evidence of RDS. Immediate extubation to CPAP or NIPPV should be considered following surfactant provided baby is stable.

Surgery

It is required for TEF, CDH, choanal atresia, congenital lobar emphysema and CCAM.

PREVENTION

Antenatal Steroids

Cochrane review which included 21 studies came to the conclusion that treatment with antenatal steroids does not increase risk to mother of death, chorioamnionitis or puerperal sepsis. Treatment with antenatal corticosteroids is associated with overall reduction in neonatal death (RR 0.69 95% CI 0.58-0.81), RDS (RR 0.66, 95% CI 0.59 to 0.73), cerebroventricular hemorrhage (RR 0.54, 95% CI 0.43 to 0.69), necrotizing enterocolitis (RR 0.46, 95% CI 0.29 to 0.74), respiratory support, intensive care admissions (RR 0.80, 95% CI 0.65 to 0.99) and systemic infections in the first 48 hours of life (RR 0.56, 95% CI 0.38 to 0.85).

Any woman in preterm labor 24-34 weeks of gestation irrespective of PROM, hypertension, diabetes should receive injection betamethasone 12 mg intramuscular every 24 hr × 2 doses or injection dexamethasone 6 mg IM every 12 hr × 4 doses.

GBS Prophylaxis

Guidelines were published by CDC in 2002 which have lately been revised in 2010. Pregnant women should undergo vaginal-rectal screening for GBS colonization at 35-37 weeks. Intrapartum antibiotic prophylaxis is recommended for women who have previously delivered an infant with GBS disease, women with GBS bacteriuria in the current

pregnancy, women with positive GBS screening result in current pregnancy, and women with unknown GBS status who deliver at less than 37 weeks gestation, have an intra partum temperature of 100.4°F or greater, or have a rupture of membrane for 18 hr or longer. Penicillin remains the preferred agent with ampicillin as an acceptable alternative.

CONCLUSION

Respiratory distress is common immediately after birth, typically caused by abnormal respiratory function during transition from fetal to neonatal life. It is manifested by tachypnea, nasal flaring, intercostals or subcostal retractions, audible grunting and cyanosis. It should also be kept in mind that not all respiratory distress may be due to pulmonary pathology. A low threshold for hospital admission is necessary. Neonatal respiratory distress may be transient; however persistent distress requires a rational diagnostic and therapeutic approach to optimize outcome and minimize mortality.

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CHAPTER 12

Respiratory Distress Syndrome

Naveen Gupta

Abstract

Respiratory distress syndrome (RDS) is seen primarily in the preterm neonate and is due to mostly pulmonary surfactant deficiency. Lung atelectasis leads to ventilation-perfusion mismatching, hypoxia, and eventual respiratory failure in the untreated infant who has RDS. RDS is diagnosed by physical findings consistent with respiratory distress and characteristic radiographic findings. Treatment of RDS begins antenatally with the administration of maternal steroids to women at risk of preterm delivery between 24 and 34 weeks' gestation. The use of repeat doses of antenatal steroids is under investigation but is currently not recommended outside of randomized, controlled trials. Surfactant has been approved for use since 1990 and has been successful in decreasing rates of RDS. Natural surfactant is currently recommended for use, but synthetic surfactant that contains proteins to mimic surfactant proteins is being investigated. In general, prophylactic use of surfactant is recommended over rescue treatment in infants at high risk for developing RDS, but the determination of which infants are at high risk for developing RDS remains a clinical one. The push toward use of less invasive ventilation strategies in the treatment of RDS has led to several trials of nasal continuous positive airway pressure (nCPAP). Several complications of the recommended treatments for RDS have been identified, but the benefits far outweigh the risks. Finally, there remains a need for long-term follow-up studies on preterm neonates treated for RDS to assess neurodevelopmental outcomes.

Abbreviations

- BPD: bronchopulmonary dysplasia
- CLD: chronic lung disease
- FRC: functional residual capacity
- GBS: group B *Streptococcus*
- iNO: inhaled nitric oxide
- IVH: intraventricular hemorrhage
- nCPAP: nasal continuous positive airway pressure
- NIH: National Institutes of Health
- NIMV: nasal intermittent mandatory ventilation
- PIE: pulmonary interstitial emphysema
- PVL: periventricular leukomalacia
- RDS: respiratory distress syndrome
- SP: surfactant protein
- SRT: surfactant replacement therapy

DEFINITION

Respiratory distress syndrome formerly known as hyaline membrane disease, occurs in incompletely developed lungs and is, therefore, a disease of prematurity. Immature

lungs are functionally deficient in mature surfactant. The absence of surfactant in the liquid film lining of alveoli causes an increase in surface tension and alveolar collapse. If not treated, such atelectasis causes an increased work of breathing, intrapulmonary shunting, ventilation-perfusion mismatch, hypoxia, and eventual respiratory failure.

EPIDEMIOLOGY

Respiratory distress syndrome is seen almost exclusively in preterm infants, before the lungs begin to manufacture adequate amounts of surfactant. In fact, the risk of RDS decreases with increasing gestational age: 60 percent of babies born at fewer than 28 weeks' gestation, 30 percent of babies born between 28 and 34 weeks' gestation, and fewer than 5 percent of babies born after 34 weeks' gestation develop RDS. Other factors that increase the risk of RDS include male sex, maternal gestational diabetes, perinatal asphyxia, hypothermia, and multiple gestations. Antenatal steroids and prolonged rupture of membranes decrease the risk of RDS. With the advent of therapies for

Table 1: Normal lung development

<i>Phase</i>	<i>Embryonic</i>	<i>Pseudoglandular</i>	<i>Canalicular</i>	<i>Saccular</i>	<i>Alveolar</i>
Gestation (weeks)	0 to 7	7 to 17	17 to 27	28 to 36	36+
Structures	Trachea and bronchi	Conducting airways and terminal bronchioles	Respiratory bronchioles, alveolar ducts, primitive alveoli	Enlarged peripheral airways and thin alveolar wall	Definitive alveoli
Type II pneumocytes	Absent	Immature; undifferentiated	Immature; differentiated	Developing lamellar bodies	Mature

RDS, including antenatal steroids and SRT, mortality from RDS has decreased from nearly 100 percent to less than 10 percent in recent years.

PATHOPHYSIOLOGY

Normal Lung Development

The period of viability begins at around 23 weeks' gestation, when the fetal lung begins to transition from the canalicular to the saccular stage of development (Table 1). During the saccular stage, peripheral airways enlarge and distal airways begin to dilate while their walls begin to thin. Type II pneumocytes, the cells responsible for surfactant production, are present and maturing. Although gas exchange is possible during this stage, total surface area for gas exchange is low and diffusion distance for gas exchange is high in relation to body weight and metabolic rate. Secondary septation, or alveolarization, begins at about 32 weeks' gestation. During this phase, alveoli form and mature and alveolar walls thin. All cell types proliferate during this phase, including type II pneumocytes. The overall result is a maturing lung with a larger surface area and a minimal diffusion distance for gas exchange.

Surfactant Composition and Life Cycle

Surfactant is a mixture of phospholipids and proteins. The most abundant surface-active phospholipid in mature lungs is phosphatidylcholine. Phosphatidylcholine forms a monolayer on the liquid film lining of the alveolus, lowering the surface tension of that film. In addition to phospholipids, surfactant contains four major proteins: surfactant proteins (SPs) A, B, C, and D (Table 2). SP-A helps to regulate surfactant secretion and uptake; SP-B and SP-C facilitate adsorption and spreading of phospholipids on the liquid film lining of the alveoli. SP-D may play a role in surfactant reuptake and recycling.

Pulmonary surfactant is manufactured in the Golgi apparatus and stored in lamellar bodies of type II pneumocytes. Once secreted by the lamellar bodies into the extracellular space, surfactant is organized into tubular myelin, adsorbed into the air-water interface, and formed into a lipid monolayer. The surface-active properties of

Table 2: Surfactant proteins and their functions

<i>Surfactant proteins</i>	<i>Functions</i>
SP-A	Part of the host innate immune defense Facilitates the formation of tubular myelin Regulates surfactant secretion and uptake
SP-B	Promotes adsorption and spreading of pulmonary surfactant
SP-C	Promotes adsorption and spreading of pulmonary surfactant
SP-D	Part of the host innate immune defense May play a role in pulmonary surfactant reuptake and recycling

the lipid monolayer decrease the surface tension of the air-water interface and prevent alveolar collapse. The majority of surfactant constituents are believed to be recycled, either through reuptake by type II pneumocytes or by alveolar macrophages.

An infant born before the alveolarization stage of lung development has underdevelopment of alveolar sacs and difficulty with oxygenation and ventilation. Similarly, an infant born before this stage of lung development experiences a delay in production and secretion of functional surfactant. Such surfactant deficiency is the major reason for poor lung function in the preterm neonate.

Although the preterm neonate does produce a small amount of surfactant, this surfactant contains low amounts of phospholipids and SPs. It is estimated that infants who have RDS have surfactant pools of less than 10 mg/kg compared with pools of up to 100 mg/kg in term infants. Such surfactant deficiency necessitates increased work of breathing to distend alveoli, which the preterm neonate may not be able to provide. Diffuse atelectasis ensues and leads to an overall decrease in functional residual capacity (FRC) of the lungs. If an infant is allowed to breathe from an inadequate FRC, lung injury can occur. Lung injury leads to protein exudation and edema, which can inactivate surfactant further. The acidosis and hypoxia that results from atelectasis and lung injury further interferes

with surfactant production. The combination of these events leads to respiratory failure.

CLINICAL FEATURES

Respiratory distress syndrome presents at the time of or soon after birth, and symptoms worsen over time. Clinical symptoms of RDS are the same as those of any other respiratory distress: tachypnea, nasal flaring, chest wall retractions, expiratory grunting, and central cyanosis. In the extremely preterm infant, the only clinical symptom of RDS may be apnea. It is important to remember that some infants who have RDS exhibit all of these symptoms, and others may show none.

An accurate history is important in diagnosing RDS. As stated, RDS is more prevalent in earlier gestational ages, so an accurate estimation of gestational age is necessary. Other historical factors must be discerned, such as antenatal steroid therapy; maternal history of gestational diabetes; course of labor, including prolonged rupture of membranes, maternal fever, group B *Streptococcus* (GBS) status and antibiotic therapy; method of delivery; and need for resuscitation.

INVESTIGATIONS

Along with the history and physical examination, a chest radiograph is needed for the diagnosis of RDS. The typical chest radiograph shows diffuse atelectasis and the classic “ground-glass” appearance of the lung fields. Air bronchograms, which are air-filled bronchi superimposed on the relatively airless parenchyma of the lung tissue, also are seen commonly on chest radiograph. Importantly, the appearance of GBS pneumonia on chest radiograph can be identical to that of RDS. Empiric antibiotics to address GBS infection should be started until such disease is ruled out. Arterial blood gas measurements show hypercarbia and hypoxia and eventually, in the unsupported infant, metabolic acidosis. In all, a preterm infant must have clinical signs of respiratory distress and a classic chest radiograph to be diagnosed with RDS.

MANAGEMENT

Antenatal Steroids

Antenatal steroid administration to women at high risk of preterm delivery prior to 34 weeks’ gestation has been standard of care since the 1994 National Institutes of Health (NIH) Consensus Conference. A Cochrane review by Roberts and Dalziel from 2006 confirmed the benefits of antenatal steroids, which include decreases in neonatal death, intraventricular hemorrhage (IVH), and RDS. Antenatal steroids are believed to decrease the incidence of RDS by accelerating maturation of the fetal lung.

Early studies on the use of antenatal steroids did not include data on babies who were delivered before 28 weeks’ gestation, so there was a question of whether antenatal steroids would be beneficial in this age group. The Roberts and Dalziel review shows that when steroids are administered initially at 26 weeks’ gestation, there is a decreased incidence of RDS that is not seen if steroids are administered before 26 weeks’ gestation. However, the incidence of IVH still may be reduced if steroids are administered at fewer than 26 weeks’ gestation. Therefore, because of the apparent benefit to preterm infants in terms of decreased IVH, antenatal corticosteroid administration is recommended for preterm infants starting at 24 weeks’ gestation.

Both betamethasone and dexamethasone have been studied and found to be more effective than placebo, but these steroids have not been examined head-to-head. The Roberts and Dalziel review suggests that beta methasone may cause a larger reduction in RDS than dexamethasone. Baud and colleagues found that antenatal exposure to betamethasone, but not dexamethasone, is associated with a decreased risk of periventricular leukomalacia (PVL) in preterm infants, but there is no difference in the incidence of cerebral palsy. With this limited evidence, two doses of beta methasone administered 24 hours apart is currently the recommended steroid for antenatal use.

Antenatal steroid administration has been shown to be beneficial if provided fewer than 24 hours before delivery. Therefore, steroid administration is recommended before delivery of preterm infants 24 to 34 weeks’ gestation unless delivery is imminent. Furthermore, a reduction in RDS has been seen in infants born up to 7 days after the first dose of antenatal steroids was administered. No benefit is seen in infants who receive the first dose of steroids more than 7 days before birth.

Because antenatal steroids seem to be of benefit only when administered from just before birth to 7 days before delivery, the utility of repeated antenatal steroid dosing has been studied. The latest Cochrane review on the subject, conducted by Crowther and Harding in 2007, suggests that repeat doses of prenatal steroids do reduce the incidence and severity of neonatal lung disease in the first few postnatal weeks. They recommend repeat doses of corticosteroids in women at risk for preterm birth when the first course of steroids was administered more than 7 days previously because of the short-term benefits to the fetal lungs. They do, however, warn about the possibility of decreased birth weight and head circumference at birth, which has been reported. For example, repeat antenatal steroid courses in fetal sheep result in increased lung maturation as well as increased growth restriction. Guinn and colleagues showed that the composite neonatal morbidity, including severe RDS, bronchopulmonary dysplasia (BPD), severe IVH, PVL, sepsis, necrotizing

enterocolitis, or perinatal death, was not reduced by using weekly courses as compared with one course of antenatal steroids. Because the true risk-to-benefit ratio of using repeat doses of antenatal steroids is not known, the 1994 and 2000 NIH Consensus Conference recommends the use of repetitive courses of steroids only in the context of randomized, controlled trials.

SURFACTANT

SRT was approved for use by the United States Food and Drug Administration in 1990. Immediate improvement in oxygenation, along with improved aeration on chest radiograph within 1 hour, is seen after administration of SRT. SRT reduces the incidence of RDS, death, pneumothorax, pulmonary interstitial emphysema (PIE), and IVH in preterm infants. Although most available evidence suggests that SRT increases survival rates without increasing the risk of disability, the risk of long-term disability is unknown due to few reported follow-up studies on the preterm infants who have received surfactant.

Surfactant is administered directly into the lungs via an endotracheal tube. Other methods of surfactant administration, including aerosolization, nebulization, and instillation via bronchoalveolar lavage, have been found to be ineffective. Surfactant administration via laryngeal mask airway is being studied. Surfactant can be administered as either two or four fractional doses in either two or four different body positions; clinical evidence is not sufficient to recommend an optimal number of fractional doses. Surfactant can be administered as either a bolus or an infusion into the endotracheal tube; again, data in humans are insufficient to recommend an optimal method of surfactant administration. Interestingly, data examining the distribution of surfactant in mechanically ventilated rabbits showed that bolus instillation resulted in reasonably homogeneous pulmonary surfactant distribution, while tracheal infusion resulted in extremely uneven pulmonary distribution.

Natural and synthetic surfactant preparations exist, and both are effective in the treatment and prevention of RDS. Natural surfactants are derived from animal lungs (bovine or porcine) and contain phospholipids with SP-B and SP-C; first-generation synthetic surfactants contain only phospholipids without proteins. A Cochrane meta-analysis by Soll and Blanco conducted in 2001 comparing natural surfactant to first-generation synthetic surfactant confirmed that natural surfactant more effectively reduces the risk of pneumothorax and lowers mortality rates in infants treated for RDS. There is also a marginal decrease in the risk of BPD when using natural surfactant. Although natural surfactants appear to be associated with higher rates of IVH, grade 3 and 4 IVH rates are not increased. The conclusion of this meta-analysis is that natural

surfactants are the more desirable choice over the first-generation synthetic surfactants, which is likely due to the inclusion of the SPs in the natural surfactant.

Synthetic surfactants containing peptides that mimic SPs recently have been developed and tested. In a meta-analysis of two studies comparing protein-containing synthetic surfactant to natural surfactant, no statistically significant differences were found between the two groups in terms of death or chronic lung disease (CLD), and clinical outcomes were generally similar. Further studies comparing these two groups are needed.

The use of prophylactic versus selective administration of surfactant has been studied thoroughly. Prophylactic SRT involves intubation and surfactant administration in preterm infants at high risk for RDS and usually occurs after the initial resuscitation and within 10 to 30 minutes of birth. Prophylactic SRT has the advantage of establishing a normal surfactant pool before damage due to a low FRC, and an increased work of breathing can occur. Its major disadvantage is the possibility that an infant who would not have developed RDS may be intubated and treated with surfactant. Selective, or rescue, SRT is the administration of surfactant to preterm infants who already have developed RDS. The two types of selective SRT are early and late. Early selective SRT is administered within 1 to 2 hours of birth; late selective SRT occurs 2 or more hours after birth. The advantage of selective SRT is the avoidance of overtreatment, but in those infants who develop RDS, the delay in treatment allows lung inflammation and damage to occur.

In the Cochrane review by Soll and Morley in 2001, the use of prophylactic surfactant in infants at high risk of developing RDS was compared with selective surfactant treatment at the time of respiratory failure. Prophylactic surfactant treatment was associated with a significant reduction in the risk of pneumothorax, PIE, mortality, and BPD or death. A secondary analysis of infants of fewer than 30 weeks' gestation found a significant decrease in the risk of mortality and the risk of BPD or death. The conclusion of this study is that prophylactic surfactant is beneficial in preterm infants believed to be at high risk for developing RDS, but the best method of determining if an infant is at high risk for developing RDS remains unclear.

Because the incidence of RDS decreases with increasing gestational age, it becomes likely that prophylactic treatment with surfactant once gestational ages approach 28 to 30 weeks results in a good percentage of overtreatment. In these cases, it may make more sense to treat selectively with surfactant. The most recent Cochrane review examining early versus late selective surfactant administration found that early selective SRT decreased neonatal mortality, pneumothorax, PIE, and the incidence of CLD and death at 36 weeks' postmenstrual age when compared with late selective SRT.

Finally, in 1999, a Cochrane review compared multiple versus single doses of natural surfactant for the treatment of RDS. The reason for this comparison was the observation that some infants seemed to relapse after initial surfactant treatment. In this meta-analysis, a more sustained response in the treatment of RDS was seen in the group of infants allowed to have multiple doses of surfactant. A decreased risk of pneumothorax and a trend toward a decreased risk of mortality also was reported.

Overall, survival without BPD has increased since SRT began, although the incidence of BPD in very low-birth weight infants is unchanged. The risk of respiratory problems later in infancy or childhood (including asthma and infection) remains high for preterm infants who were treated with surfactant and mechanical ventilation. Long-term studies are needed to assess the respiratory function of children who received surfactant as preterm infants.

VENTILATORY MANAGEMENT

Several methods can be used to ventilate the preterm neonate at risk for RDS. Surfactant administration followed by conventional ventilation has historically been the management of choice, but concerns that both positive pressure ventilation via the endotracheal tube and the duration of mechanical ventilation have direct effects on the incidence of BPD have prompted investigators to search for less harsh ventilatory strategies. Because most preterm infants who have RDS require ventilatory support and BPD is a major morbidity of many forms of ventilatory support, the hope is to find a noninvasive method of ventilation for RDS that is both safe and effective.

The initial belief was that more complex ventilation strategies, such as high-frequency oscillatory ventilation, might decrease the risk of developing BPD. However, when optimal lung volume strategies are used, there is no difference between conventional ventilators and high-frequency ventilators in terms of pulmonary and nonpulmonary outcomes. A Cochrane review on this subject from 2007 confirmed the lack of clear evidence for elective use of high-frequency ventilation over conventional ventilation because no difference was documented in mortality between the two modes of ventilation at 30 days or at term-equivalent age. Patient-triggered ventilation is a form of conventional ventilation that includes synchronized intermittent mandatory ventilation, assist control, and pressure support. Studies have shown that patient-triggered ventilation has benefits over conventional ventilation and high-frequency ventilation in terms of a decreased duration of mechanical ventilation and decreased number of days on oxygen. However, there was no significant difference in terms of a decrease in lung injury between the three ventilation strategies.

The noninvasive ventilation strategy of nCPAP is believed to work by improving oxygenation without

increasing PaCO_2 through the stabilization and recruitment of collapsed alveoli. The idea is that nCPAP will help to achieve the adequate FRC that is necessary to avoid the development of RDS because increased FRC means increased alveolar surface area and less intrapulmonary shunt. The avoidance of endotracheal intubation saves the infant from the barotrauma and volutrauma seen with the use of mechanical ventilators. A Cochrane review from 2002 states that although a higher rate of pneumothorax was seen, there was an overall reduction in respiratory failure and mortality in preterm infants who had RDS and were treated with nCPAP. Large randomized, controlled trials to evaluate this possibility are underway.

The COIN trial (continuous positive airway pressure or intubation at birth) is a recently published randomized trial addressing whether the use of nCPAP shortly after birth would decrease the rates of death and BPD (defined as the need for oxygen at 36 weeks gestational age). A total of 610 infants from gestational ages 25 to 28 and 6/7 weeks were randomized at 5 minutes after birth to receive either nCPAP or intubation and mechanical ventilation. Outcomes between the two groups were assessed at 28 days, 36 weeks gestational age, and before discharge. There was a significantly lower risk of death or need for oxygen at 28 days in the nCPAP-treated infants, but early nCPAP did not significantly decrease the rates of death or BPD compared with intubation and ventilation at 36 weeks gestational age. Infants in the nCPAP group required fewer overall days of ventilation, but also had a significant increase in pneumothoraces compared with mechanically ventilated infants. The overall conclusion of the study was that early nCPAP was not detrimental to preterm infants whose gestational ages were between 25 and 28 and 6/7 weeks.

COMPLICATIONS AND TREATMENT OF RESPIRATORY DISTRESS SYNDROME

A major pulmonary complication of RDS is the development of BPD, which is generally defined as the need for oxygen supplementation at 36 weeks' corrected gestational age. Importantly, BPD is not caused by RDS; rather, it can be the result of the many treatments of RDS. The "new BPD," a term coined by Jobe in 1999, describes a syndrome that results from processes that interfere with lung development, not a syndrome resulting only from injury. These processes can include chorioamnionitis, oxygen administration, high tidal volumes, mechanical ventilation, postnatal sepsis, and postnatal corticosteroids. Accordingly, it is possible to develop BPD without having RDS, but BPD absolutely can occur in preterm infants who developed and were treated for RDS. Other complications of RDS in the preterm infant include IVH, patent ductus arteriosus, sepsis, and pulmonary hemorrhage, which likely result from a combination of prematurity, RDS, and its treatments.

Complications from the treatments for RDS are inevitable, but based on risk-to-benefit ratios of the treatments, the complications are mostly tolerable. Antenatal steroids do not have true short-term complications when examined in meta-analyses; there has been no associated increase in maternal death, maternal infection, fetal death, neonatal CLD, or neonatal birth weight. Concerns of decreased birth weight as well as trends toward increased incidence of IVH and long-term adverse behaviors have been voiced with the use of multiple repeat doses of antenatal steroids, but never consistently proven. Interestingly, in a 30-year follow-up of infants who received antenatal corticosteroids, no change in adult size or blood lipid or cortisol concentrations was documented, but there was a slight increase in the incidence of insulin resistance. These results may have implications for the hypothesis of the fetal origins of adult disease.

Mild complications of surfactant administration may include transient oxygen desaturation, apnea, and bradycardia, but such complications typically improve rapidly. More serious complications include endotracheal tube blockage and pulmonary hemorrhage. After administration, surfactant may distribute unevenly to only one lung or certain lobes. A second dose generally follows the same course as the first, which can lead to continued atelectasis of certain areas of the lungs. As mentioned, natural

surfactant administration causes an increase in grade 1 and 2 IVH compared with synthetic surfactant. Finally, after surfactant administration, the clinical signs of a PDA may develop earlier in the clinical course.

Complications of mechanical ventilation are not specific to infants being treated for RDS. Air leak syndromes, including PIE and pneumothorax, are more common when the poorly compliant lungs in RDS are mechanically ventilated. Pneumothorax is also associated with the use of nCPAP.

LONG-TERM PROGNOSIS

Survival of infants who have RDS has improved greatly with the use of antenatal steroids and SRT. Preliminary data in infants treated with antenatal steroids suggest the possibility of less neurodevelopmental delay. Overall, however, information regarding neurodevelopmental outcomes in the preterm infants treated for RDS is lacking, and long-term follow-up studies are needed.

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CHAPTER 13

Mechanical Ventilation of Newborns: Current Perspectives

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Despite increasing interest in continuous positive airway pressure (CPAP) and other forms of noninvasive respiratory support, mechanical ventilation remains the mainstay of treatment of babies with respiratory failure. This saves life, even in the smallest of the babies born with extremely low birth weight but also causes a number of iatrogenic complications which limits their short- and long-term outcomes. Much has been learnt since then about the pathophysiology of ventilator induced lung injury (VILI)¹ and in response, newer modes of ventilation have been devised in order to try and minimize this. Whatever method is used, the goal of mechanical ventilation remains the same, which is to optimize tidal volume delivery, reduce the work of breathing and avoid iatrogenic complications.

A variety of newer modes of ventilation are now available on the neonatal units but they often cause confusion, as different nomenclatures have been used to describe the same thing. This has been made worse by the manufacturing industry that often chooses the term arbitrarily. It is therefore best to understand first the difference between various ventilatory modalities these newer ventilators can offer. This is made easier if one uses a classification of ventilatory devices based on a hierarchical system.²

At any one time, a ventilator can only work by using pressure or volume as control mechanism (called control variable or parent mode), which is set by the clinician. Most machines now provide the facility to operate the ventilator in either pressure or volume control mode. Both pressure and volume controlled modes have their inherent advantages and disadvantages and not surprisingly some of the newer ventilators have combined the desirable features of both (hybrid modes, see below).

In either mode, whether controlled by pressure or volume, the ventilator breaths can be delivered in a variety of ways. For this, the ventilator needs to know when to start inspiration, when to limit or sustain inspiration and

then when to end inspiration and cycle to the expiratory phase. These are known as the phase variables (daughter modes) which are interchangeable and can be set by choosing time, flow, pressure or volume. Modern ventilators allow the clinician therefore to create and deliver different breath types by using different modalities to trigger and regulate the phases of ventilation. For example, in traditional time-cycled, pressure limited (TCPL) mode of ventilation, pressure is used to limit the inspiratory flow and time is used to cycle inspiration into expiration. In more modern modes such as pressure support ventilation (PSV), pressure is used to limit inspiratory flow, but it is inspiratory flow, rather than time, that is used to cycle inspiration into expiration (known as flow cycling). These newer modalities are made possible by the use of sensitive flow sensors in conjunction with fast microprocessors running advanced software algorithms.

The following section describes the differences between the pressure-targeted and volume-targeted modes, including hybrid modalities such as volume-guarantee (VG), volume assured pressure support ventilation (VAPS) and pressure regulated volume control (PRVC).

PRESSURE VERSUS VOLUME-CONTROLLED MODES

Pressure-controlled or pressure-targeted modes allow the clinician to set the peak inspiratory pressure to deliver a flow of gas into the chest along a pressure gradient. As the lungs become filled with gas, the pressure gradient between ventilator and alveoli drops, and so does the flow, until a point is reached when the delivered pressure equals the airway pressure, when flow stops. Although the pressure is fixed, Pressure-control, however, does not guarantee consistent tidal volume delivery. This depends on the lung compliance. Thus, tidal volume delivered will be

lower when lungs are stiff but as compliance improves, the tidal volume delivered at a given pressure also improves. Therefore, in the context of surfactant deficient lung disease, the clinician must anticipate the tendency to over-distend the lungs as compliance improves, either with time or in response to treatment, such as exogenous surfactant administration.

In contrast, volume-controlled modes, the ventilator asks for a set tidal volume to be delivered and machine will deliver this regardless of the pressure required to do so. Therefore, when lungs are less compliant, the ventilator will generate higher peak pressures to achieve set volume but will reduce the pressure as compliance improves, always attempting to maintain the target tidal volume as set by the clinician. This rise in pressure (PIP) often used to cause anxiety to the clinicians but it must be realised that in context of efficacy and safety of ventilation, it is the volume (Volutrauma) and not the pressure (Barotrauma) which is more important.³

The flow waveform, as in the manner in which the flow is delivered to the patient, also differs between these two modes. With pressure-controlled modes, the flow accelerates rapidly until set pressure is reached, resulting in rapid filling of the lung in early inspiration. In contrast, volume-controlled ventilation produces a square flow waveform, in which alveolar filling is slow and peak pressure and volume are achieved at the end of inspiration. These different types of inspiratory flow delivery have inherent advantages depending on the pathophysiology of the lung. For example, pressure-targeted modalities are “front-end loaded” and may be more effective in treating stiff, atelectatic lungs, whereas in volume-controlled mode, it is “back-end loaded” and might work better in high lung volume states or where the disease is more varied.

Cochrane review looking at 693 infants from twelve randomized trials (nine parallel trials and three crossover trials) found the use of volume targeted modes resulted in a reduction in the combined outcome of death or bronchopulmonary dysplasia (typical RR 0.73 (95% CI 0.57 to 0.93), reductions in pneumothorax (typical RR 0.46 (95% CI 0.25 to 0.84), days of ventilation (MD -2.36 (95% CI -3.9 to -0.8)), hypocarbia (typical RR 0.56 (95% CI 0.33 to 0.96), and the combined outcome of periventricular leukomalacia or grade 3-4 intraventricular hemorrhage (typical RR 0.48 (95% CI 0.28 to 0.84). Infants ventilated using volume targeted ventilation modes had reduced death and chronic lung disease compared with infants ventilated using pressure targeted modes.⁴ Of all the studies included in the meta-analysis, the only one to provide longer term data with regards to neurodevelopmental and general health outcomes were from our own unit. This study looked at 109 children, of whom 94 survived to discharge and found that the efficacy of volume-controlled ventilation in very preterm and very low birth weight

babies appeared to be maintained on long-term evaluation.⁵

HYBRID MODES

Attempts have been made to combine the features of both pressure-targeted and volume-controlled ventilation resulting in a number of hybrid modes. These include volume-guarantee (VG), pressure regulated volume control (PRVC) and volume assured pressure support (VAPS). They are primarily pressure-controlled modes of ventilation but make use of a computer controlled algorithm in order to adjust the rise and fall of pressure to produce tidal volume delivery, using expired tidal volume measures of previous breaths to calculate the pressure requirements to achieve set volume. Volume assured pressure support ventilation makes within the breath (intrabreath) adjustment of pressure and/or inspiratory time until the desired volume has been provided.

VOLUME GUARANTEE VENTILATION

Volume guarantee™ ventilation, available on Draeger Babylog® 8000 ventilators, can be best described as a dual loop synchronized mode that delivers time cycled pressure limited breaths but allows the pressure to be adjusted to deliver a tidal volume in the range as set by the clinician. It achieves this by use of an auto feedback mechanism based on expired tidal volumes of previous breaths. The maximum pressure limit is set about 20 percent above the pressure needed to deliver this tidal volume constantly.

Potential advantages of Volume guarantee™ include less risk of volutrauma as the clinician set tidal volume is not exceeded when lung compliance improves, reduced peak pressures when baby makes significant contribution to tidal volume thus reducing chances of barotraumas, more stable tidal volume delivery and autoweaning of peak inspiratory pressures, thus protecting against barotrauma. The feedback loop, however, may have limitations. As adjustments to PIP are made in small increments to avoid overcompensation and are based on the exhaled tidal volumes, the delivered tidal volume cannot compensate for large breath to breath fluctuations (such as with large leaks).

Volume guarantee™ is the most widely used method of providing volume targeted ventilation, but not so well studied in randomized clinical trials. Of the published trials of VG, most are in forms of small crossover trials relating to endpoints based on short-term physiological changes. There is a lack of published data about the relevant long-term clinical outcomes. Cheema and Ahluwalia first investigated the feasibility and efficacy of Volume guarantee™ in 40 premature newborn infants (mean birth weight 1064 gm, gestation 27.9 wk) with symptoms of respiratory distress, in a four hour cross over trial. They

found that the mean peak inspiratory pressure and mean airway pressure using VG with either synchronous intermittent positive pressure ventilation (SIPPV) or synchronous intermittent mandatory ventilation (SIMV) was lower than that with either SIPPV or SIMV alone. No untoward effects were noted during the study period. VG as used in this study seemed to be a feasible ventilation mode for preterm neonates and achieved equivalent gas exchange using statistically significant lower peak airway pressures, both during early and recovery stages of RDS.⁶

VOLUME ASSURED PRESSURE SUPPORT VENTILATION

This mode is available on the VIP Bird Gold® infant/ pediatric ventilator and can be best described as variable flow volume ventilation and blends pressure support ventilation and volume controlled ventilation. A guaranteed tidal volume delivery is provided with each breath. Each breath starts as a variable flow pressure support breath. The ventilator will measure the delivered tidal volume when the inspiratory flow has decelerated to a minimum set level. If the delivered tidal volume equals or exceeds the set tidal volume, the pressure support breath is allowed to continue and is flow cycled. If the targeted tidal volume is not achieved the breath changes to a volume controlled breath with constant flow waveform and inspiration is continued till the set tidal volume is delivered.

PRESSURE REGULATED VOLUME CONTROL

Pressure regulated volume control (PRVC) is another mode of ventilation which attempts to combine the benefits of pressure limited and volume control ventilation. This is available on Servo 300A and the Servo-i ventilators (Maquet). It is a flow cycled mode that offers the variable flow rate of pressure control ventilation with a targeted tidal volume. Like volume guarantee, PRVC is also a form of closed loop ventilation in which pressure is adjusted according to tidal volume delivered. The new Servo-i ventilator features y-sensor measurements ensuring better measurement and more accurate delivery of set-tidal volume.

The clinician sets a target tidal volume and the maximum pressure to deliver the tidal volume. The micro-processor of the ventilator attempts to use the lowest pressure with a decelerating flow waveform to deliver the set tidal volume. The first breath is delivered at 10 cm H₂O above peak end expiratory pressure (PEEP) and is used as a test breath to enable the microprocessor to calculate the pressure needed to deliver the set tidal volume based on the patient's compliance. The next three breaths are delivered at a pressure of 75 percent of the calculated pressure needed. If targeted tidal volume is not delivered, the inspiratory pressure

is increased by 3 cm of H₂O for each breath till the desired tidal volume is reached. If targeted tidal volume is exceeded the inspiratory pressure is decreased by 3 cm of water. Inspiratory pressure is regulated by the ventilator between PEEP and 5 cm H₂O below the clinician set upper pressure limit.

In PRVC, the pressure is adjusted on the average of the previous four breaths and so variations in delivered tidal volume could still occur.

SYNCHRONISED MODES OF VENTILATION

As described earlier, both pressure and volume-controlled parent modes can be delivered in a variety of ways by using different phase variables. This section describes the commonly used synchronized modes in newborns.

SYNCHRONIZED INTERMITTENT MANDATORY VENTILATION

In this mode, the ventilator attempts to synchronize the onset of delivering a breath to the baby with the onset of a spontaneous patient breath. However, only a set number of breaths will be delivered by the ventilator according to the breath rate as set by the clinician. For example, if the rate was set at 40 breaths per minute, the ventilator will deliver 40 synchronized breaths to the baby, and will try and deliver these evenly throughout the baby's breathing cycle. It achieves this by setting breath periods, or timing windows, which are longer with slower rates. The first time the patient initiates a breath within a timing window, the ventilator will support that breath. If the patient takes another breath within the same timing window, this breath will not be supported, or will be supported only at the baseline (PEEP) level. If the baby was to breathe at a rate lower than the set rate, or has an apnea, then intermittent mandatory breaths will be delivered at the set rate. The clinician can set the peak inspiratory pressure if pressure targeted, or tidal volume, if volume targeted. The clinician also sets the inspiratory time, flow and SIMV rate.

In this sense, there is only marginal improvement in SIMV design as compared to conventional IMV. Most of the parameters are still set by the clinician; hence the chance of asynchrony is still present.

Most clinicians prefer SIMV as a weaning mode (at slow set rates), as it provides only partial ventilator support as baby can breathe spontaneously between assisted breaths. By noting the tidal volumes generated by the unsupported breaths, the clinician can judge suitability for extubation. This however can also be a drawback. As these breaths are not supported beyond PEEP, the work of breathing becomes harder on slow rate SIMV, especially as the baby is breathing to fight the high resistance of the endotracheal tube.

PRESSURE SUPPORT VENTILATION

To overcome this drawback, pressure support ventilation (PSV) can be combined with SIMV to provide additional support to spontaneous breaths alongside the synchronized mandatory breaths. PSV aims to support each spontaneous breath with additional pressure in order to overcome the resistance encountered from a narrow endotracheal tube and the dead-space of the ventilator circuit.⁷ With PSV, the patient controls the onset and end of inspiration (flow cycles) and thus inspiratory time. The mode also provides variable inspiratory flow as compared to fixed flow settings (such as in time-cycled pressure-limited modes) to provide a flow waveform synchronized to what the patient is attempting to achieve. The clinician is only left to set the peak inspiratory pressure provided. PSV cannot be used as a mode on its own as, unlike A/C, it does not provide a backup rate in cases of apnea or insufficient patient flow to trigger support. It is more commonly married with SIMV to provide effective weaning without tiring the patient out, and allows observation of respiratory drive before extubation.

ASSIST-CONTROL VENTILATION

In Assist-control ventilation also known as A/C ventilation, patient triggered ventilation or SSIPV on Draeger ventilator, the ventilator attempts to identify when the patient initiates a breath and if the patient's effort exceeds the trigger threshold, the ventilator will deliver a mechanical breath. If the patient is unable to trigger or is breathing below the set backup rate, a ventilator-delivered breath will be provided. In this mode, every patient-triggered breath beyond a threshold will be supported, regardless of the rate. Therefore, if the patient is constantly breathing above the set backup rate, reducing this value will have no effect. Patient triggered ventilation has an advantage over SIMV in that it supports every breath that meets the trigger threshold, thereby providing adequate minute ventilation with minimal work of breathing. Once again, PTV can be either time- or flow-cycled, but only the latter produces both inspiratory and expiratory synchrony.

PROPORTIONAL ASSIST VENTILATION

Proportional assist ventilation (PAV) is a fully adaptive mode which attempts to provide a breath in total synchrony with the patient. This is not only with regards to initiation and end of a breath but the ventilator will also adapt the intrainspiratory flow to provide a breath waveform that matches what the patient is attempting to do. In order to achieve this, the ventilator continuously measures the respiratory effort of the baby, adjusting pressure and flow in a proportionate way. Whereas in PTV, the clinician imposes peak inspiratory pressure, pressure rise time, and duration of lung inflation, in PAV, this is all determined by

what the patient is attempting actively during the cycle of a breath. The clinician is only left to set the 'gain' of this enhancement, and this brings about the idea of resistance and elastance. Resistance being the sum of tissue resistance (friction from lung tissue moving against each other) and airway resistance (the frictional resistance of the airways to flow of gas) and can be derived from the pressure difference (in cm H₂O) over flow (in l/min). Elastance is the reciprocal of compliance and is the tendency of a hollow organ to recoil towards its original dimensions upon removal of distending force. The gain that can be set is that of resistive unloading which is the work applied to overcome the resistance during inspiration, and elastic unloading, being the work applied to overcome the elastic resistance to inflate the lungs.

Clinical data regarding PAV is limited. One trial involving 36 very low-birth-weight infants found PAV to maintain similar gas exchange to more traditional IMV and patient triggered modes but with smaller pressures (15 to 44% reduction).⁸ Another paper highlights the problems that can be encountered with PAV by subjecting it to a series of *in vitro* tests. Artificial lung models were developed to mimic three different lung pathologies (respiratory distress, bronchopulmonary dysplasia and meconium aspiration syndrome). This study noted oscillations seen in airway pressure waveforms due to autotriggering, occasionally resulting in high peak pressures. There was also a significant delay seen between the onset of a breath and the ventilator initiating a mechanical breath. This was up to 100 milliseconds, which equates to a third of the baby's inspiratory breath left unsupported.⁹

NEURALLY ADJUSTED VENTILATORY ASSIST

Neurally adjusted ventilatory assist is described as mechanical ventilation controlled by brain signals or more specifically, vagus nerve stimulation of the diaphragm that might help to improve the synchrony between ventilator and patient. The act of breathing depends on rhythmic discharge from the respiratory center of the brain. This discharge travels along the phrenic nerve, excites the diaphragm, which leads to muscle contraction, negative pressure in the airways and inflow of air into the lungs. Traditionally, the ventilator detects flow generated by the patient from a sensor located somewhere between the endotracheal tube and the ventilator. NAVA attempts to capture the initiation of a breath at its onset from the respiratory centers in the brain, with the aim to provide improved synchrony. As the ventilator is cycled as soon as neural inspiration begins, mechanical coupling between the muscles of respiration and the ventilator should be improved. In addition, the level of assistance provided during inspiration is determined by the patient's own respiratory center demand.

One paper in 2009 looked at patient-ventilator interaction with neurally adjusted ventilatory assist in seven very low-birth-weight infants with an average birth weight of 936g (range 676–1266 g); gestational age 26 weeks (range 25–29). They were studied before and after extubation, initially during conventional ventilation, and then NAVA. They demonstrated that during conventional ventilation, the mean trigger delays were not different from NAVA, however 13 ± 8.5 percent of ventilator breaths were triggered on average 59 ± 27 ms prior to onset of diaphragmatic electrical activity. Conventional ventilation also cycled-off prior to NAVA (120 ± 66 ms prior, $p < 0.001$). Neural expiratory time was longer ($p = 0.044$) and respiratory rate was lower ($p = 0.004$) during NAVA. It was concluded that in low birth weight infants, NAVA can improve patient-ventilator interaction, even in the presence of large leaks.¹⁰ However, this was a very small study and further trials are required on our preterm population in order to determine its clinical usefulness and safety.

CONCLUSION

Although most clinicians still use their own preferred method, they should keep aware of new developments in the field of mechanical ventilation. Whatever ventilation modality is used, it is important to understand that the respiratory failure in newborns is a multisystem disease. Good outcomes will be determined by providing appropriate multiorgan support such as adequate nutrition, cardiovascular support and protection against infection. It should also be understood that respiratory failure is a dynamic condition which may require a change in ventilatory strategy depending on the course of the disease.

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CHAPTER 14

Mechanical Ventilation in Neonates

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The care of sick neonates has significantly improved over last 3 decades. The most important factors have been better obstetric services (use of antenatal steroid, better fetal monitoring), good respiratory support (use of mechanical ventilation and surfactant), nutritional support (early initiation of enteral feeding and parenteral nutrition) and prevention of nosocomial infection. Out of all these, mechanical ventilation has been most attractive and “high tech” fancy field for all neonatologists and pediatricians. As a result many pediatricians now want to establish this modality at their center to provide better care. Though it is a healthy sign which will give good dividends in the long run, it is important to realize that mechanical ventilation is more of an art than science and one learns while doing it more often. All centers doing ventilation experience a learning curve and it is important to modulate according to the local needs but certain principles should always be followed.

It is not possible to discuss all aspect of mechanical ventilation here but certain important points would be discussed here.

Topics to be Covered

- How neonatal mechanical ventilation differs from pediatric ventilation.
- Basic infrastructure before starting mechanical ventilation.
- Which babies require ventilation?
- Various modes of ventilation.
- Starting, monitoring and weaning of ventilation.
- Supporting services.
- Nutritional management.
- Monitoring and follow up of ventilated babies.

NEONATAL VENTILATION VERSUS PEDIATRIC VENTILATION

Neonate is not a small child and the ventilation requirements and strategies vary. The main differences to be highlighted are:

- Neonatal ventilators should have a constant gas flow as normal respiratory rate of a neonate is much more than pediatric patients and they breathe spontaneously in between the ventilator breaths and intermittent gas flow increases their work of breathing.
- Though there are advantages and disadvantages of each type of ventilation, most neonatal centers use pressure controlled, time cycled ventilation in neonates against volume-controlled ventilation in pediatric patients. An exception can be chronic lung disease patient in which volume controlled ventilation may be desirable.
- CPAP mode of ventilation is much more effective in a number of neonatal respiratory disorders (commonest being HMD, apnea of prematurity) unlike in pediatric patients. There is renewed interest in CPAP as a mode as it has also shown to reduce the incidence of chronic lung disease.
- Most neonatal ventilation is short-term ventilation averaging 3 to 5 days.
- High frequency ventilation with its unique features is being used in many neonatal disorders.

BASIC INFRASTRUCTURE BEFORE STARTING VENTILATION

- *Personnel:* It is imperative to have round the clock coverage by a doctor well versed with ventilation (theoretical as well as practical experience of at least 3-6 months)

and specially trained nurses around the clock (with at least 3 month of training in a unit doing ventilation).

- Protocol book for departmental policy, procedures and day to day decision-making.
- *Facilities:*
 - Portable X-ray machine
 - ABG machine.
- Procedures to be mastered Intercostal tube drainage, arterial line cannulation, PN administration.

Which Babies Require Ventilation?

Exhaustive list of indications can be found in any textbook, but what is important to remember is that initiation of ventilation is mostly a clinical decision in face of respiratory failure (not maintaining normoxemia or saturation) or impending respiratory failure (maintaining of normoxemia with increased work of breathing). Blood gas value of low PaO_2 (<50 mm Hg) or high PaCO_2 (>50 mm Hg) sometimes may warrant ventilation despite not so evident clinical indication.¹

Various Modes of Ventilation

- CPAP
- IMV
- SIMV
- SIPPV
- High frequency ventilation.

CPAP was first used in neonates by Gregory in 1971 and was found very effective especially in preterm babies primarily because of its effect on improvement of functional residual capacity. Over years it has become clear to the medical fraternity that many neonates can be saved only by using CPAP alone. Later IMV became the most commonly used mode in neonatal ventilation. Synchronization came a little late in neonatal ventilation because of faster respiratory rate in neonates and hence a need of low response time for synchronization. The advent of microprocessor technology has made SIMV possible in neonates. Despite a number of theoretical benefits of SIMV over IMV (less barotraumas, less air leak syndrome), the only proven benefit in randomized controlled trials is reduced number of days on ventilator which in itself is a big advantage making it a useful mode in every neonate. Various sensors used for SIMV are flow sensor (in Drager 8000), pressure sensor (Siemens 300) and abdominal capsule (Infant star).² In SIMV mode, only a fixed number of breaths are synchronized and the baby may still take more number of spontaneous breaths which are not synchronized. In SIPPV mode, all the spontaneous breaths taken by the neonate are synchronized and hence the rate is decided by the patient. In both SIMV and SIPPV modes, the inspiration is synchronized but the expiration is not. In flow cycled ventilation, even the expiration can be synchronized and this mode is labeled different in different ventilators e.g. PSV in Drager ventilation. Hence

in PSV, both the rate and the inspiration time are decided by the patient. In all these modes, FiO_2 , PIP, PEEP and Flow are operator dependent.

High frequency ventilation with its unique features of low Vidal volume and high respiratory rate strategy has been shown to be of help in some patients of PPHN, congenital diaphragmatic hernia and air leak syndrome. The most common indication of use of HFO in our experience has been as rescue therapy when conventional ventilation is not able to achieve normoxemia.

Starting, Monitoring and Weaning from Ventilation

- Before starting any baby on conventional ventilation it is important to know normal values of neonatal respiratory function.

Tidal Volume ml/ kg	6-8
Compliance ml/ cm	2-3
H_2O / kg	
Resistance cm	20-40
H_2O /L/min	
Tidal pressure change (cm H_2O)	5-6
I: E ratio	1:2 to 1:6
Time constant	0.25 second
FRC	30 ml/kg
Desirable PaO_2	50-80 mm Hg in preterm 60-90 mm Hg in term
Desirable PaCO_2	35-45 mm kg in initial phase of ventilation Up to 60 mm Hg later
O_2 saturation	88-92% in preterms and 91-95% in term babies

- *Desirable specification of neonatal ventilator:* Preferably use those ventilators which give set and measured values, so we can be sure that baby is getting the same settings which we have set on ventilator. Preferably do not use those ventilators for ventilating newborns which are capable of ventilating pediatric and adult patients also. As these ventilators do not give correct values of delivered tidal volume in neonates.

Accurate and early control of FiO_2	0.21 to 1.00
PEEP	0 to 25 cm H_2O
Rate	0-120 per minute
Peak pressure	0 to 80 cm H_2O
Ti	0 to 60 sec
TE	0 to 30 sec
Constant gas flow	
Low compliance of the patient ventilator circuit (Use specified circuit by manufacturer)	
Humidification	
Monitors and alarms	

- *Steps of starting MV:*
 - Intubation (oxygen delivery during intubation very crucial) followed by IPPR by self-inflating mask to achieve adequate SpO_2 and chest expansion
 - Fixation of ET making sure that the tube doesn't slip in or out
 - Cutting ET to 4 cm beyond angle of mouth to decrease the dead space
 - Continue IPPR till connected to ventilator
 - Putting ventilation circuits (low compliance, preferably disposable) using gloves
 - Connected to O_2 and compressed air source (preferably central, stationed outside the unit)
 - Set humidifier temperature to 37°C or 39°C depending on type of humidifier. Closed system to deliver sterile water for humidification into the humidifier
 - Use circuits with heated wires, so that gases are always delivered at set temperature. Keeping heated wires in both inspiratory and expiratory circuits make it expensive and most units use heated wires in inspiratory circuits and water trap in expiratory circuit
 - Check the “set values” making sure that the desired setting will be delivered
 - Always set alarms. Most common reason of alarms is that their values are not set
 - Attach to endotracheal tube.
- Ventilatory setting depends primarily on the indication of ventilation, the peak pressure/ FiO_2 requirements judged by bag and tube ventilation.³⁻⁶
 - Ventilating a normal lung (indication apnea of prematurity or central depression): PIP 12-14 cm H_2O , PEEP 3-4 cm H_2O , FiO_2 0.21-0.25, RR 40-45 BPM, IT 0.3–0.35, Flow rate 6-8 L/mt
 - Ventilating a diseased lung
 - With low FRC (e.g. HMD) PIP 18-20 cm H_2O , PEEP 5-6 cm H_2O , FiO_2 depending on $\text{SpO}_2/\text{PaO}_2$, RR 50 to 60 bpm, IT 0.3 to 0.35 sec
 - With high FRC (e.g. MAS) PIP 18-20 cm H_2O , PEEP 2-3 cm H_2O , RR 30-40 bpm
 - We do not need to remember these values, these are rough guidelines, as each diseased lung is different. Clinically by observing chest rise and adequate air entry, we can adjust PIP values. In ventilators providing measured tidal volume (e.g. Drager babylog), we can adjust PIP, so that measured tidal volume lies between 4-6 ml/kg
 - PEEP is increased until retractions disappear. If while ventilating a baby PEEP is 5 and FiO_2 is 80 percent, this is wrong combination. We should try to recruit lung areas by increasing PEEP. Chest X-ray should be done within 30 minutes to look whether we are providing optimum PEEP. In CXR, lung should not be expanded more than 8 posterior intercostal spaces. If lung expansion is more, PEEP is decreased and if lung expansion is low, PEEP can be increased to recruit lung and decrease FiO_2 . In ventilators providing measured tidal volume (e.g. Drager babylog), if measured tidal volume decreases on increasing PEEP, PEEP is reduced.⁷
 - Drager babylog gives C20/C ratio which is the ratio of compliance of last 20 percent of lung expansion to total compliance. It should be more than 80 percent (0.08). If it is less, it indicates overinflation.⁸
- *Further evaluation on ventilation:*
 - It is important to remember that as all these values are empirical, we need to confirm whether we are adequately ventilating or not by doing blood gas analysis which should be done every 4 hours for first 24 hours and then depending on the progress of the disease. Value of minute ventilation at which adequate PaCO_2 values are obtained can be noted and alarms of minute ventilation can be set, thus reducing number of arterial blood gases. Normal values for minute ventilation are 160-200 ml/kg/min⁹
 - Taking care of hemodynamic status, nutritional status and infection prevention.
- *Clinical strategy of ventilation:*
 - To improve oxygenation
 - Increase PIP/ PEEP (look at chest rise, if not adequate increase PIP otherwise PEEP. If chest retractions, increase PEEP), increase IT, increase flow rate, increase rate in this sequence. All these parameters increase Mean Airway Pressure
 - Increase FiO_2
 - Improve ventilation
 - Increase TV (\uparrow PIP or decrease PEEP), increase RR thereby increasing minute ventilation.
 - Effect of individual variables
 - \uparrow PIP \rightarrow \uparrow MV (minute ventilation), \uparrow MAP (mean airway pressure)
 - \uparrow PEEP \rightarrow \downarrow MV, \uparrow MAP
 - \uparrow Ti- \uparrow MAP
 - \uparrow FiO_2 \rightarrow \uparrow Oxygenation
 - Arterial blood gases for monitoring ventilation: If PaO_2 is decreased and PaCO_2 is increased, then increase PIP and vice versa. If both PaO_2 and PaCO_2 is low, PEEP is increased and vice versa.
- *Trouble shooting during ventilation:* If a baby on ventilator, starts desaturating suddenly look for the following possibilities.^{10,11} Remember DOPE SIPP which stands for displacement, obstruction, pneumothorax, equipment failure, shock, infection, PDA, PPHN. Trained personnel and resuscitation equipment near the ventilated baby should always be ready. The causes can be related to baby or the ventilator including ventilator circuits. Quickly check that baby is not disconnected from ventilator (could occur in a active struggling baby

or while change of position or after taking weight) and ventilator is not disconnected from power supply. Hand ventilate the baby

- If air entry and breath sounds are decreased—then look for tubal displacement/tubal obstruction/pneumothorax
- If air entry and breath sounds improve by increasing pressure, look for partial tube block or worsening of lung disease (by doing CXR)
- If baby does not improve but breath sounds and air entry are normal, look for shock, PPHN, PDA
- If baby improves on similar pressures during hand ventilation, look for ventilator related problems/compressor/O₂ and air supply pressures (at least 50 psi)

We can check, set and measured parameters in most neonatal ventilators in case of acute deterioration. Look for following values:

- Difference in pressure
- Difference in FiO₂ (faulty blender)
- Look at graphs (help in tubal block, pneumothorax, etc.)
- % leak
- TV and MV changes.
- h. *Weaning from ventilation:* The weaning has to be a thinking process depending on the condition for which baby was ventilated, present ventilatory setting and hemodynamic status. Now aggressive weaning is followed to cut short duration of ventilation.^{12,13}

Weaning Strategies

- Reduction in PIP and FiO₂ should go hand in hand
- Reduction in rate, once PIP has been reduced to low levels 12 to 14 cm H₂O
- Faster weaning if the disease has recovered fast (e.g. HMD after surfactant administration, central depression after naloxone administration, delayed transition in asphyxiated neonates)
- Nasal IMV as soon as setting are not very high
- From IMV to SIMV as rates come down less than 40 bpm
- Extubation from SIMV rate of 20/mt to oxygen hood (shorter ventilation) or nasal CPAP (in case of prolonged ventilation >5 days)
- Prophylactic methylxanthines can be used in peri-extubation period in preterm neonates¹⁴
- No routine use of nebulization or steroids before/after extubation.

SUPPORTIVE SERVICES DURING VENTILATION

- a. Strict infection control strategies:
 - Use of disposable ventilatory circuits
 - Change of circuits every week or if visibly soiled
 - Closed system of adding water to the humidifier

- Proper hand washing techniques
- No routine ET suctioning (if resistance is displayed, do suction when resistance increase by more than 150%)
- Strictly measure the distance to which suction catheter is inserted to avoid formation of subglottic stenosis by repeated deep suction.
- b. Thermal homeostasis.
- c. Fluid and electrolyte homeostasis.
- d. Use tegaderm when applying tape to fix endotracheal tube to avoid abrasions on cheek after removal of tube.
- e. No routine use of antibiotics just because baby is ventilated.
- f. No routine sedation. Remember most common reason for agitation during ventilation is inadequate ventilatory support.

Nutritional Support

- Start enteral feeds at the earliest as early as D1 to D2 if baby is hemodynamically stable and does not have abdominal distention or abnormal residues. Remember ventilation is not a contraindication for baby to be on full feeds.
- Start parenteral nutrition if neonate is not expected to come on total feeds by D5 of life. Start amino acids with 3 to 3.5 gm/kg on D1 and intralipid at a rate of 1.5gm/kg which can be increased to 3 to 3.5 gm/kg depending on serum triglyceride levels (acceptable <200 mg%). It is very important to realize that nutrition support is the most important factor in successful extubation in babies on prolonged ventilator.

Family Support

Parents must be constantly kept informed regarding the condition of the baby, the possible time frame of recovery, the finances involved and the need of follow up even after discharge. Mother should work like a nurse to her baby apart from giving early stimulation and expressed breast milk.

MONITORING DURING MECHANICAL VENTILATION

- Assessment of ventilator gas exchange, oxygen transport and consumption
 - Continuous SpO₂ monitoring by pulse oximeter
 - Continuous TcCO₂ (transcutaneous CO₂ monitor)/Endotracheal CO₂ monitoring
 - Continues temperature monitoring
 - Continuous IBP monitoring
 - Intermittent blood gas monitoring
- Simultaneous monitoring of other systems and functions
 - CRT
 - CVS evaluation for PDA, CVP, ECHO
 - Biochemical stability

- Monitoring for complication
 - XRC for air leak, tube placement, collapse, BPD, cardiomegaly
 - Transillumination of chest for pneumothorax
 - Cranial USG for PVH, IVH, hydrocephalus
 - Infection – tracheal aspirates, blood cultures
 - Skin – avoid burns, abrasions, infections
 - Hb – maintain blood letting record, micro sample techniques
 - Eye check up for babies <32 weeks/ <1500 gm at 4 weeks
 - Catheter maintenance–infection, blockade, thrombosis.

Follow-up Program

It is very important to follow all ventilated babies for early detection and management of general morbidities (growth retardation, apnea, respiratory infection, aspiration) and CNS morbidities (neurodevelopmental, handicap, hydrocephalus, periventricular leukomalacia, cerebral palsy), hearing loss, speech problems, refractive errors, etc.

SUMMARY

Neonatal ventilation combined with other support services has definitely improved the survival of sick neonates. It is an art, which has to be learned over a period of time. It needs a team approach to provide good results. It is important to remember “LOVE” (laws of ventilatory efficiency):

- Know your ventilator well.
- Know the pathophysiology for which you are ventilating and choose appropriate strategy.
- Change your strategy according to change in pathophysiology.
- Other support services (nutrition, infection prevention, etc.)

It is important to combine it with other useful strategies like antenatal steroids, surfactant therapy, early ventilation, gentler ventilation and nutritional support, to provide optimum results.

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CHAPTER 15

High Frequency Ventilation

Pankaj Garg, Saurabh Singh

Ventilation has been the cornerstone of the treatment of neonates with respiratory distress. In this era of surfactant and sophisticated conventional ventilation, there are still some neonates who can not be adequately ventilated or suffer problems related to the ventilation during the process of recovery. Therefore, respiratory insufficiency remains one of the major causes of neonatal mortality. Intensification of conventional ventilation with higher rates and airway pressure also leads to an increased incidence of barotrauma. The high shearing forces resulting from large pressure amplitudes damage lung tissue (volutrauma) and therefore incidence of chronic lung disease increases with the increase in the survival of preterm babies. It was hoped that high frequency ventilation with its unique features might resolve some of these desperate situations. Though this novel mode of ventilation has not universally shown the benefits but in expert hands it stands a chance of reducing the incidence of chronic lung disease and has definitely added another important weapon in the ventilation armamentarium with some unique advantages.

There are three types of HFV¹: Jet ventilation, high frequency oscillation (Sensor medics) and high frequency flow interrupters (Baby log and Infant star). These types are defined primarily by the way they create high frequency pressure and flow changes in the airways and whether they employ active or passive exhalation. Jet ventilators deliver a jet of gas through a specialized endotracheal tube directly into the trachea. Oscillators vibrate a volume of gas using a piston or diaphragm to compress and then rarefy the air mixture in the ventilatory circuit. Flow interrupters create a gas pulse by intermittently interrupting a high flow source. Only HFO employs an active exhalation phase. Jet ventilation is no longer in use in most of the centers. Rest of our discussion will be focused on the other two types of high frequency ventilation.

Since HFV was first described by Lunkenheimer in the early seventies in apneic dogs, this method of ventilation has been further developed and is now applied all over world.

CHARACTERISTIC FEATURES

In conventional ventilation oxygenation and ventilation are closely linked and ventilator adjustments to either will affect the other. In HFOV, they can be treated separately and optimized independently.

There are three distinguishing features of high frequency oscillatory ventilation—the frequency ranges from 5 to 50 Hz (300 to 3000 bpm), active inspiration and active expiration and tidal volumes about the size of the dead space volume.

The efficacy of HFV is primarily due to improvement in pulmonary gas exchange but it can also have favorable influence on respiratory mechanics and hemodynamics.

During conventional ventilation direct alveolar ventilation accomplishes pulmonary gas exchange. According to the classic concept of pulmonary ventilation the amount of gas reaching the alveoli equals the applied tidal volume minus the dead space volume. At tidal volumes below the size of the anatomical dead space this model fails to explain gas exchange.² Instead, considerable mixing of fresh and exhaled gas in the airways and lungs is believed to be the key to the success of HFV in ventilating the lung at such very low tidal volumes. The details of this augmented gas exchange are still not fully understood. The various suggested mechanisms are:

Augment Longitudinal Gas Transport and Enhanced Dispersion³

This is based on Taylor dispersion principle. In this process, an initially plane bounding surface between two gases

develops into a pike-shaped profile as the velocity of one of the gases increases (Fig. 1).

DIRECT ALVEOLAR VENTILATION

A small part of proximal alveoli is still ventilated directly. Hence, gas exchange takes place as in conventional ventilation.

Intra-alveolar Pendant

Different regions of the lung have different compliance and resistance. Therefore, neighboring units with different time constants are ventilated out of phase, filling and emptying at different rates. Due to this asynchrony these units can mutually exchange gas, an effect known as pedelluft (Fig. 2).

Effect on Respiratory Mechanics and Hemodynamics

The application of a high MAP will recruit additional lung volume by opening regions of the lung with poor inflation. An increase in compliance will result. At the same time, a better ventilation perfusion ratio with reduced intrapulmonary right to left shunting is observed. In PPHN, the rapid decrease in paCO_2 during HFV can reduce pulmonary vascular resistance.

The optimal lung volume strategy recruits alveoli and lung segments and once an optimal lung volume is achieved recruitment, lung volume and oxygenation can be maintained with a lower MAP (Fig. 3).

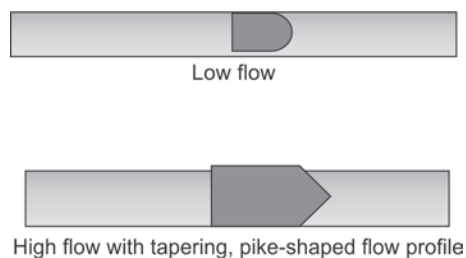


Fig. 1: Taylor dispersion: Boundary surface between two gases with different flow velocity. Gas exchange occurs at the boundary surface through lateral diffusion

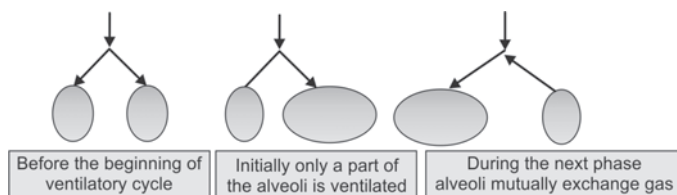


Fig. 2: Intra-alveolar pendant during the next phase the alveoli mutually exchange gas

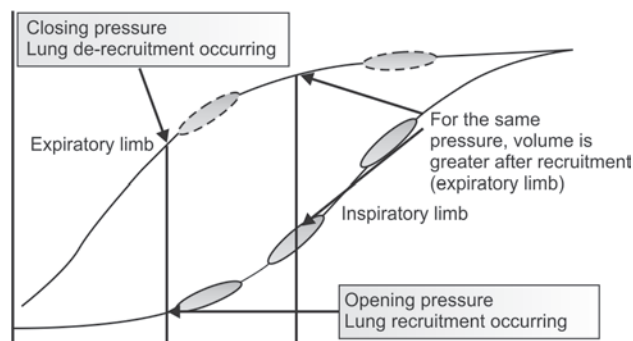


Fig. 3: Optimal lung volume strategy

CHARACTERISTIC PARAMETERS AND CONTROL VARIABLE OF HIGH FREQUENCY VENTILATION

Three parameters determine oscillatory ventilation. Mean airway pressure (MAP) around which the pressure oscillates, the oscillatory volume (TV) which result from the pressure swings and the oscillatory frequency (f).

- **MAP:** In CPAP + HFV mode, MAP equals the set PEEP level. When IMV ventilation cycles are superimposed as is possible in Dräger ventilator, MAP also depends on the PIP and the frequency. The crucial physiologic effect of such continuously applied inflation pressure is the opening of atelectatic lung areas, resulting in marked recruitment of lung volume.
- **Amplitude:** It ranges from 0 to 100 percent and influences the oscillatory volume directly. During HFV volumes similar to the dead space volume (2-2.5 ml/ kg) should be the target.
- **Oscillatory frequency:** The oscillatory frequency measured in units of hertz ($\text{hz} = 1/\text{s}$), influences the oscillatory volume and the amplitude depending on the ventilator type used. Normally, lower frequencies permit higher volumes.
- **Gas transport coefficient DCO_2** (a parameter used in Dräger ventilation): In conventional ventilation the product of tidal volume and frequency, known as minute ventilation, aptly describes pulmonary gas exchange. But in HFO, CO_2 elimination correlates well with DCO_2

$$\text{DCO}_2 = (\dot{V}\text{T})^2 \times f$$

$$\text{VT} = \text{oscillatory volume, } f = \text{frequency.}$$

As frequency is inversely related to tidal volume, a reduction in frequency most of times lead to increase DCO_2 .

CURRENT STATUS OF HIGH FREQUENCY VENTILATION

In newborns HFV has first been employed as a *rescue treatment* when conventional ventilation fails. There are very few controlled trials (total 4:2 in preterms and two in term and near term neonates), which address this issue and the results are summarized here. The HIFO trial⁴ didn't

show much advantage with the side effect of increased risk of IVH while the trial by Keszler⁵ and colleagues showed more rapid improvement in PIE and lower mortality rates. These trials were done at a time when surfactant and antenatal steroids usage was not on routine basis hence recent trials done by Clark⁶ and Engle appears more applicable to current times. Clark et al showed improved gas exchange and less treatment failure with HFV with no difference in CLD, IVH or death. Eigle et al⁷ showed similar results making more grounds for future studies to look for long term benefits which have been scanty till date. From a scientific viewpoint, the prospectively randomized studies represent the most valid approach to testing efficacy of HFV but from a clinical viewpoint, the data from sequential patient series provide justification for trials of HFV for infants failing to respond to CMV, because these reports demonstrate that there is an incompletely defined subset of infants who fail CMV and respond to HFV dramatically.

The second commonest place where HFV is used is when *barotrauma* has already occurred or is imminent, e.g. air leak syndromes (pneumothorax, PIE). There are theoretical reasons to believe that HFV leads to less barotrauma though published data has contradictory results.

Some centers have started using HFV as a *primary treatment for hyaline membrane disease in preterm neonates*. To date, there have been 15 randomized controlled clinical trials of elective use of HFV versus CMV for the treatment of premature neonates who have respiratory insufficiency or RDS.^{8,9} One additional study compares the use of HFV versus CMV in term and near-term infants. The data from these 16 randomized controlled trials of HFV have yielded conflicting results. Five of the 16 trials demonstrated that early elective use of HFV improved pulmonary outcomes, in particular, decreased the incidence of chronic lung disease, as compared with CMV. The 11 remaining trials showed no difference in pulmonary outcomes when using HFV versus CMV. Differences in high-frequency ventilators used, ventilation strategies, definitions of chronic lung disease, study populations, and study center experiences over time, as well as the inability to blind the treatment intervention, may be the derivation of such incongruent results regarding early use of HFV versus CMV. Likewise, some of the studies were conducted before routine use of exogenous surfactant.¹⁰ There is no evidence from the current review of the literature that elective use of HFV, in the form of HFOV or HFFI provides any greater benefit to premature infants who have RDS than CMV. The data are limited and the results are mixed as to whether HFJV may reduce the incidence of CLD. At this time, preferential use of HFV as the initial mode of ventilation to treat premature infants who have RDS is not supported. There are trends towards increase in all grades of IVH¹⁰ and in periventricular leukomalacia in earlier meta-analysis. The problem in this meta-analysis is that it is dominated by the large HIFI study¹⁰ which did not use the recommended high volume strategy (high MAP-high

PEEP) and surfactant was not available at that time. Subsequent studies most of which used high volume strategy and/or used surfactant, have not shown an increased rate of IVH. Caution is warranted in interpreting these results as the treatment is not blinded, the benefits and harms have not been reported in infants born at different gestational ages or of different birth weights and long-term effects are not yet known.

Use in PPHN

Review of the literature¹¹ supports the use of HFV with iNO to maximize oxygenation and treatment effects in hypoxemic respiratory failure, in particular in babies who have pulmonary hypertension.

Use in Treatment of Bronchopleural or Tracheoesophageal Fistula

The current literature lacks any randomized trials to support the use of HFV over CMV in the treatment bronchopleural or tracheoesophageal fistula.

Likewise, in cases of congenital hernia and during surgical correction, HFV has been successfully used as a primary treatment.

GUIDELINES FOR USE OF HIGH FREQUENCY VENTILATION

Principles of Operation

Currently available HFOV are easy to set up and use. There are few operator available controls, but they are very potent in their potential effects on pulmonary gas exchange.

Transition from Conventional Ventilation

In applying an open lung strategy, Paw is gradually increased by steps of 1 cm H₂O to 2 cm H₂O, with the goal of reducing the FiO₂ to less than or equal to 0.6 while achieving target oxygen saturation (SaO₂) values. During this phase, hemodynamics should be carefully monitored, and at the occurrence of a minimal decrease of blood pressures (i.e. more than 2 mm Hg in the preterm infant), airway pressures have to be reduced and the oxygen response conserved before eventually further increasing airway pressures again. Once appropriate saturation is achieved and FiO₂ could be lowered to less than or equal to 0.6, airway pressure should be reduced stepwise in increments of 1 cm H₂O to 2 cm H₂O (moving downward on the deflation limb of the pressure/volume curve that exhibits hysteresis) as long as SaO₂ can be maintained, the ultimate goal being to find the lowest pressure allowable to maintain "good" saturation. Chest radiography is recommended after finding the optimal Paw to ensure adequacy of lung expansion and avoid over-distention.

HFV: Start

MAP (PEEP): 2 to 5 cm above MAP of conventional ventilation, if necessary increase MAP until paO_2 improves, X-ray done after 30 minutes.

HFV frequency: Start with 10 Hz, adjust after seeing paCO_2

HFV amplitude: Start with 30 to 50 percent, watch thorax vibrations

HFV volume: 2 to 2.5 ml/kg

HFV: Continuation

Hypoxia	Increase MAP up to 25 cm H_2O , alternatively apply sustained inflation at low lung volume apply sigh maneuver every 20 minutes for 10-20 seconds at 10 to 15 cm H_2O above MAP
Hyperoxia	Reduce FiO_2 down to about 0.5, very carefully decrease MAP
Hypercapnia	Increase DCO_2 (by decreasing frequency or increasing amplitude)
Hypocapnia	Decrease DCO_2 (by increasing frequency or decreasing amplitude)
Overinflation	Reduce MAP, decrease f, discontinue HFO
Hypotension	Volume expansion, inotropes, reduce MAP, discontinue HFO

HFV failure—when ventilation deteriorates even at 5Hz, maximal amplitude and optimal MAP, switch back to conventional ventilation. If ventilation/oxygenation doesn't improve within 2 to 6 hours you should consider the patient a non-responder to HFV.

Weaning from Oscillatory Ventilation

Weaning from HFO should be a slow and thoughtful process. Weaning depends on the basic lung pathology for which HFO was started. If it is an overinflated lung or with atelectasis, reduction of MAP takes priority over FiO_2 . In all other situations FiO_2 is reduced first. Reduction of FiO_2 /MAP should be slow remembering that a change in MAP does not instantaneously change oxygenation. In a stable clinical situation one should wait 30 to 60 minutes before assessing the effect of the new setting. When FiO_2 is reduced to 0.5, MAP is reduced by 1 to 2 cm H_2O at a time until 8 to 9 cm H_2O . Amplitude is reduced to 40 to 50 percent and frequency kept >10 Hz depending on the initial settings. On these settings, IMV breaths are increased gradually, which means reduction in time on HFO. Gradually IMV rates are increased to 25 breaths per minute at which stage, HFO can be switched back to conventional ventilation.

Monitoring During HFO

- Vital parameters must be closely monitored. HFO at high MAP >10 cm H_2O can reduce cardiac output as evidenced with the help of echocardiographic

contractility of myocardium and quantitative evaluation of tricuspid insufficiency. Particularly in severely ill infants it is wise to measure the CVP regularly. A notable increase can herald cardiorespiratory decompensation at very high airway pressure. Also prolonged CFT and reduced urine output may indicate compromised cardiac function.

- The state of lung expansion has to be assessed by periodic chest radiographs. It is optimal on the 8th to 9th posterior rib level. When IMV is superimposed on HFV it is important to take the radiograph in the expiratory phases of the mandatory cycles.
- First blood gas should be within 15 to 20 minutes after starting HFO to see paCO_2 . HFO can reduce paCO_2 very fast with its detrimental effects like IVH and periventricular leukomalacia. Frequent blood gases should be done to keep paCO_2 between 35 to 45 mm Hg H_2O . Preferably transcutaneous paCO_2 monitoring should be done. With low tidal volume EtCO_2 readings are often erroneous.
- In-line suction must be used. Press *Stop* button briefly on SensorMedics while briefly inserting and withdrawing catheter. PAW is maintained throughout.

Rationale for pausing: The oscillator causes a pressure pulse in the airways. When suctioning if the SensorMedics is not turned off the secretions get pushed back down because of this pulse pressure. So you are having ineffective clearance of secretions. There is also the potential of air trapping with active piston movement.

Strategies for Various Lung Diseases

- HFV for diffuse homogeneous lung diseases (HMD, diffuse pneumonia, bilateral lung hypoplasia)
 - Goal:* Lung expansion, less barotrauma
 - Begin with MAP 2 to 5 cm H_2O above that of conventional ventilation
 - Increase MAP until paO_2 rises, or CVP increases, signs of over-inflation appear
 - Reduce FiO_2 to 0.3 to 0.5, then continue weaning
 - Settings of frequency and amplitude depend on the necessity of CO_2 removal.
- HFV for nonhomogeneous lung diseases (Focal pneumonia, pulmonary hemorrhage, meconium aspiration, unilateral lung hypoplasia, BPD)
 - Goal:* Improved oxygenation and ventilation at minimum MAP
 - Risk:* Partial overexpansion
 - Begin with MAP like or below that on conventional ventilation
 - HFV frequency low, e.g. 7 Hz
 - Then increase MAP slowly until paO_2 slightly rises; keep MAP constant.
- HFV for air leaks (Pulmonary interstitial emphysema, pneumothorax)

Goal: Improved oxygenation and ventilation at minimum MAP, accept lower paO_2 and higher paCO_2

- Don't superimpose IMV for the risk of further barotrauma
- Place the baby on the side of air leak
- Adjust MAP below that of conventional ventilation, if possible
- HFV frequency low, 7 to 8 Hz
- Reduce pressure prior to FiO_2
- Continue HFV for 24 to 48 hours after improvement.

• **HFV for PPHN**

Numerous authors have reported effective therapy of PPHN with HFV. Continuous application of high MAP, uniform opening of the lungs, diminished pulmonary vascular resistance, improved ventilation perfusion match are the suggested mechanism, which help. The favorable oxygenation along with improved CO_2 reduction additionally counteracts pulmonary vasoconstriction.

Goal: To optimize lung volume and perfusion; to improve hypoxia and hypercapnia while minimizing barotrauma.

- Before switching to HFV, hypovolemia and hypotension should be corrected
- HFV frequency <10 Hz
- HFV amplitude 100 percent
- MAP on the level of conventional ventilation, increase as needed for oxygenation
- IMV rate 0 to 15 bpm
- Reduce FiO_2 prior to MAP
- Maintain HFV 24 to 48 hours after recovery
- Always: Minimal handling, use sedation or relaxation.

Complications and Side Effects

- *Irritation:* Babies are often irritated by HFV at first and require deeper sedation. However, they often become quite in accordance with improved oxygenation and adequate paCO_2 levels.
- *Secretion:* Even small amount of secretions or foam after surfactant administration can considerably affect the efficacy of HFV. This is reflected in a decrease in oscillatory volume. Sufficient humidification of inspired gas is mandatory.
- *Hemodynamics:* Often a slight reduction in heart rate and refractory apnea is attributed to an increased vagal activity during HFV. High MAP can compromise both venous return to the heart and cardiac output as well as lead to an increase in pulmonary vascular resistance.
- *Intracranial hemorrhage:* Whether HFV promotes IVH or not has been discussed for a long time. The critical

condition of the patients is probably connected with this presumed effect. More recent studies, during which HFV was applied early, don't report a higher incidence of such complications as compared to conventional ventilation.

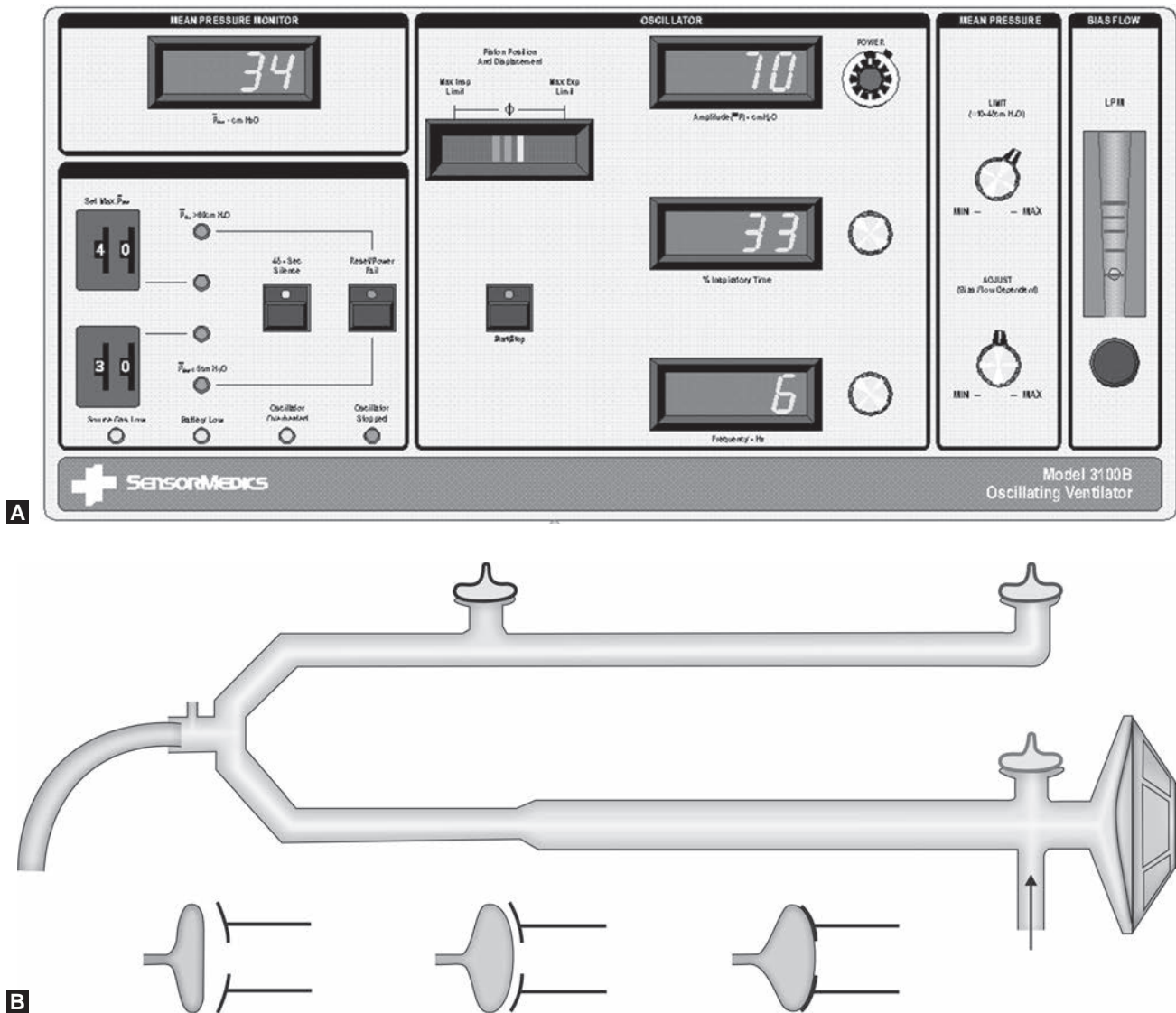
- *Overinflation:* Pulmonary overinflation in obstructive lung diseases (e.g. MAS) is the most frequent complication and cause of failure of oscillatory ventilation. Here air trapping may occur especially with higher frequencies and inappropriate I:E ratio. With improved HFO strategies both barotrauma and air leaks have been reduced.
- *Necrotizing tracheobronchitis:* Local irritation leading to necrosis of the tracheobronchial systems can occur as complication of HFJV but also of HFOV and conventional ventilation. Inadequate humidification and excessive MAP are named as pathophysiological causes. In recent studies no significant differences have been observed in two types of ventilation.
- *BPD:* With respect to the development of BPD and CLD, the published literature shows contradictory results.¹²
- *Others:* In some cases air embolism has been reported. This complication can also occur during conventional ventilation with high pressures.

Contraindications

Pulmonary obstruction is the only relative contraindication known. There is no publication that IVH or coagulopathy are contraindication of HFV.

Limitation of HFV

The success of HFV largely depends on the power of the HF ventilator, which is characterized by the size of the oscillatory volumes at sufficiently high frequencies. Compliance and dead space of the patient circuit has crucial impact. With a low compliant circuit, the oscillatory volumes can be considerably increased. Presently available HFV (Babylog 8000, Infant star) allow ventilation with infant up to 2 kg. Depending on weight and lung mechanics, one should however expect occasional failure due to insufficient oscillatory volumes in the upper frequency range. SensorMedics is very strong oscillator and can effectively oscillate a 30 kg patient (Figs 4A and B). In SensorMedics high frequency ventilator, pressure (Amplitude) controls CO_2 elimination and continuous distending pressure controls O_2 . Continuous distending pressure is bias flow dependent. Higher flow leads to higher CDP. Adjust knob is green control line and limit knob is blue control line. Inspiratory time is adjusted at 33 percent to prevent air trapping. Piston is centered with the help of piston centering knob.



Figs 4A and B: SensorMedics machine

CONCLUSION

Most causes of neonatal respiratory failure require mechanical ventilation are amenable to treatment with HFOV or CMV. For either technique to be successful, lung volumes need to be optimized for the underlying condition, and pressure exposures must likewise be similarly regulated. Only by the careful application of the chosen technique can ventilator induced lung injury be avoided. HFV application has also highlighted the importance of man behind the machine which makes the difference. Studies coming from some centers have consistently shown better results than from some other centers. It appears that HFV is now a salient member of the still growing armamentarium available for taking care of babies with respiratory distress.

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Continuous Positive Air Pressure and Noninvasive Ventilation

Pankaj Garg, Ankur Kumar

INTRODUCTION

Continuous positive air pressure (CPAP) is positive pressure applied to the airways of a spontaneously breathing baby throughout the respiratory cycle. Attitudes to the relative merits of intubation and ventilation and noninvasive ventilation CPAP and nasal intermittent positive pressure ventilation (NIPPV) have evolved since Gregory's study. Advocates of noninvasive ventilation cite the reduced risk of trauma to the larynx and trachea, infection and acute and chronic lung disease with this form of support. The rationale for use of CPAP is to support the airways and avoid alveolar collapse to a level below FRC.

How does CPAP work?

Continuous positive air pressure (CPAP) supports the breathing of premature infants in a number of ways.^{1,2} The upper airway of the preterm infant is very compliant and therefore prone to collapse. CPAP splints the upper airway and therefore reduces obstruction and apnea. CPAP assists expansion of the lungs and prevents alveolar collapse. In doing so it reduces protein leak and conserves surfactant.

Physiology and how CPAP Helps

Preterm babies cannot maintain FRC due to various reasons:³

- Not able to generate enough negative pressure to achieve an effective FRC
- Has low laryngeal tone to maintain PEEP by grunting
- Fluid clearance from lung depends on gestational age of baby because of immature amiloride sensitive Na channel
- Lack of fat laden superficial fascia in the neck → which stabilize the airway
- Not able to mobilize effectively the genioglossus muscle that normally stabilizes the pharynx

- Insufficient numbers of alveolar channels for collateral ventilation
- Chest wall is soft and horizontal ribs and flatter which reduces the potential for lung expansion
- During REM sleep, intercostal muscle activity may be lost
- PDA predisposing to pulmonary edema
- Deficient surfactant.

Effects of CPAP in the infant with respiratory distress:

- Reduces upper airway occlusion by decreasing upper airway resistance and increasing the pharyngeal cross sectional area
- Increases the FRC
- Reduces inspiratory resistance by dilating the airways. This permits a larger tidal volume for a given pressure, so reducing the work of breathing
- Increases the compliance and tidal volume of stiff lungs with a low FRC by stabilizing the chest wall and counteracting the paradoxical movements
- Regularizes and slows the respiratory rate
- Reduces the incidence of apnea
- Increases the mean airway pressure and improves ventilation perfusion mismatch
- Conserves surfactant on the alveolar surface
- Diminishes alveolar edema

Continuous Positive Air Pressure Delivery

CPAP Interfaces⁴

Nasal CPAP devices (Fig. 1) fall into four groups:

1. A long nasopharyngeal tube
2. A single nasal prong
3. Nose masks
4. Short binasal prongs.

Pooled analysis of randomized trials demonstrated that short binasal prongs are more effective at preventing reintubation than single nasal prongs.⁵

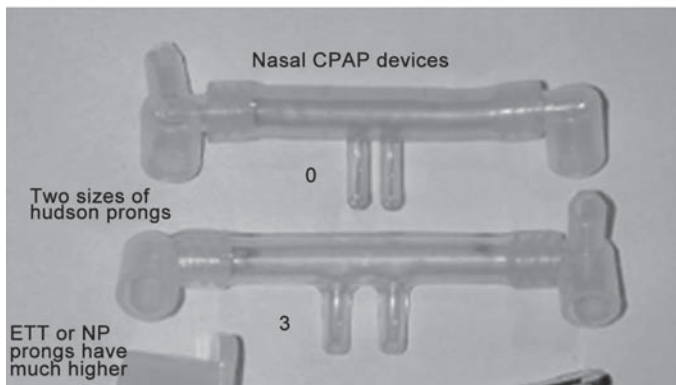
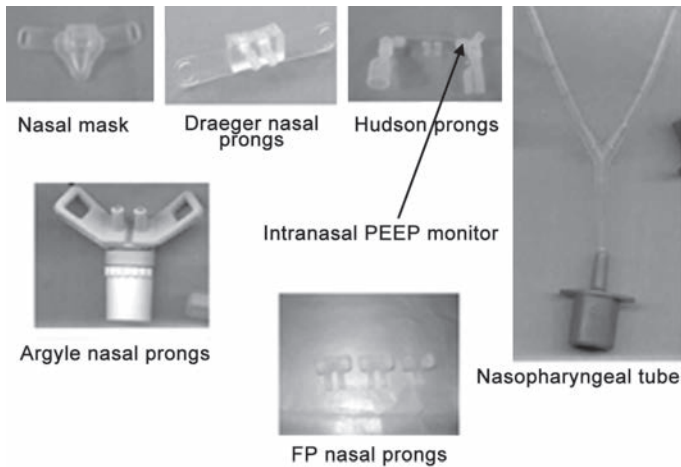


Fig. 1: Different types of nasal interfaces

The way CPAP pressure is generated is distinct from the interface device. There are four techniques for generating nasal CPAP.⁴

1. **Bubble CPAP:** With this technique gas flows past the nasal device and the pressure is generated in the circuit by placing the distal limb of the CPAP circuit under a known depth of water. Gas flow is increased until continuous bubbling is achieved (Fig. 2).
2. **Ventilator CPAP:** The ventilator PEEP (end-expiratory pressure) valve controls the CPAP delivered.
3. **Variable flow nCPAP devices:** These devices have an integrated nasal interface and pressure generator. They use a higher gas flow than other devices and pressure is generated by increased resistance as the gas leaves the nasal device. The pressure is determined by altering the flow of gas into the device (Fig. 3).
4. **High flow nasal cannulae:** High flow cannulae deliver gas flows >2 L/ min into the nostrils through small prongs which are loose in the nostrils. Low flow cannulae are used to deliver supplemental oxygen whereas high flow cannulae are used because it is thought that they provide some CPAP.⁶

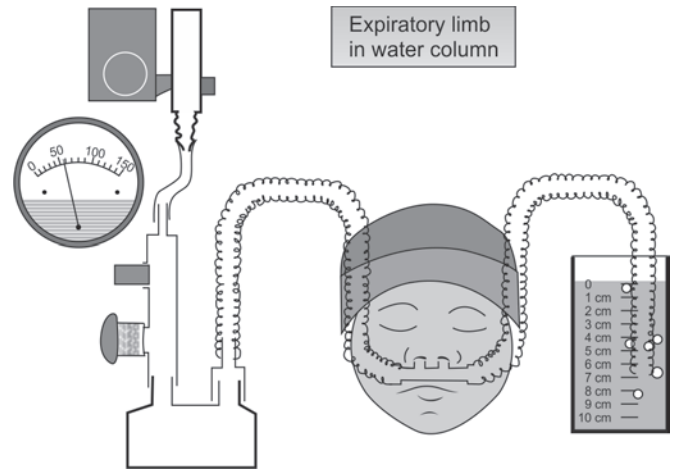


Fig. 2: Bubble nCPAP

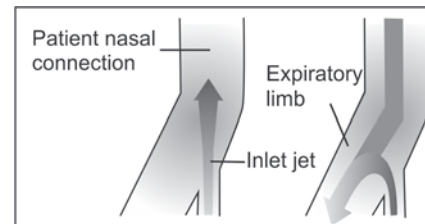


Fig. 3: Variable flow/fluidic flip

Problems of nCPAP⁷

1. **Leak at the nose and mouth:** It has been reported that the pharyngeal pressure drops markedly when the CPAP supported infant opens his mouth. The use of chin strap or pacifier is recommended to reduce mouth leak for effective CPAP support. However, it should not be so tight as to prevent the infant from yawning or crying but tight enough to prevent leaking at rest.
2. **Nasal trauma:** It is mostly caused by incorrect positioning of the prongs. To prevent injury the nasal device must not be pushed up against the columella. Injury can also occur inside the nose and erode the nasal septum if the prongs are not positioned straight into the nostrils.
3. **Gastric distention:** Gastric distention is common in the CPAP supported infant (CPAP belly syndrome). Frequent decompression of the stomach with an orogastric tube is necessary to promote comfort, preventing the distended stomach from splinting the diaphragm and compromising respiration.

How to Prevent Nasal Septal Injury?

Nasal septal injury is absolutely preventable by checking following things:

- Snugly fitting nasal prongs
- Secure caps
- Light weight interface
- Correct positioning and attachment of corrugated tubing (bubble)
- Velcro moustache (Hudson prong, bubble CPAP)
- Careful, frequent observation: give rest
- Careful positioning of the infant.

Indications for nCPAP⁴

- *Delivery room nCPAP:* The data from animal studies suggest that providing positive end-expiratory pressure (PEEP) during resuscitation reduces the alveolar-arterial oxygen gradient proportional to the level of PEEP applied, lowers indicators of acute lung injury, improves alveolar surfactant pool size, and improves oxygenation and ventilation/perfusion matching. Many studies suggested that treating very preterm infants with nCPAP in the delivery room could reduce the intubation rate and incidence of BPD without increasing mortality or morbidity.
- *Respiratory distress syndrome*
- *Prophylactic CPAP for very preterm:* CPAP is a noninvasive method with benefits in the treatment of the respiratory distress in preterm newborn of 28 to 32 gestational weeks. Using early CPAP may reduce necessity for surfactant, mechanical ventilation and BPD.
- *Postextubation:* A systematic review concludes nCPAP provided immediately after extubation to preterm infants reduced the rate of respiratory failure without clinically important side effects.

CURRENT PERSPECTIVE OF USE OF CPAP

CPAP was first reported in 1971 for supporting breathing of preterm neonates by Gregory GA.⁸ In the seventies, Dr. Jen-Tien Wung⁹ at the Columbian Presbyterian Medical Center, New York developed the bubble CPAP system using short nasal prongs. Columbia University, where the predominant mode of respiratory support was the use of nasal CPAP, had the lowest incidence of CLD without any significant difference in mortality. This renewed the interest of neonatologists in CPAP. The recent experience from Columbia University has been presented in more depth by Ammari et al,¹⁰ who reviewed the courses of 261 infants <1250 gram and reported their outcomes at 72 h of age based on the initial respiratory support modality. After resuscitation and stabilization at delivery, the bubble CPAP is routinely used as initial treatment in breathing very-low-birth-weight infants with RDS within 5 to 10 minutes of birth. Notably, only 51 percent of the infants who were CPAP failures and 53 percent of infants ventilated from birth received surfactant. Withholding surfactant treatment in such cases might have contributed to both

mortality and morbidity and cannot be evaluated because of incomplete patient details. In COIN trial, Colin J Morley¹¹ randomly assigned 610 infants who were born at 25 to 28 weeks' gestation to CPAP or intubation and ventilation at 5 minutes after birth. At 28 days, there was a lower risk of death or need for oxygen therapy in the CPAP group than in the intubation group (OR 0.63; 95% CI, 0.46 to 0.88; P = 0.006). There was little difference in overall mortality. The incidence of pneumothorax was 9 percent in the CPAP group, as compared with 3 percent in the intubation group (P<0.001). There were no other serious adverse events. The CPAP group had fewer days of ventilation.

NASAL INTERMITTENT POSITIVE PRESSURE VENTILATION⁴

Any mode of assisted ventilation that delivers positive pressure throughout the respiratory cycle with additional phasic increases in airway pressure, without the presence of an endotracheal tube. These additional phasic increases in airway pressure either synchronized or non-synchronized depending on the delivery system used. Nasal intermittent positive pressure ventilation (NIPPV) provides the benefits of CPAP with the addition of positive pressure breaths.

Terminology Used

- SNIPPV—synchronized nasal intermittent positive pressure ventilation
- NP-SIMV—nasopharyngeal synchronized intermittent mandatory ventilation
- N-SIMV—nasal synchronized intermittent mandatory ventilation
- N-SIPPV—nasal synchronized intermittent positive pressure ventilation
- N-BiPAP—nasal bilevel positive airway pressure
- NIMV—nasal intermittent mandatory ventilation
- NI-PSV—noninvasive pressure support ventilation

How does NIPPV Work?

The mechanism of action of NIPPV remains uncertain. It is unclear whether mechanical inflations during NIPPV are transmitted to the lungs. Moretti showed that some synchronized breaths were transmitted, but asynchronous breaths were not.

Delivery of NIPPV

Devices to generate NIPPV: Conventilators can be used to deliver nonsynchronized NIMV. The only specialized devices which attempt to provide synchronized NIPPV are the Infant Flow SiPAP and infant flow advance — IFDa (Viasys Healthcare, Conshohocken, PA, USA).

Nasal interface: Mask or prong.

How to start NIMV: Ventilator settings:

- No studies have investigated how different settings influence the effectiveness of NIPPV
- In published studies PEEP has ranged from 3 to 6 cm H₂O
- Range of peak pressures during NIPPV including the same PIP as pre-extubation, 2 to 4 cm H₂O higher than pre-extubation PIP 'to see the chest rise' or specific target pressures (16–20 cm H₂O)

However, the delivered pressure may be lower than the set pressure due to leak at the nose and mouth.

Indications

- RDS as a primary treatment
- Apnea of prematurity and
- Postextubation.

Criteria to discontinue NIMV

- Blood gas: If pH <7.2 and PCO₂ >65 mm
- Inability to improve gas exchange or increased work of breathing
- Hemodynamic instability.

SYNCHRONIZATION

Synchronizing NIPPV inflations with an infant's own breaths is theoretically advantageous. Flow sensors are not used because of large and variable leaks at the nose. Nonsynchronized NIPPV may deliver high pressure during spontaneous expiration, increasing the risk of raised upper airway pressure and pneumothorax. No trials have compared synchronized with nonsynchronized NIPPV, or examined the accuracy of synchronization devices in NIPPV.

NIPPV augments CPAP by superimposing ventilator inflations on nasal CPAP. Reviews of randomized controlled trials of NIPPV versus nasal CPAP show that NIPPV is more effective in preventing failure of extubation and may be useful in preterm infants with apnea.¹² No studies have described the use of NIPPV as first line therapy for early respiratory distress.

Complications of NIPPV

- Nasal trauma
- Gastric distention
- Pneumothorax.

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INTRODUCTION

Neonatal jaundice or hyperbilirubinemia during the neonatal period is one of the most common clinical condition requiring evaluation and treatment during the first few weeks after birth. It is also one of the most common reason for readmission during the first few weeks after birth and accounts for considerable health care expenditures worldwide.^{1,2} Neonatal jaundice may cause kernicterus or chronic postkernicteric bilirubin encephalopathy (CPKE), a severe neurologically debilitating condition.³ CPKE is largely a preventable condition and therefore it is essential to monitor neonates for jaundice and implement appropriate therapy in a timely manner.⁴ In developed countries, the incidence of severe jaundice (total serum bilirubin [TSB] ≥ 20 mg/dL) and associated bilirubin encephalopathy is low, however, in developing countries such as India and Africa, this preventable disease still occurs in epidemic proportion.⁵⁻¹⁰

BILIRUBIN METABOLISM

To better understand the etiology and pathophysiology of neonatal jaundice, it is essential to first understand bilirubin metabolism. Bilirubin is produced in a two-step process involving catabolism of heme which is present in hemoglobin, myoglobin, and other hemoproteins such as cytochromes and catalase.^{11,12} Although hemoglobin is the primary source of bilirubin, other sources may account up to 20 percent of bilirubin load, specifically in premature infants. In the first step of the 2-step process of catabolism, heme undergoes series of oxidation and reduction to be first broken down by microsomal heme oxygenase to biliverdin and simultaneously releasing carbon monoxide and ferrous iron. The first step is a rate limiting step. Moreover, heme-oxygenase enzyme is inducible not only by its substrate but also by oxidative stress strongly

indicating its putative role in antioxidant defense mechanism. Bilirubin is a known potent antioxidant and may have important role in prevention of free oxygen radical injuries commonly seen among premature infants.¹³ In the second step of heme catabolism which occurs in cytosol, biliverdin is reduced to bilirubin by biliverdin reductase. In this two step catabolic process, an equimolar concentration of carbon monoxide is produced and excreted via lungs and therefore end tidal carbon monoxide or carboxyhemoglobin concentration (corrected for ambient carbon monoxide) can be used as an index measure of bilirubin production.¹⁴ The bilirubin production in neonates is about 2 to 3 times greater than that of adults because of shortened erythrocyte life span (~80 days compared to ~120 days in the adult), increased turnover of hemoproteins, and cessation of hematopoiesis at birth leading to increased heme degradation.¹⁵ Hemolytic disorders such as G6PD deficiency, ABO incompatibility, Rhesus incompatibility, and hereditary spherocytosis are disorders associated with excessive bilirubin production.

The native form of bilirubin produced as a result of heme catabolism is an unconjugated bilirubin. Its bichromophoric tetrapyrrole structure, two dipyrroles separated by a saturated linkage, leads to its yellow color.¹⁶ The native bilirubin in its usual conformation (IX- α , Z,Z isomer) has its two rigid dipyrrole units internally hydrogen bonded to each other such that no polar (or ionizable) groups are exposed making it quite nonpolar and insoluble in water at normal pH.¹⁶ The unconjugated bilirubin is a lipid-soluble molecule that readily crosses biomembranes, including blood-brain barrier and neuronal cell membranes. The native bilirubin has been shown to be neurotoxic in both *in vivo* and *in vitro* studies.^{17,18}

The nonpolar unconjugated bilirubin released into the blood circulation from the reticuloendothelial system binds immediately to albumin which appears a protective

mechanism as bilirubin bound to albumin does not cross intact blood-brain barrier. The emerging literature suggests that free or unbound unconjugated bilirubin and not bilirubin bound to albumin crosses intact blood brain barrier and causes neurotoxicity.¹⁸⁻²³ There appears to be two major bilirubin binding sites on albumin and on an average each gram of albumin binds 8 mg/dl of unconjugated bilirubin in term neonates. In premature infants, the albumin concentration, bilirubin binding capacity, and bilirubin binding affinity (or strength of binding) is lower compared to term infants, increasing the risk of bilirubin toxicity.²⁴ The bilirubin bound to albumin can be displaced by strong displacers such as sulfa drugs, ibuprofen, ceftriaxone, and therefore medications known to strongly displace bilirubin are not recommended in the presence of unconjugated hyperbilirubinemia.^{17,25} In addition, in premature infants, several clinical factors such as intravenous fat emulsions, steroid usage, infection, etc. can be associated with elevated free fatty acid concentration, a known endogenous bilirubin displacer that has been shown to compete for bilirubin albumin binding sites. Therefore, to prevent a displacing effect, intravenous fat emulsion intake is limited in the presence of unconjugated hyperbilirubinemia. Recent studies suggest that the displacing effect of intravenous fat emulsion is gestational age dependent and is not seen in premature infants >30 weeks gestational age.^{26,27}

Unconjugated bilirubin bound to albumin is transported to liver where bilirubin dissociates from albumin and enters the hepatic cell by a process of carrier mediated diffusion. The carrier mediated diffusion into the hepatic cell and subsequent intracellular transport to endoplasmic reticulum is facilitated by two carrier proteins, Y and Z proteins (or organic anion transporters). In the endoplasmic reticulum of the hepatocytes, uridine diphosphoglucuronate glucuronosyl transferase (UGT) catalyzes transfer of one glucuronic acid molecule from the activated uridine diphosphoglucuronic acid (UDPGA) to bilirubin to form bilirubin monoglucuronide. Although bilirubin monoglucuronide is water soluble and can be easily excreted, additional conjugation occurs by the transfer of one molecule of glucuronic acid from one molecule of bilirubin monoglucuronide to another, resulting in the formation of bilirubin diglucuronides. This process is catalyzed with the help of transglucuronidase present in the canalicular border of the hepatic cell membrane. The conjugation process results in alteration of bilirubin molecule such that it prevents intramolecular hydrogen bonding and renders it water soluble. The maturational deficient activity of hepatic UGT during the first few hours to days after birth may contribute to unconjugated hyperbilirubinemia, specifically in premature infants. Hypothyroidism and inherited disorders such as Crigler-Najjar syndrome type 2 are associated with decreased activity of conjugating enzyme while Crigler-Najjar

syndrome type 1 is associated with absent hepatic UGT activity.

The water soluble conjugated bilirubin is then excreted from the hepatocyte into the biliary tree. The excretion process appears to be energy dependent as it occurs against a concentration gradient because bilirubin bile concentration is several folds greater in biliary tract than in hepatocytes. In the presence of hepatic cell injury or bilirubin obstruction, excretion is adversely affected leading to conjugated hyperbilirubinemia.

In the intestine, conjugated bilirubin can be deconjugated to unconjugated bilirubin in the presence of an alkali media or with the help of an enzyme beta-glucuronidase that is abundantly present in the intestinal mucosa, specifically in premature infants. The deconjugated bilirubin because of lipid solubility can then be reabsorbed (enterohepatic circulation) increasing the bilirubin load in the circulation. The enterohepatic circulation may account up to 25 percent of bilirubin load or TSB in the circulation, specifically in premature infants. The rest of bilirubin is converted to stercobilin by bacterial flora in the intestine and excreted in feces. Enteral feeding favors establishment of bacterial flora in the gut and helps conversion to stercobilin. Therefore, infants not receiving enteral feeding may have increased enterohepatic circulation.

It is evident from the understanding of bilirubin metabolism that bilirubin exists in four different forms in the blood:

- Unconjugated bilirubin not bound to albumin (also called free unconjugated bilirubin)
- Unconjugated bilirubin bound to albumin
- Free conjugated bilirubin
- Conjugated bilirubin bound to albumin also called 'δ' bilirubin. The free unconjugated bilirubin is present in extremely small amount under normal conditions. Hyperbilirubinemia is classified as either unconjugated hyperbilirubinemia or conjugated hyperbilirubinemia based on the relative proportion of bilirubin forms. The biochemical assays commonly used to measure and differentiate conjugate and unconjugate bilirubin concentration are based on van den Bergh reaction using diazo reagents. The direct reaction with diazo reagent reflects free conjugated bilirubin and not the 'δ' bilirubin, while indirect reaction with diazo reagent reflects unconjugated bilirubin (bound or free). Unconjugated hyperbilirubinemia is defined as an indirect-serum bilirubin concentration of ≥ 2 mg/dl. Conjugated hyperbilirubinemia is defined as direct serum bilirubin concentration ≥ 2 mg/dL and more than 20 percent of TSB concentration. The etiology and pathogenesis of conjugated or direct hyperbilirubinemia during neonatal period is much different from unconjugated hyperbilirubinemia and is beyond the scope of this chapter.

PATHOLOGY OF BILIRUBIN-INDUCED NEUROTOXICITY

Bilirubin has specific predilection for specific areas of brain that includes various cranial nerve nuclei particularly the cochlear nuclei, vestibular nuclei and oculomotor nuclei; various brainstem nuclei, particularly the reticular formation of the pons; the inferior olivary nuclei; the cerebellar nuclei, particularly the dentate; the basal ganglia, specifically, globus pallidus and subthalamus; the hippocampus, specifically, the sectors H2-3; and cerebellar vermis.¹⁷ Current literature suggests that auditory system is the most sensitive system to overt bilirubin induced neurotoxicity.¹⁷ Recent studies have shown that unconjugated bilirubin induced toxicity leads to neuronal cell death by both apoptosis and necrosis.^{28,29} Bilirubin neurotoxicity has been associated with long-lasting reduced neuritic outgrowth.²⁸ Unconjugated bilirubin has also been shown to affect myelination process by damaging oligodendrocytes.^{29,30}

CLINICAL MANIFESTATION

Neonatal jaundice is an extremely common neonatal problem with ~60 percent of late preterm and term infants have yellowish discoloration of skin, a clinical manifestation associated with transient elevations of serum bilirubin. Very premature infants (less than 32 weeks gestational age) may not manifest yellowish discoloration and usually need bilirubin levels to diagnose neonatal jaundice or hyperbilirubinemia. Overall, the incidence of hyperbilirubinemia defined as TSB ≥ 2 mg/dl is higher among premature infants compared to term infants with most premature infants developing some degree of hyperbilirubinemia. In developed countries, because of close monitoring and timely evaluation, only 5 to 15 percent of term neonates develop TSB levels greater than 12.9 mg/dl and even fewer develop severe jaundice (TSB levels ≥ 20 mg/dl).³¹ The true incidence of severe jaundice in developing countries is unknown but is thought to be much higher than that in developed countries.⁶

During fetal life, unconjugated bilirubin produced in fetus is easily transferred across placenta into maternal circulation and therefore neonates are rarely born with clinical manifestation of jaundice. The yellow discoloration of the skin and sclera is not usually seen until the TSB is >5 mg/dl. It is first seen on the face and then spreads down the body in a cephalocaudal progression. In order to appreciate clinical jaundice, examination should be done in the presence of adequate light and the skin should be blanched with a dermal pressure. Jaundice may be difficult to detect in darker-skinned infants and moreover estimation of TSB using inspection of anatomic progression of jaundice is often subjective and unreliable. Unconjugated bilirubin in the skin appears yellow or orange, whereas, conjugated bilirubin appears more greenish.

In term neonates, unconjugated hyperbilirubinemia typically peaks on day 2 to 5 of life at ~ 10 to 12 mg/dl among Asians, and ~ 5 to 6 mg/dl among Caucasians and Africans. The hyperbilirubinemia then decrease over the next few weeks to levels less than 2 mg/dl. This mild degree of hyperbilirubinemia is explained by physiological imbalance between bilirubin production and excretion during the first few days after birth and is considered physiological in the absence of known causes of pathological jaundice. In premature infants, physiological jaundice is more severe and peaks on day 5 to 7 compared to term infants. This is mainly explained by delay in maturation of hepatic conjugating enzymes in premature infants.

Additional clinical manifestations that may be present in term and late preterm neonates with jaundice include signs of dehydration, hemolysis, and/or acute bilirubin encephalopathy. The signs of dehydration secondary to insufficient enteral intake include lethargy, significant weight loss ($>10\%$ of birth weight), dry mucous membranes, decreased urine output, poor capillary refill, sunken eyes and fontanelle and poor skin turgor. Signs of hemolysis include pallor and enlarged spleen and liver.

All late preterm and term infants with moderate and severe neonatal jaundice should be evaluated for signs of acute bilirubin encephalopathy. In the early phase, infants manifest lethargy, hypotonia, and poor suck. In the intermediate phase, infants display high-pitched cry, irritability, and hypertonia (retrocollis-opisthotonos) alternating with drowsiness and hypotonia. During this phase, they may also develop a fever often confusing with a possible diagnosis of sepsis. Infants who reach the late phase may have increased retrocollis-opisthotonos, cessation of feeding, bicycling movements, inconsolable irritability and crying, seizures and coma. Some of these infants who display the late phase of acute bilirubin encephalopathy often die but majority who survive are likely to progress and develop CPKE. The bilirubin-induced neurological dysfunction (BIND) score has been proposed to monitor neurological manifestation of infants with acute bilirubin encephalopathy. BIND score may be a prognostic indicator for later CPKE.³² In premature infants, there are usually no specific clinical manifestations of acute bilirubin encephalopathy. Recent literature suggests that apnea may be the primary manifestation of acute bilirubin encephalopathy in premature infants.²¹

The manifestation of CPKE may take several years to develop and therefore infants with severe jaundice (TSB ≥ 20 mg/dl or those meeting American academy of pediatrics (AAP) criteria for exchange transfusion) should be closely followed and monitored at least during the first 5 years.^{17,33} The signs of CPKE include high frequency sensorineural hearing loss, auditory neuropathy spectrum disorder, upward gaze palsy, choreoathetoid palsy, and dental enamel hypoplasia.¹⁷ Emerging evidence suggests that sensorineural hearing loss and/or auditory

neuropathy spectrum disorder may be the sole manifestation of CPKE in premature infants.¹⁷ Auditory neuropathy spectrum disorder is defined as abnormal auditory neural function in the presence of normal outer hair cell function.^{17,34} Although emerging data suggests that neonatal jaundice may be associated with autism, further well defined studies are required to corroborate this association.³⁵

EVALUATIONS

All newborn infants with clinical jaundice should have TSB concentration measured and plotted on AAP nomogram for need of therapy or to predict probability of developing severe hyperbilirubinemia.³³ The AAP recommends interpretation of TSB levels in terms of the infant's age in hours and not in days. In other words, consider a scenario when TSB levels are measured on day 2 at two separate time points, 24.1 hours and 47.9 hours. A TSB level of 8 mg/dl at 24.1 hours is concerning and warrants further evaluation and a close follow-up, while the same level at 47.9 hours is less concerning. Further laboratory evaluation depends on the magnitude of hyperbilirubinemia. If the TSB concentration is above the 95th percentile for age or is rapidly rising and crossing percentiles, hemolytic jaundice should be ruled out using tests such as Coomb test, blood groups of infant and mother, peripheral smear for abnormal cells, reticulocyte count, and serial hematocrit. The rate of rise in TSB of >0.5 mg/hour in late preterm and term neonates and failure to respond to intensive phototherapy irrespective of age are also indicative of hemolytic jaundice. A thorough history and examination is also warranted as it may uncover a likely cause of jaundice. Several clinical factors have been associated with severe jaundice including breast milk feeding, ABO incompatibility, G6PD deficiency, East Asian ethnicity (China, Japan, Korea), clinical jaundice observed in the first 24 hours of life, cephalhematoma or significant skin bruising, history of previous sibling treated with phototherapy, late preterm infants, and male gender.³³ Some of these risk factors are further described below. Recent evidence suggests that combining risk factors with pre-discharge TSB or transcutaneous bilirubin concentration improves prediction of severe jaundice.^{36,37}

BREAST MILK AND BREAST FEEDING JAUNDICE

There is a strong association between breastfeeding and an increased incidence of neonatal hyperbilirubinemia.³⁸⁻⁴¹ The jaundice associated with breastfeeding during the first postnatal week has been referred to as breastfeeding jaundice. This occurs primarily because of difficulties in lactation resulting in decreased milk intake with fewer calories. The resultant decreased caloric intake or starvation along with delayed meconium passage increases enterohepatic circulation with secondary increase in bilirubin load. This

is usually seen with primigravida mothers, mothers who have delivered via cesarean section, and with late preterm infants. A timely counseling by a lactation consultant or a physician encouraging mothers for frequent breastfeeding (8 to 12 times per day) may prevent breastfeeding jaundice.⁴² The jaundice associated with human milk feeding that occurs beyond the first postnatal week is referred to as breast milk jaundice although there is considerable overlap between the two entities with breastfeeding jaundice often leading to breast milk jaundice. Breast milk associated jaundice has been associated with acute bilirubin encephalopathy and CPKE.⁴³ Animal studies suggest that milk contains beta-glucuronidase which can deconjugate bilirubin in the intestine facilitating enterohepatic circulation. Recent studies suggest that genetic polymorphism in UGT-1A1 or organic anion transporter genes also predispose infants who are receiving human milk to have prolonged and severe unconjugated hyperbilirubinemia.⁴⁴ Breastfeeding should be continued unless the TSB is ≥ 20 mg/dl. Even in such cases, only brief discontinuation of breastfeeding (~24 hours) is recommended. The bilirubin level should decrease with discontinuation of breast feeding. As breast milk feeding is resumed, TSB level will transiently increase by 1 to 3 mg/dl before gradually decreasing over several days despite continuation of breast milk feeding. This therapeutic response is highly indicative of breast milk jaundice.

Male Gender

Although the reasons are unknown, several studies have reported increased risk of severe jaundice in male neonates compared to female neonates.^{33,45} The higher prevalence of Gilbert syndrome and G6PD deficiency among males partly explain the increased incidence of severe jaundice in male neonates. There also appears to be increased susceptibility to bilirubin-induced injury in male neonates based on available literature.⁴⁶

Late Preterm Infant (34 to 37 Weeks Gestational Age)

Neonatal hyperbilirubinemia is more common and pronounced in late preterm infants compared to term infants.⁴⁶ There is a delay in postnatal maturation in hepatic bilirubin conjugation capacity in late preterm infants which may partly explain a higher incidence of severe jaundice in late preterm infants compared to term infants.⁴⁷ Moreover, late preterm neonates who are breastfed are also prone to lactation failure because of immaturity in sucking and swallowing and may therefore contribute to the genesis of severe jaundice in this population.⁴⁸ More importantly, the signs of bilirubin encephalopathy appear at an earlier postnatal age in late preterm infants compared to term infants suggesting that late preterm infants are more vulnerable to bilirubin-induced neurotoxicity.⁴³

ABO Hemolytic Disease

In developed countries, ABO incompatibility is the most common cause of hemolytic disease in neonates. In parts of developing countries where anti-D immunoglobulin G (RhoGAM) is routinely given to mother to prevent rhesus sensitization, ABO incompatibility is rapidly becoming the most common cause of hemolytic disease. ABO hemolytic disease has a variable clinical presentation with most presenting with rapidly progressive jaundice during the first couple of days after birth. However, compared to Rh D incompatibility where 100 percent of infants have positive direct antiglobulin test (Coombs) test, only 20 to 30 percent of infants with history of ABO incompatibility have positive direct Coombs test. Of these with positive direct coombs test, only 20 percent develop moderate to severe jaundice because of neutralizing of maternal IgG antibody by placental antigens and weak nature of A or B antibody.⁴⁹ A positive direct Coombs test indicate that anti-A or anti-B antibodies are attached to red cells but do not indicate hemolysis. A corroborative evidence of hemolysis is needed to diagnose ABO hemolytic jaundice. In term, infants with ABO incompatibility, other causes of hemolysis should be considered in the absence of positive Coombs test, however it is also important to remember that Coombs test has significant false negative rate in ABO incompatible neonates with hemolysis.^{50,51} More recently, co-existence of Gilbert syndrome (genetic polymorphism in UGT1A1) with coombs negative ABO incompatibility was shown to increase the risk of severe hyperbilirubinemia.⁵²

Glucose-6-phosphate Dehydrogenase (G6PD) Deficiency

G6PD deficiency is the most common and clinically significant red cell enzyme defect, affecting as many as 5 million newborns worldwide each year.^{53,54} G6PD deficiency is an X-linked condition primarily affecting hemizygous males and homozygous females but may affect heterozygous females (by way of nonrandom X chromosome inactivation). Several trigger factors such as illness, sulfa drugs, fava beans, naphthalene in moth balls, etc. are known to cause acute hemolysis in G6PD deficient infants. Besides hemolysis, G6PD deficient infants may have genetic polymorphisms involving UGT1A1 or organic anion transporter gene with impaired ability to conjugate bilirubin and hepatic uptake, respectively.⁵³ Infants with unexplained severe jaundice should be investigated for G6PD deficiency. It is important to recognize that G6PD assay may be false negative soon after the episode of hemolysis and should be repeated few weeks after hemolysis to rule out G6PD deficiency.

TREATMENT OF NEONATAL JAUNDICE

The AAP subcommittee on hyperbilirubinemia recommends phototherapy or exchange transfusion using hour-specific TSB levels for three separate groups of neonates defined based on gestational age and presence of risk factors: (1) Infants at lower risk (at least 38 weeks gestation and well); (2) Infants at medium risk (at least 38 weeks gestation with risk factors [defined as isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, acidosis, or albumin less than 3.0 g/dl] or 35^{0/7} to 37^{6/7} weeks gestation and well); (3) Infants at higher risk (35^{0/7} to 37^{6/7} weeks gestation with risk factors).³³ Each neonatal or pediatric unit involved in the care of infants with moderate to severe jaundice should have easy access to bilirubin graphs published by the AAP.³³ Alternatively, one can use instruments such as BiliTool (access at www.bilitool.org) which can be easily downloaded. Bilirubin:Albumin ratios should be used as an additional risk factor but not in lieu of the TSB in determining the need for exchange transfusion.³³ There are no guidelines for infants born between 34^{0/7} and 34^{6/7} weeks gestation because of lack of evidence. Secondly, the threshold level of TSB remains the same beyond the fourth day after birth. Thirdly, infants born between 37^{0/7} and 37^{6/7} weeks gestation (although term infants) are managed as late preterm regarding treatment with phototherapy or exchange transfusion.

Phototherapy is the mainstay of treatment for moderate to severe unconjugated hyperbilirubinemia.⁵⁵ Phototherapy induces geometric and structural isomerism of native bilirubin structure resulting in products that can be easily excreted in the bile or in the urine without further conjugation.⁵⁵ Several factors affect the efficacy of phototherapy including infant's distance from the light source, surface area exposed, type of phototherapy, and dose of phototherapy. At wavelengths between 425 and 490 nm (blue green spectrum), light penetrates the skin well and is absorbed maximally by serum bilirubin. Intensive phototherapy (irradiance of at least 30 mcW/cm²/nm) delivered to as much of the infant's surface area as possible is recommended by the AAP for the management of infants with severe jaundice.³³ For infants with TSB level at which exchange transfusion criteria is recommended, intensive therapy should be started immediately while preparations for exchange transfusion are made. When intensive phototherapy is applied, ~ 30 percent decrease in TSB concentration is expected within the first 24 hours, with the most significant decrease occurring in the first 4 to 6 hours. If the TSB does not decrease with intensive phototherapy within 4 hours after initiation, then exchange transfusion should be performed immediately. For infants

demonstrating signs of acute bilirubin encephalopathy or infants with TSB >5 mg/dl above the TSB level at which exchange transfusion is indicated, immediate exchange transfusion is indicated as per AAP guidelines.

Several studies have demonstrated effectiveness of high dose (500 to 1000 mg/kg) intravenous immunoglobulin therapy in decreasing hemolysis associated with Coombs positive hemolytic disease (Rh isoimmunization and ABO incompatibility).^{33,56} The number of infants needed to treat with intravenous immunoglobulin is 3 to prevent one exchange transfusion.⁵⁶ Intravenous immunoglobulin should be given slowly (over at least 2 hours) and can be repeated at 12 hours intervals until the bilirubin level stabilizes.

PREVENTION

Severe neonatal jaundice and its sequelae including acute bilirubin encephalopathy and CPKE are largely preventable. Preventive measures include the use of RhoGAM to prevent rhesus sensitization; universal screening for jaundice using serum or transcutaneous bilirubin measurement before newborn discharge to identify at-risk infants; provision of lactation consultant and breast pumps to avoid lactation failure and associated breastfeeding jaundice; parental counseling and education before newborn discharge regarding the need for timely follow-up with a physician for jaundice to prevent severe jaundice and appropriate therapy based on bilirubin thresholds and clinical risk factors as recommended by the AAP to decrease the incidence of severe hyperbilirubinemia and bilirubin encephalopathy.

FOLLOW-UP OF INFANTS WITH SEVERE JAUNDICE

All infants with severe jaundice (TSB \geq 20 mg/dl) or with TSB level at which exchange transfusion is indicated as per AAP guidelines should be followed for abnormal neurodevelopmental outcome during early childhood. These infants should be evaluated for auditory neuropathy spectrum disorder and sensorineural hearing loss using appropriate audiological evaluations.⁵⁷ Infants with severe jaundice should be followed annually for findings of CPKE and BIND during the first 5 years even in the absence of acute bilirubin encephalopathy at the time of severe jaundice.³² Early identification and appropriate intervention may decrease the severity of CPKE.

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Approach to Cholestatic Jaundice in Newborn

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BACKGROUND

Cholestatic jaundice is a serious pathological process indicating hepatobiliary dysfunction. It results from an alteration in bile flow and/or its excretion. Early detection and prompt intervention are critical. It is of paramount importance to differentiate cholestatic jaundice from physiologic jaundice of the newborn. Physiologic jaundice usually resolves by day 14 of life and is classically unconjugated hyperbilirubinemia. By two weeks of age—a small percent of newborns are still jaundiced.^{1,2} Among these a smaller percent would have biliary atresia requiring timely diagnosis and treatment, with a majority having benign breast milk jaundice. It is recommended that any child noted to be jaundiced at 2 weeks of age should be evaluated for cholestasis.³

Retention of bile components in the serum result in the biochemical features of cholestasis. Though the pattern and severity of these serum markers (Gamma glutamyl transferase, bilirubin, bile acids, liver panel, lipid profile, etc.) vary with the etiology, an elevated conjugated bilirubin is the hallmark in patients presenting with neonatal cholestasis. Cholestatic processes in the newborn can result from a myriad of pathologies as described in Table 1.

Neonatal conjugated hyperbilirubinemia is defined by a serum conjugated bilirubin concentration above 1.0 mg/dL (17.1 micromol/L) if the total serum bilirubin is <5.0 mg/dL (85.5 micromol/L) or above 20 percent of the total serum bilirubin if the total serum bilirubin is >5.0 mg/dL (85.5 micromol/L).³ Approximately 1 in every 2,500 infants have cholestatic jaundice of varying severity.^{4,5}

INITIAL EVALUATION

Since this chapter focuses on our approach to a patient with cholestatic jaundice, the authors, rather than focusing

on the individual disorders would take a holistic approach leading to a stepwise evaluation of such patients. Of paramount importance is a detailed history and examination.

History

A comprehensive history goes a long way in patient evaluation and leading to clues regarding the etiology of conjugated hyperbilirubinemia. It is important to address some of the following specific aspects of the history as detailed below:

1. *Infections:* Conjugated hyperbilirubinemia has been well described in association with bacterial infections. This likely result from the deleterious effects of bacterial endotoxin(s) on hepatic nuclear factors and bile formation.^{6,7} In clinically asymptomatic infants, conjugated hyperbilirubinemia, especially if it occurs after 8 days of life may result from urinary tract infection.⁸ Jaundice culminating from an underlying infectious process tends to resolve once the infection has been treated. Thus, it is vital to obtain a history of maternal or infantile fever, rashes or evidence of process indicating an infectious etiology.
2. *Stools:* Pale or clay colored stools reported by parents, though not diagnostic, raise the suspicion for cholestasis and is an important component of patient history. However, it is well reported in literature for infants with biliary atresia and other cholestatic diseases to have a variable stool color and be grossly pigmented at presentation.^{3,9} Persistent pale stools have been reported to have high specificity in clinical studies indicating liver disease. Parents are not always reliable historians for stool color even when asked specifically “What color is your baby’s stool?”.^{9,10} Modest improvement was shown in studies where a score card showing normal and abnormal stool color was presented to families.¹¹ The authors recommend that patterns of

<i>Extrahepatic disorders</i>	Rotor syndrome
Biliary atresia	Dubin-Johnson syndrome
Bile duct stricture/neonatal sclerosing cholangitis	Mitochondrial hepatopathies
Choledochal cyst	Other metabolic defects
Anomalies of the pancreaticoduodenal junction	α 1-Antitrypsin deficiency
Spontaneous perforation of the bile duct	Cystic fibrosis
Inspissated bile	Hypopituitarism
Mass	Hypothyroidism
Intraductular: Stone, rhabdomyosarcoma	Neonatal iron storage disease
Extraductular: Hepatoblastoma, neuroblastoma	Infantile copper overload (Menkes syndrome)
<i>Intrahepatic disorders</i>	Hemophagocytic lymphohistiocytosis
Idiopathic	Arginase deficiency
“Idiopathic” neonatal hepatitis	<i>Toxic</i>
Intrahepatic cholestasis, persistent	Total parenteral nutrition–associated cholestasis
Severe intrahepatic cholestasis with progressive hepatocellular disease	Fetal alcohol syndrome
Alagille syndrome (syndromic paucity of the intrahepatic bile ducts, arteriohepatic dysplasia)	Other drugs (maternal or used in neonatal intensive care)
Nonsyndromic paucity of the intrahepatic bile ducts	<i>Cholestasis associated with infection</i>
Intrahepatic cholestasis, recurrent	Sepsis with possible endotoxemia (urinary tract infection, gastroenteritis)
Benign recurrent intrahepatic cholestasis	Syphilis
Hereditary cholestasis with lymphedema (Aagaard syndrome)	Toxoplasmosis
Anatomic	Listeriosis
Congenital hepatic fibrosis or infantile polycystic disease (liver and kidney)	Congenital viral infections
Caroli disease	Cytomegalovirus
Metabolic or endocrine disorders	Herpes virus (herpes simplex and human herpes virus 6)
Disorders of amino acid metabolism	Cocksackievirus
Tyrosinemia	Echoviruses
Disorders of lipid metabolism	Rubella virus
Cholesterol ester storage disease (Wolman)	Hepatitis B virus
Niemann-Pick disease	Other hepatitis viruses
Gaucher disease	Human immunodeficiency virus (HIV)
Disorders of carbohydrate metabolism	Parvovirus B19
Galactosemia	<i>Chromosomal</i>
Fructosemia	Trisomy 18
Glycogen storage disease type IV	Trisomy 21 (Down syndrome)
Disorders of bile acid metabolism, primary	Donohue syndrome (leprechaunism)
β -Hydroxysteroid δ 5-C27 steroid dehydrogenase/ isomerase	<i>Vascular disorders</i>
δ 5–3-Oxosteroid δ 5 β -reductase (multiple mutations)	Budd-Chiari syndrome
Disorders of bile acid metabolism, secondary	Perinatal asphyxia
Zellweger syndrome (cerebrohepatorenal syndrome)	Multiple hemangiomata
Peroxisomal enzymopathies	Cardiac insufficiency
(Adapted from W Allan Walker, Ronald E Kleinman, Philip M Sherman, Benjamin L Shneider, Ian R Sanderson: Pediatric Gastrointestinal Disease)	<i>Miscellaneous</i>
Disorders of bile acid transport	Congenital disorders of glycosylation
	Shock, hypoperfusion
	Intestinal obstruction
	Neonatal lupus
	ARC syndrome (arthrogryposis, renal tubular dysfunction, and cholestasis)

3. Persistent or intermittent irritability or vomiting may indicate metabolic disease or sepsis. A history of lethargy, seizures or delayed milestone achievement may indicate metabolic disease, hypothyroidism or panhypopituitarism. A family history of early childhood

deaths or jaundice can indicate an inherited disorder like progressive familial intrahepatic cholestasis (PFIC), cystic fibrosis, alpha-1 antitrypsin deficiency, etc.

4. *Parenteral nutrition:* It is important to inquire about the use of parenteral nutrition. Parenteral nutrition has been in use since the 1960s. It has been one of the most promising modalities of nutrition in neonates and older pediatric patients with lost or impaired gut functions. There are over several thousand patients permanently dependent on parenteral nutrition (PN) for survival. In addition, there are several fold higher numbers of patients requiring PN for varying duration during hospital stay or home care. Unfortunately, its use is associated with complications of sepsis and Parenteral Nutrition Associated Liver Disease (PNALD).¹² The clinical spectrum of PNALD includes steatosis, disruption in glucose and lipid metabolism, cholestasis, cholelithiasis, hepatic fibrosis, biliary cirrhosis, development of portal hypertension and liver failure. Among the various postulated mechanisms, a lack of enteral feeding resulting in the disruption of enterohepatic circulation appears to be a major contributor towards PNALD, with its greatest predilection in patients on total parenteral nutrition and no enteral nutrition. Thus both the duration and the percentage of parenteral nutrition versus enteral nutrition being provided to a patient are critical in the development of PNALD.¹³

Physical Examination

General Examination

Assessment of general health including vital signs and anthropometric parameters is essential.³ Infants with metabolic disease or infections may be ill appearing or with poor growth, alternatively patients with biliary atresia are generally healthy other than being jaundiced. Like biliary atresia, patients with Alagille syndrome appear healthy, however, they may have characteristic triangular facies and physical appearances.¹⁴ Fundoscopic examination may give clues to a congenital infection or metabolic diseases as would infants tone, vigor and general symmetry. Skin rashes, jaundice, petechiae or bruising are important to document and cannot be ignored. Abdominal examination is essential to evaluate hepatic or splenic enlargement, contour, consistency. Polysplenia is associated with a subtype of biliary atresia. Hepatosplenomegaly may indicate a storage disorder. The presence of abdominal masses, ascites, prominent veins or umbilical hernia may indicate pathology. Patients with Alagille syndrome have a characteristic cardiac systolic murmur and thus a thorough cardiac exam is of paramount importance.^{15,16}

The detection of cholestasis is dependent largely on the clinical recognition of jaundice, along with subtle clues obtained on history and examination as no screening test is predictive of cholestasis. Though, each of these findings is an imperfect method of detecting cholestasis, it forms the basis for further evaluation.^{17,18}

LABORATORY STUDIES

Blood

To establish cholestasis it is important to obtain conjugated bilirubin levels. It is equally important to determine extent of hepatic dysfunction in an effort to evaluate etiology and further intervention. The authors recommend a complete liver panel to include total and conjugated bilirubin, serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST), serum alkaline phosphatase, albumin level and gamma-glutamyl transpeptidase (GGT). Elevated GGT can indicate bile duct damage and raises concerns for biliary atresia.^{19,20} Such an evaluation in conjunction with transaminases may also help in diagnosing conditions like progressive familial intrahepatic cholestasis (PFIC) as well as neonatal cholestasis. In addition marked serum bile acid elevation is also indicative of PFIC especially with modestly elevated conjugated bilirubin and GGT levels.^{21,22} Though transaminases can help determine hepatic injury they may not accurately define hepatic synthetic abilities. Such evaluation of hepatic biosynthetic capacity may be assessed by prothrombin and partial thromboplastin time (PT, PTT), as they require clotting factors produced by the liver. Serum albumin and glucose concentrations would also similarly help.^{23,24} Elevated blood ammonia may indicate an impaired hepatic ability to clear endogenous substances. A complete blood count, platelet count, blood culture, urine culture and urine analysis may help point to an infectious etiology. Urine reducing substances are known to be elevated in patients with galactosemia provided a lactose containing milk (including breast milk) is being fed.^{25,26} Serum bicarbonate or pH disturbances are indicative of metabolic diseases. Other tests to include are thyroid function test, sweat chloride or mutation analysis for cystic fibrosis, lipid panel (cholesterol elevation seen with Alagille syndrome) and alpha 1 antitrypsin level with Pi typing. Radiological evidence of butterfly vertebrae in a cholestatic infant raises suspicion for Alagille syndrome. Use of specific markers for infective hepatitis like CMV, EBV, including a viral hepatitis panel (Hepatitis A-E) might be a consideration.²⁷⁻²⁹ As the etiological processes resulting in cholestasis are varied and can govern laboratory testing, specific situation may warrant additional testing.

IMAGING STUDIES

Ultrasonography

Abdominal ultrasonography being a noninvasive and a relatively widely available test is commonly used as the initial test. It serves as an effective initial tool to assess the hepatobiliary structures. When correlated with pathologic, surgical, and subsequent clinical examinations, the sensitivity and specificity of a small or absent gallbladder in detecting obstruction is reported at 73 percent and 67 percent, respectively. Indicators for biliary atresia include the inability to visualize the gallbladder and the presence of a triangular cord sign (triangular or band like periportal echogenic density >3 mm in thickness).³⁰⁻³² An ultrasound is however quite helpful in the diagnosis of choledochal cysts. It can also determine echotexture disturbances of the hepatic parenchyma indicative of parenchymal injury.

Hepatobiliary Scintigraphy

A HIDA scan or Hepatobiliary Imino-Diacetic Acid scan involves uptake of technetium-labeled imino-diacetic acid analogs by the hepatocytes and its subsequent excretion into the biliary system. It requires an adequate hepatocellular function and patent biliary tract. An abnormality in this pathway is thus identifiable, helping differentiate biliary atresia from neonatal hepatitis. A 83 percent sensitivity and 33 specificity of scintigraphy has been reported in detecting obstruction. This wide variability is likely due to its institution and operator dependability and variations in use among different centers.^{33,34} A normal uptake but impaired excretion is indicative of biliary atresia, alternatively patients with neonatal hepatitis have appropriate excretion, though delayed uptake due to parenchymal injury.^{3,35,36} Pretreatment for five days with phenobarbital (5 mg/kg/day) has been advocated in some studies as a means to improve the accuracy by enhancing isotope excretion, however due to the potential for delaying a diagnosis, such is not routinely practiced. Scintigraphy helps in determining the patency of the biliary track and differentiating biliary atresia from neonatal hepatitis, however, it should not be used as the sole differentiating criteria.³⁷⁻³⁹ A duodenal aspirate has been used for assessing bile excretion into the duodenum. The test is based on the evaluation of the duodenal aspirate for bilirubin. At a 91 percent sensitivity and 43 percent specificity, with the need for potential fluoroscopic placement of the duodenal tube, this test is not routinely performed.^{3,40,41} However it may have a special importance in situation where other tests are not available or deemed unfeasible.

ADDITIONAL EVALUATION

Cholangiogram

Due to the time sensitivity of biliary atresia management a timely diagnosis is critical. If the above mentioned evaluation is indicative of biliary atresia a percutaneous or intra-operative cholangiogram would be the next logical step. In large studies, it is considered the gold standard in the diagnosis of biliary atresia. A Kasai Surgery (hepatoportoenterostomy) is indicated if contrast is unable to fill the biliary tract or reach the intestine.⁴²⁻⁴⁵

Endoscopic Retrograde Cholangiopancreatography (ERCP)

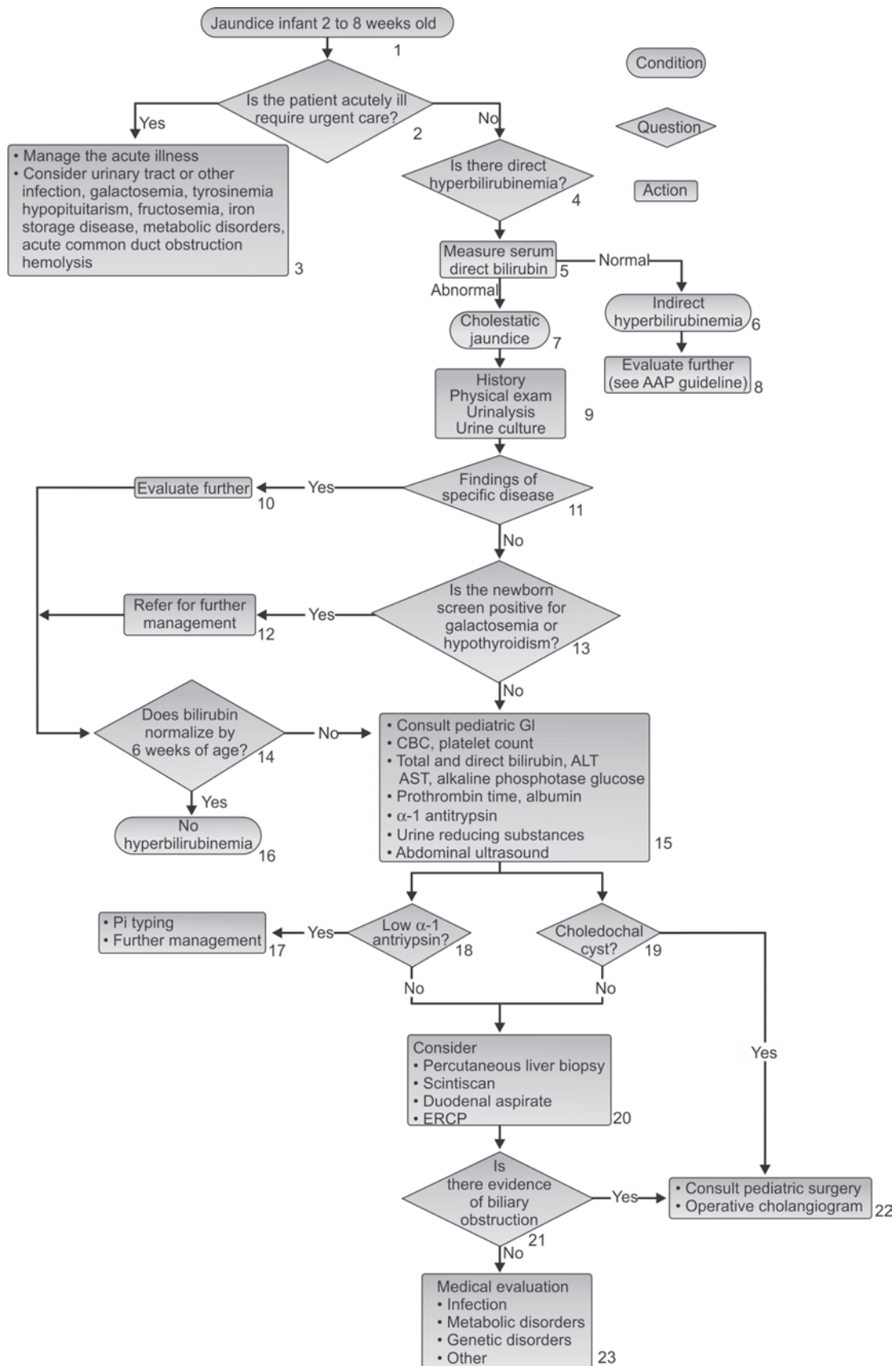
An endoscopic intubation of the biliary tract with contrast injection and radiological evaluation is another method to assess the biliary system with high sensitivity and specificity.⁴⁶⁻⁴⁸ However, due to its limited availability at pediatric centers and size restrictions due to the infant population, it is done only at a few select specialized centers.^{49,50} Alternatively, a magnetic resonance cholangiopancreatography (MRCP) might be another consideration. Though the negative and positive predictive values of MRCP in the detection of biliary atresia are reported at 91 percent and 75 to 96 percent, respectively, it cannot be relied upon exclusively.⁵¹⁻⁵⁵

Liver Biopsy

Due to the relative safety and high yield of the test a percutaneous liver biopsy is a recommendation for most infants with undiagnosed cholestasis. Data suggests interpretation is best if done by pathologists experienced in pediatric liver diseases.⁵⁶⁻⁵⁹ The timing of biopsy is important as results may be equivocal even in patients with biliary atresia if performed before 6 weeks of age.^{56,60,61}

In summary, evaluating neonatal cholestasis is a complex process, however a step by step approach can guide logical decision making. An algorithm developed by the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition Cholestasis Guideline Committee can prove helpful and is recommended by the authors (Flow chart 1). A practicing pediatrician comes across several jaundiced patients and vigilance is crucial in detecting and selecting patients requiring further evaluation. As treatment is directed by the patient status and etiopathogenesis of the underlying condition, it is discussed in subsequent chapters.

Flow chart 18.1: Cholestasis clinical practice guideline. Algorithm for a 2 to 8-week-old infant (North American Society for Pediatric Gastroenterology, Hepatology and Nutrition Cholestasis Guideline Committee)



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CHAPTER 19

Recent Advances in the Diagnosis and Management of Neonatal Sepsis

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Neonatal sepsis is one of the most important causes of morbidity and mortality in newborn. Among the low birth weight and preterm babies, neonatal septicemia is the most important cause of mortality especially in developing countries including India. Neonatal septicemia is defined as generalized systemic infection of the newborn, associated with pure growth of bacteria from one or more sites. The exact incidence of neonatal infection in India is not known. There is lack of authentic community data on neonatal sepsis. Bang et al from Gadchiroli district of Maharashtra has reported an incidence of 6.5 percent and 53 percent as a cause of mortality in the newborn period.¹ According to National Neonatal Perinatal Database (NNPD) 2 from hospitals, the incidence ranges from 0.1 percent to 4.5 percent with an overall mortality rate varying from 22 to 30 percent. In the Western literature, the incidence of neonatal sepsis ranges from 0.01 to 0.8 percent.³ With an estimated 25 million births occurring in India and approximately 2 percent incidence of sepsis, the figure for neonatal sepsis in India would be 500,000 babies every year with about one-third, i.e. 170,000 babies succumbing to the disease.

DEFINITION

Neonatal sepsis can broadly classified into early-onset sepsis (<72 hours) and late onset sepsis (>72 hours). Early onset sepsis (EOS) often presents as a fulminant, multi-system illness within 72 hours of delivery and is mainly due to bacteria acquired before and during delivery whereas late onset sepsis (LOS) is due to bacteria acquired after delivery (nosocomial or community sources) and can present as either a fulminant or a smoldering infection. EOS presents with prominent respiratory signs while LOS has more varied presentations.

National Neonatology Forum of India defines neonatal sepsis as follows:

Proven sepsis: The baby presents with clinical picture of sepsis and isolation of pathogens from blood, CSF, urine or other body fluids or autopsy evidence of sepsis.

Probable sepsis: Newborn with clinical picture suggestive of sepsis with one or more of the following criteria:

- Existence of predisposing factors, e.g. maternal fever foul smelling liquor or prolonged rupture of the membrane (>12 hours) or gastric polymorphs more than 6/high power field.
- Positive septic screen (two of the four parameters to be present)
- Total leukocytes count $<5,000/\text{mm}^3$, immature to total neutrophil count ratio >0.2 , C-reactive protein positive and micro ESR $>15 \text{ mm/1st hour}$ or $>\text{age}$ in days + 3.
- Radiological evidence of pneumonia.

Sepsis syndrome: When septicemia is associated with altered organ perfusion (hypoxia, increased blood lactate, oliguria and altered mental state) it is termed as sepsis syndrome. If untreated, this condition leads to early septic shock with decreased capillary refilling and low blood pressure, which can be reversible with appropriate treatment. If untreated this state progresses quickly into refractory shock and leads to multiorgan system dysfunction.

ORGANISMS CAUSING NEONATAL SEPSIS

The etiological agents causing neonatal sepsis vary from region to region and also whether it is community acquired or in hospital set up. It also depends upon the early on set or late onset sepsis. Early onset sepsis is vertically acquired infection from mothers or delivery room settings where maternal gastrointestinal and genital

flora would predominate. In contrast, late onset sepsis is acquired from the environment in the hospital/home and the organisms would be determined by the prevailing microflora of the surroundings. The common organisms reported by NNPD Survey showed 3.8 percent incidence of neonatal sepsis from pooled hospital data with *Klebsiella*, *Staph. aureus*, *Esch. coli*, *Pseudomonas*, *Enterobacter*, Coagulase negative *Staphylococcus*, *Acenatobacter* and *Candida* as the predominant organisms. Group B *Streptococcus*, which is a common etiological agent of early onset sepsis in Western countries is rarely encountered in Indian scenario.^{2,4-7} In the Indian subcontinent, the distinction between EOS and LOS is somewhat blurred.⁸ The clinical presentations of EOS and LOS are different and risk factors are different, but the organisms causing the EOS and LOS are similar and so are their sensitivity profile.^{1,9}

RISK FACTORS FOR EARLY ONSET NEONATAL SEPSIS

Perinatally acquired neonatal bacterial infection usually manifests within the first 3 days of life and is also termed as early onset sepsis. There are several risk factors for neonatal infection.¹⁰ Table 1 depicts the risk factors for sepsis. A good history especially maternal history and elicitation of risk factors are of great importance in the assessment of individual baby and the need for empirical antibiotic therapy. Asymptomatic baby at high risk should receive empiric antibiotic therapy pending culture reports. On the contrary those at low risk should be evaluated and observed. Risk factors are additive and presence of more than two risk factors increases the risk of sepsis manifold (Table 1). Most of the risk factors defined are from the west where group B *Streptococcus* is the etiological agent for early onset sepsis. Some of the risk factors are discussed as follows:

- *Prolonged rupture of membranes (PROM)*: The risk of sepsis in newborns born to mothers with rupture of membranes for more than 24 hours has been reported to be 1 percent compared to a baseline incidence of 0.1 to 0.5 percent.
- *Chorioamnionitis*: It clinically manifests with maternal fever, abdominal/uterine tenderness, foul smelling or purulent amniotic fluid and fetal tachycardia or silent wherein there is histologic evidence of inflammation, but no symptoms or signs. Chorioamnionitis increases the risk of sepsis by 2 to 3 times. A number of diagnostic tests have emerged as markers of chorioamnionitis (Table 2). If PROM is associated with chorioamnionitis, the risk of sepsis increases by four-fold.
- *Prematurity and low birth weight*: Preterm babies are deficient in immunoglobulin concentration, complement function

Table 1: Risk factors for neonatal sepsis

Maternal factors

- Fever
- Urinary tract infection, diarrhea
- Prolonged rupture of the membrane >24 hours.
- Foul smelling amniotic fluid
- Maternal amnionitis
- Maternal genital tract infection and genital colonization
- Socioeconomic factors: Poor socioeconomic status, poor nutrition and hygiene

Neonatal factors

- Preterm and low birth weight
- Perinatal asphyxia
- Vigorous resuscitation
- Invasive procedures
- Congenital malformations, e.g. meningomyelocele
- Male child

Table 2: Diagnostic tests for chorioamnionitis

- Amniotic fluid Gram stain for bacteria, leukocytes ($>50/\text{mm}^3$), culture, leukocyte esterase, glucose concentration $<20 \text{ mg/dl}$, C-reactive protein positive and broad based PCR and IL-6.
- Maternal leukocytosis ($>12,000/\text{mm}^3$), serum C-reactive protein positive, serum IL-6.
- Evidence of oligohydramnios on ultrasound, low biophysical profile.
- Polymorphonuclear leukocytes and intracellular organisms in gastric aspirate of the neonates.

and phagocytic activity. They have 3 to 10 times higher risk of developing sepsis than term infants. Chorioamnionitis may coexist and may trigger for preterm labor. Association of chorioamnionitis and low birth weight increases the risk of sepsis to 16 percent compared to association with normal weight babies.

- *Perinatal asphyxia*: Asphyxia is associated with depressed immune function. In addition, several interventional procedures increase the risk of infection. Presence of low Apgar score (6 or less at 5 minutes) along with prolonged rupture of membranes has shown to increase the risk of infection by 4 percent and 27 percent.
- *Male gender*: Boys have 2 to 6 times higher risk of development of neonatal sepsis.
- *Other factors*: Maternal fever, genitourinary tract infection, poor socioeconomic condition and feeding artificial milk are other risk factors attributed for sepsis.

CLINICAL DIAGNOSIS OF NEONATAL SEPSIS

The early and efficient diagnosis of neonatal bacterial sepsis remains a difficult task since most of the symptoms and signs

of sepsis in the neonatal period are of nonspecific nature. The spectrum and severity of symptoms required to decide in the evaluation of sepsis is a matter of clinical judgement. The symptomatology of sepsis is mostly individual baby to specific and always cannot be dictated by a written protocol. The nonspecific nature of the symptomatology makes it very difficult to clinically diagnose sepsis and if there is delay in initiation of treatment till obvious clinical signs develop, it may be too late to prevent the mortality. On the contrary, if presumptive antibiotic treatment is initiated, there is always a risk of overtreatment. It is estimated that between 11 and 23 noninfected newborns are treated in neonatal intensive care nurseries for every one with documented infection.

The manifestation of sepsis depends on whether it is early onset' or 'late onset' and association of serious bacterial infection, e.g. meningitis, septicemia, pneumonia, bone and joint infection, urinary tract infection and necrotizing enterocolitis. Table 3 depicts differences in early and late onset neonatal sepsis.

The common nonspecific symptoms for possible bacterial sepsis include¹¹⁻¹⁴ respiratory distress, lethargy, fever or hypothermia, hypo- or hyperglycemia, hypotonia, grunting, vomiting, feeding intolerance, abdominal distention, apnea, cyanotic spells, seizures, poor perfusion/shock, petechiae or purpura, unexplained jaundice, or not looking well. Specific data for some of the symptoms are available to aid in decision making. In term babies, respiratory distress after excluding transient tachypnea of newborn is more likely to be secondary to sepsis or pneumonia. The newborn with meconium aspiration syndrome should be considered infective unless proved otherwise. About 10 percent of full term newborns with fever ($>37.8^{\circ}\text{C}$) not due to environmental causes will have bacterial sepsis. Shock, convulsion, bulging anterior fontanelle are other important signs. An unexplained

increase in the serum direct bilirubin concentration may be associated with bacterial sepsis. World Health Organization (WHO) in the integrated management of childhood illness module for young infants 7 days to 2 months of age suggested following criteria to diagnose possible serious bacterial infection¹⁵ (Table 4).

The decision to evaluate and treat a neonate with possible sepsis based on symptoms and signs is a matter of clinical judgment. If a baby looks very sick, develops significant respiratory distress, fever or shock, it should be treated as bacterial sepsis with antibiotic pending culture results. Beyond these, the clinician must rely on careful history with special emphasis on maternal history, thorough physical examination, assessment of severity of symptoms and laboratory investigations.

LABORATORY DIAGNOSIS

Although the isolation of microorganisms from blood, CSF or urine remains the gold standard for confirmation of neonatal sepsis, several nonculture methods of diagnostic tests have been developed with very good sensitivity and negative predictive value. In relation to neonatal sepsis following terms needs little elaboration.

- *Sensitivity*: If infection is present, how often is the test result abnormal?
- *Specificity*: If infection is absent, how often is the test result normal?
- *Positive predictive value*: If the test result is abnormal, how often is the infection present?
- *Negative predictive value*: If the test result is normal, how often is infection absent?

Following table (Table 5) shows the calculation of diagnostic value of tests:

Table 3: Differences in early and late onset sepsis

	Early onset	Late onset
• Time of onset	Less than 72 hours	>72 hours
• Complication of pregnancy/delivery	Present	May or may not be present
• Source of organism	Maternal genital tract	Hospital environment
• Usual clinical presentation	Fulminant multi-system	Slowly progressive
• Meningitis	Rare	Common
• Organisms	<i>Esch. Coli</i> , <i>Klebsiella</i> , <i>Proteus</i> , <i>Staph. aureus</i> Coagulase negative <i>Staph.</i>	<i>Klebsiella</i> , <i>Staph aureus</i> , coagulase negative <i>staph.</i> , <i>Pseudomonas</i> species.
• Mortality	30-50%	15-30%

Table 4: Classification of sick young infants for bacterial infection (WHO)

Signs	Classify as
<ul style="list-style-type: none"> • Convulsion or • Fast breathing (60 breaths per minute or more) or • Severe chest in-drawing or • Nasal flaring or • Grunting or • Bulging fontanelle or • Pus draining from ear or • Umbilical redness extending to skin or • Fever (37.5°C or above or feels hot) or low body temperature (less than 35.5°C or feels cold) or • Many or severe skin pustules or • Lethargic or unconscious or • Less than normal movement 	→ Possible serious bacterial infection
<ul style="list-style-type: none"> • Red umbilicus or draining pus • Skin pustules 	→ Local bacteria infection

Table 5: Interpretation of diagnostic value of tests

Screening test	Blood culture positive	Blood culture negative	Total
CRP +ve	a (80)	b (50)	All CRP +ve $a + b = 130$
CRP -ve	c (20)	d (150)	All CRP -ve Babies $c + d = 170$
Total	All septic babies $a + c = 100$	All nonseptic babies $b + d = 200$	All babies $a + b + c + d = 300$

Sensitivity of CRP test would be = Proportion of septic babies (Blood culture +ve) who are CRP +ve = $a/a+c = 80/100$ or 80 percent. This is also known as true positive rate.

Specificity = Proportion of nonseptic babies who are CRP -ve = $d/b+d = 150/50+150 = 75$ percent. This is also known as true negative rate.

Positive predictive value = Proportion of CRP+ve babies who are septic = $a/a+b = 80/80+50 = 61.5$ percent.

Negative predictive value = Proportion of CRP -ve babies who are nonseptic = $c+d/c = 20+150/20 = 85$ percent.

Diagnostic tests with maximal (100%) sensitivity and negative predictive value are desirable for diagnosis of neonatal sepsis. This indicates if infection were present, the result would be always abnormal and if results were normal, infection would always be absent. A good specificity and positive predictive value is also acceptable.

Definitive, Specific Diagnostic Tests

Isolation of organism from blood or a central body fluid is the standard and most specific method to confirm the diagnosis of neonatal sepsis. The main drawback is that, the results are available after 48 to 72 hours. Another dilemma often faced by the clinicians is the high percentage of cases (up to 40%) where no bacteria can be isolated from blood even in highly suspected cases of sepsis.

Blood Culture

The standard microbiological procedure is to collect about 1 ml of blood by sterile venepuncture in a blood culture bottle. If, there is already umbilical arterial catheterization, blood sample can be collected from the indwelling catheter but collection of blood from an indwelling umbilical venous catheter is not reliable. The blood culture should be incubated for at least 72 hours before being considered negative. In a study conducted by Geme JW¹⁶ et al, 13 percent of positive blood culture did not grow until beyond 72 hours. The late growing organisms were anaerobes and coagulase negative staphylococci. Blood culture although considered to be “gold standard” in the confirmation of diagnosis of septicemia has been found to

be negative in 20 percent cases where infection was proven by immediate postmortem culture and autopsy.^{17,18} In the mildly symptomatic neonate and at the earliest onset of septicemia, the false negative blood culture rate would be very high. In addition, up to 50 percent of the cases with congenital bacterial pneumonia proved by tracheal aspirate culture, blood culture is negative. Therefore blood culture should not be considered as the final arbiter for the clinical diagnosis of neonatal infection.

Automated systems for continuous monitoring of blood cultures coming into routine use have shortened the time to identify positive blood cultures. In most cases of neonatal sepsis, a blood culture will become positive within 24 to 36 hours. This was illustrated in a study of 455 positive blood cultures from 222 preterm and term infants evaluated for neonatal sepsis. An automated blood culture system identified 77, 89, and 94 percent of all microorganisms within 24, 36, and 48 hours of incubation in aerobic conditions, respectively.¹⁹

In a prospective observational study from India, 101 cases of suspected neonatal sepsis were used to compare the manual method of blood culture with an automated BacT/Alert system for detection of neonatal septicemia. The mean times to positivity with the manual and BacT/Alert 3D systems were 53.1 h and 14.3 h, respectively ($p < 0.001$). With conventional methods the detection rate is 89.1 percent by day 2 and 99.5 percent by day 4.²⁰

Cerebrospinal Fluid Examination and Culture

All neonates with suspected septicemia as a primary diagnosis should have a lumbar puncture.^{21,22} Newborns suffering from meningitis may have specific symptoms and 20-30 percent of neonates with sepsis may have associated meningitis. Moreover, 15 percent of babies with positive CSF culture may have negative blood culture. The interpretation of CSF cytology and biochemistry in newborn is often difficult.

The concentration of glucose is not significantly altered by a traumatic lumbar puncture. Therefore a low CSF glucose in the setting of a traumatic LP is abnormal. Nothing much is gained by using the various formulas for adjusting the WBC count in a traumatic CSF, based on the RBC counts. Adjustment merely results in a loss of sensitivity with marginal gain in specificity.²³ Ideally, the WBC cell count must be performed within 30 minutes of drawing the sample. It must be noted that CSF WBC and glucose rapidly fall with time, giving spurious results.²⁴

Traditionally, the following cut-offs have been used: 30 cells, more than 60 percent of polymorphs, glucose less than 50 percent of blood glucose, protein more than 150 mg/dl in term babies and 180 mg/dl in preterm babies.

Urine Culture

Urine culture by bag specimen is highly unreliable and should not be obtained by this method. The urine specimen

should be obtained by sterile bladder tap only in suspected cases of urinary tract infection. Urine culture sample is very difficult to obtain and has a very low yield of organism especially in first 72 hours.²⁵

Tracheal Aspirates

Tracheal aspirate samples are useful in first 12 hours of life. Sherman²⁶ et al demonstrated that a positive tracheal culture may be found in 44 percent of babies with pneumonia where blood culture was sterile. Furthermore, there is a positive correlation of tracheal aspirate Gram stain for bacteria with clinical or pathological pneumonia and has a 47 percent predictive accuracy in bacteremic infants.

Polymerase Chain Reaction

Polymerase chain reaction (PCR) is a definite advancement in the armamentarium in the diagnosis of bacterial infection. However, the prohibitive cost and difficult technique precludes its use in the routine evaluation of neonatal sepsis.

Latex Particle Agglutination Test

Latex particle agglutination test (LPA) is a relatively simple test to perform but is not very sensitive. The standard kits for group B *Streptococcus*, *Pneumococcus* and *Meningococcus* are available and hence can not be used routinely.

Nonspecific Diagnostic Septic Screening Tests

The difficulties in accurate diagnosis of neonatal septicemia have prompted investigators to evaluate many adjunctive diagnostic tests many of which can be done in the clinical side laboratories that may indicate infection without identifying the infecting organisms. Because of the severity of the disease, it is essential for these indirect tests not to miss any case (have 100% sensitivity) and to rule out convincingly sepsis when it is not present (have a high negative value). Therefore, to achieve both the above goals, one must be willing to treat some infants who are truly not infected. A battery of tests have been evaluated either alone or in combinations in order to improve diagnostic accuracy.²⁷⁻³⁰ Table 6 summarizes the tests and their sensitivity and specificity.

White Blood Cell Count

The work of Manroe et al²⁷ has increased the utility of this test through the establishment of normal reference ranges for total neutrophil counts and indices of immature neutrophils. A total leukocyte count of $<5000/\text{mm}^3$, total neutrophil count of $>1750/\text{mm}^3$ and an immature to total neutrophil count ratio (I/T) of >0.2 are suggestive of sepsis. From the study by Schelonka et al,³¹ the normal ranges for leukocyte indexes in 193 healthy term infants with no identifiable perinatal risk factors

for infection were at 4h of life considerably broader than those described previously by Manroe et al. Thus, if one applies the reference intervals of Manroe et al to healthy term infants, one would label huge numbers of them as being at extremely high risk for sepsis. It is important to remember that the actual physical sampling can lead to dramatic changes in the CBC results. It has been well documented that the CBC depends on the infant's age, on whether the sample is arterial or venous, and on whether the infant is crying vigorously.^{27,31,32} This means that for a given infant, a test value is not a static value; there is considerable intraindividual variability.

However, the wide range of predictive values in Table 6 are explained by many factors. Some studies have combined proven sepsis patients with suspected sepsis. In addition maternal hypertension, perinatal asphyxia and intraventricular hemorrhage may cause neutropenia. Nonspecific stresses such as asphyxia, maternal fever or stressful labor can elevate the I/T ratio. Very few studies have shown that the presence of neutrophil vacuolization or toxic granulation are also good indicators of neonatal sepsis.³³

C-reactive Protein (CRP)

C-reactive protein (CRP) is a rapidly responsive acute phase reactant, which is synthesized by the liver within 6-8 hours of stimulus of inflammatory process. It can be performed in the side laboratory by a positive CRP latex agglutination test on an undiluted sample, which corresponds to a plasma CRP concentration of 0.8 to 1.0 mg/dl. A single value of negative CRP done at the onset may not be of much significance. Therefore, in suspected sepsis, a repeat CRP test done 12 hours later is more significant. If the test is negative — it almost excludes sepsis. CRP also has a very important role in prognosis of sepsis. Normalization of CRP is a helpful tool in determining the response to antimicrobial therapy and duration of treatment. Failure to mount a CRP response is a poor prognostic sign.

Erythrocyte Sedimentation Rate

Micro-ESR is an inexpensive and easy bedside screening test for neonatal sepsis. Normal values increase with postnatal age and are equal to the day of life plus 3 mm/hour up to a maximum of 15 mm/hour. Erythrocyte sedimentation rate (ESR) is less sensitive but more specific than CRP or I/T ratio.

Other Acute Phase Reactants

Haptoglobin and orosomucoid are acute phase reactants that have been evaluated for diagnostic aids for neonatal sepsis, but their utility is limited because of their slower response to infection. A low plasma fibronectin concentration (an opsonic glycoprotein) is suggestive of neonatal sepsis. Plasma fibronectin is also depressed by respiratory

distress syndrome and perinatal asphyxia thus limiting its use.

Miscellaneous Tests

- Elastase-alpha-1-proteinase inhibitor complex rises rapidly in the course of infection and is 100 percent sensitive although not highly specific.
- C3D is a major byproduct of complement activation by endotoxin or antigen antibody complexes and is elevated in infected neonates.
- Endotoxin, which can be measured by Limulus amoebocyte lysate test is found in the plasma of many neonates with infection.
- Direct visualization of bacteria in neutrophils stained by acridine orange is an important diagnostic test in neonatal sepsis.
- Neutrophils from septic patients may reduce the dye nitroblue tetrazolium (NBT) more quickly than those from normal healthy patients.
- Gastric aspirate for polymorph count and culture has limited value in the diagnosis of neonatal sepsis. However, this test is indicative of high risk because of exposure to chorioamnionitis.

NEWER DIAGNOSTIC MODALITIES

Procalcitonin

A propeptide of calcitonin, is released into the blood 3 to 6 hours after endotoxin injection and increases up to 24 hours; the increase does not correlate with calcitonin levels and occurs even in subjects who have had thyroidectomy. Very high serum procalcitonin levels are present in neonates with proven or clinically diagnosed bacterial infection; early decrease of these concentrations reflects appropriate antibiotic therapy.³⁴ Compared with CRP, procalcitonin has the advantage that it increases more rapidly; however, the significant rapid variations of basal levels after birth, and the need for several different cut-off values with changing neonatal age, have limited the diffusion of this marker in comparison to the CRP.³⁵ Nevertheless, a recent meta-analysis suggested that procalcitonin showed better accuracy than the CRP test for the diagnosis of late-onset sepsis.³⁶

Cytokines and Receptors

The cascade of events initiated by the bacterial infection starts with the activation of macrophages thereby releasing several inflammatory cytokines and growth factors. The cytokines released are tumor necrosis factor (TNF- α), interleukin beta (IL- β) and interleukin-6 (IL-6). Interleukin-3 (IL-3) and colony stimulating factors (CSFs) are the growth factors liberated by the macrophages. These mediators trigger the inflammatory reaction with formation of acute phase reactants by the liver and activation of

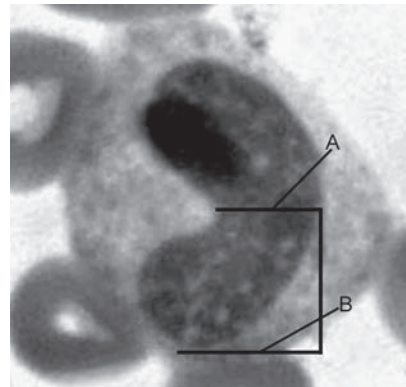


Fig. 1: Band cell: The ratio A:B should be more than 1/3 to differentiate it from segmented polymorphonuclear cell

neutrophils. The increase in cytokines levels is therefore observed much earlier than the hematological values (Fig. 1). Several cytokines have been evaluated for the early diagnosis of neonatal sepsis.

Interleukin-6 (IL-6) and interleukin-1 receptor antagonist (IL-1ra) are two important diagnostic markers for neonatal sepsis. The level of these two markers increases 2 days before clinical diagnosis of sepsis. IL-6 although is a very early marker, the level becomes normal later even if infection continues. The simultaneous determination of CRP can obviate this problem because the rise in plasma CRP levels occurs 12 to 48 hours after the onset of infection, at a time when IL-6 level would have fallen.

Specific Leukocyte Surface Antigens

They are known to be expressed in substantial quantities after inflammatory cells are activated by bacteria or their cellular products. In newborns, cell surface antigens have been studied in connection with congenital, early and late onset sepsis. Neutrophil CD11b and CD64 have been found to be promising markers for diagnosis of early and late infections respectively. CD11b is a subunit of the b2 integrin adhesion molecule. It is normally expressed at a very low concentration on the surface of nonactivated neutrophils.^{37,38} Its expression, however, increases considerably within a few minutes after the inflammatory cells come into contact with bacteria and endotoxins.^{39,40}

CD64 is a highly effective marker for the diagnosis of late onset infection.³⁷ CD64 is normally expressed in very low concentrations by unstimulated neutrophils. It is considerably upregulated on the trigger of bacterial invasion³⁷ and has been shown to be involved in the process of phagocytosis and intracellular killing of pathogens. More importantly, neutrophils from preterm infants express CD64 during bacterial infections to the same degree as those from term infants, children, and adults.³⁷

Granulocyte colony stimulating factor (G-CSF) is a hematopoietic growth factor produced by several types

of cells such as monocyte-macrophages, epithelial cells, endothelial cells and fibroblasts. Polysaccharide is a major stimulus for G-CSF production in sepsis. The higher level of G-CSF has been found to be associated with a sensitivity of 95 percent for prediction of sepsis and a specificity of 73 percent if the level is >200 pg/ml.

The best combination for newer markers for sepsis would be estimation of IL-6 and IL-1ra one to two days before the onset of symptoms. IL-6, IL-1ra, IL-8, CD 11b, G-CSF, TNF, CRP and hematological indices on day 0, CRP, IL-6 (or G-CSF) and hematological indices on day 1, and CRP on the following days to monitor response to treatment. CD64 is probably one of the most useful infection markers for diagnosis of late onset nosocomial sepsis. In addition, the use of multiple markers, in particular, combining an early sensitive marker with a late specific test will further enhance the diagnostic accuracy of these mediators in identifying infected cases. These promising markers may be used for early termination of antibiotic treatment in noninfected infants. However, none of the current diagnostic markers are sensitive and specific enough to influence the judgment to withhold antimicrobial treatment independent of the clinical findings. Until further evidence from larger studies are available, daily routine screening for prediction of neonatal infection is not warranted.

Broad Based PCR

A broad based PCR with amplification of bacterial DNA, i.e. 16 Sr DNA has been used for identification of bacteria but the cost is prohibitive.

WBC—White blood cell count; I/T—immature to total neutrophil ratio; CRP—C-reactive protein; ESR—Erythrocyte sedimentation rate – NBT—Nitro blue tetrazolium dye test (Flow chart 1).

Anti-inflammatory cytokines: IL-4, IL-10, TGF-B1, G-CSF. Inhibition of T.

Sepsis Screen

As is evident from Table 6, no single test is of high diagnostic value. Therefore, a combination of at least 2 or more tests, if abnormal, leads to an increase in predictability for early onset sepsis. Sepsis screen has been found to be cost effective in decreasing the use of antibiotic in the nursery.

Proteomics and Genomics

Modern applications of molecular pathology embraces various disciplines: genomics (sequence DNA), transcriptomics (mRNA identification), proteomics (protein identification) and pharmacogenomics (genes that define the behavior of drugs). Proteomics is the study of expressed proteins in a tissue, cell, or organism at a given moment. It is clinically more significant and easier to translate into diagnostic tools and therapeutic strategies than genomics, which studies DNA.

The science of proteomics has been applied to the search for biomarkers and production of protein profiles that can rapidly help the prediction, early diagnosis, and

Flow chart 1: Cytokines and acute phase reactants

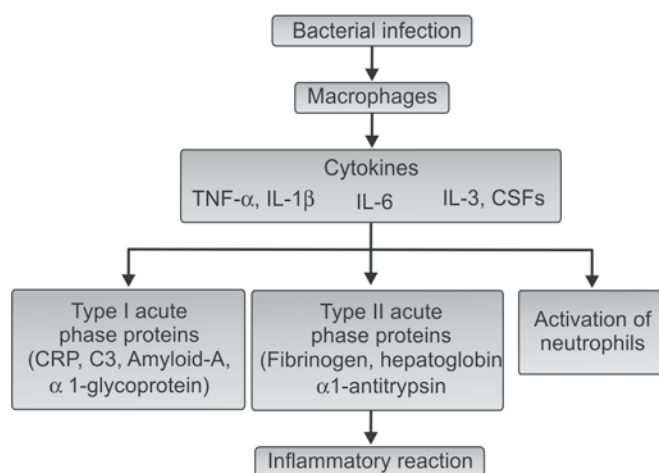


Table 6: Performance of adjunctive tests in diagnosis of neonatal sepsis

Test	Sensitivity	Specificity	Positive predictive value%	Negative predictive accuracy%
• Total WBC <5000/mm ³	21	91	27	91
• I/T ratio >0.2	90-100	50-78	11-51	99-100
• CRP	47-100	83-94	6-83	71-99
• Micro ESR	27-50	83-97	24-43	94-97
• Neutropenia <1750 mm ³	38-96	61-92	20-77	96-99
• Haptoglobin	25-54	86-95	30-38	94.0
• Fibronectin	75	63	11	98
• C3d	74	84	44	95
• Acridine orange cyto spin	38-77	94	59	NA
• NBT test	76-100	71	37	NA
• WBC+CRP+I/T + mESR + Haptoglobin	93	88	39	99
• WBC+I/T +CRT+ mESR	100	83	27	100

treatment of human diseases.⁴¹ To analyze proteomics data from SELDI-TOF (surface enhanced laser desorption ionization time-of-flight) outputs, Buhimschi et al.⁴² developed a strategy to extract significant proteomic biomarkers characteristic for intra-amniotic inflammation, based on sequentially applied filter preferences. This strategy was called mass restricted (MR) scoring. The MR score indicate the number of identifiable markers among the following factors of innate immunity: neutrophil defensin-2, neutrophil defensin-1, S100A12 (calgranulin C) and S100A8 (calgranulin A).⁴² An MR score of 3 to 4 indicated the presence of inflammation, while a score of 0 to 2 excluded it. An MR score of 3 to 4 had the highest accuracy (92.6%) in diagnosing intra-amniotic inflammation, and was significantly better than white blood cell (WBC) count or IL-6.

Molecular techniques: There are also molecular-based approaches for diagnosis of neonatal infection:

- Whole blood directly tested by target amplification;
- Whole blood pre-enrichment before target amplification;
- Fluids from positive blood culture bottles tested by polymerase chain reaction (PCR);
- Nucleic Acid Sequence Based Amplification (NASBA);
- Nucleic Acid Amplification Tests (NAATs);
- PCR in conjunction with sequencing or microarray analysis;
- Nonamplification-based fluorescence in situ hybridization (FISH).

The sensitivity and specificity of real-time PCR assay was 96.2 percent and 100 percent respectively,⁴³ with a limit of recognition for *E. coli* and group B Streptococcus, while in another study that targeted several larger 16S rDNA, was 66.7 percent and 87.5 percent.⁴⁴

Genetic Polymorphism

The possibility of understanding the genetic contribution to response to microbial pathogens remains one of the most stimulating prospects of the unravelling of the human genome. The identification of strong associations between certain genetic polymorphisms and susceptibility to severe sepsis supports further research using appropriate association studies.⁴⁵

Recent evidence that the genetic background of the host affects the systemic response to infection has stimulated considerable interest in the evaluation of genetic susceptibility to sepsis, concerning in particular factors of the initial immune response of the innate immunity, as Toll-like receptors (TLRs), mannose-binding lectin (MBL), nucleotide-binding oligomerization domains (NODs) and cytokines.⁴⁶⁻⁴⁸

A recent meta-analysis assessed the evidence for the association of the IL-6 (-174C) polymorphism (guanidine to cytosine transition at position -174 nucleotides relative

to the transcription start site in the interleukin-6 gene) with the risk of sepsis in very light birth weight (VLBW) newborn infants. The results of six cohort studies including a total of 1323 VLBW infants found no significant association between carriage of the IL-6 (-174C) polymorphism and sepsis: pooled relative risk 0.90 (95% CI 0.62 to 1.31). These data did not support screening infants for this allele in order to guide selective antimicrobial prophylaxis.⁴⁹

MANAGEMENT PROTOCOL

Symptomatic Neonate

If the clinician has a suspicion that the baby is having probable or suspected sepsis then the baby should be immediately started on antibiotics. Here, the risk factors or maternal pretreatment with antibiotic is immaterial. The choice of antibiotic would depend upon the prevalence of organism in a particular set up and their antibiogram pattern. In most centers in India and the world, the first line of antibiotic is usually a combination of Inj. Ampicillin and Inj. Amikacin or Gentamicin. Simultaneously sepsis screening is performed, blood and CSF cultures are sent and a chest X-ray is performed. If the mother has been receiving antibiotic treatment, then irrespective of the result of the screening test and culture report (positive or negative), antibiotic treatment is continued for 7 to 10 days in case of pneumonia, 10 to 14 days for septicemia and 14 to 21 days for meningitis. If however, there was no maternal pretreatment with antibiotic and sepsis screen is normal and cultures are sterile and baby is normal, the antibiotic may be discontinued after 72 hours if baby is clinically stable (Flow chart 2).

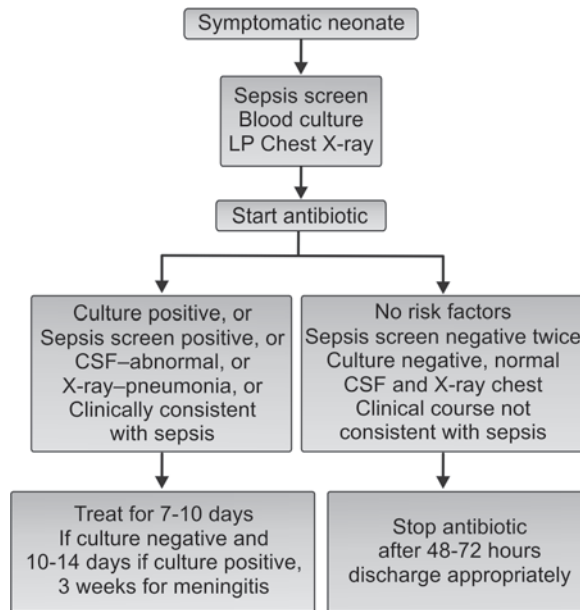
After the culture and sensitivity report is available and depending upon its pattern, antibiotic is changed. If there is clinical deterioration, irrespective of the investigation report, the second line of antibiotic i.e., a third generation of Cephalosporin and an aminoglycoside e.g., gentamicin, amikacin or netromycin are given. In case meningitis is suspected, third generation cephalosporin is started from the very beginning.

Asymptomatic Neonate

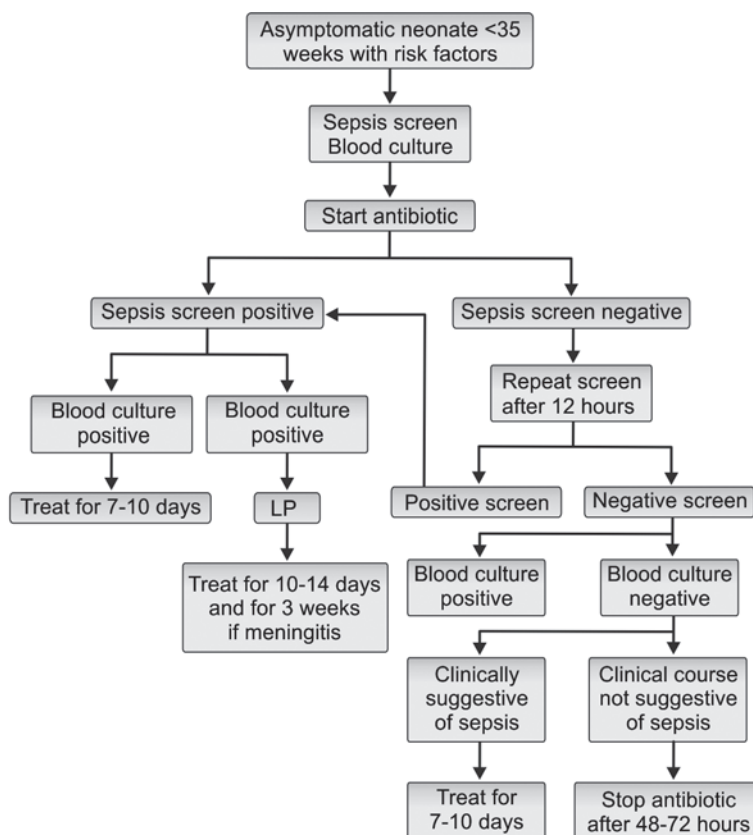
If the baby is asymptomatic and is a low-risk newborn for sepsis (one or 2 risk factors) then the baby should be observed clinically for 48 hours and a sepsis screening performed. If the baby is asymptomatic and is a high risk for infection (>3 risk factors), then sepsis screening is done and antibiotic started. If the sepsis screen is positive or negative and blood culture is negative and the mother did not receive any pretreatment, the antibiotic is discontinued after 72 hours. However, if the culture is positive, antibiotic is continued as for symptomatic baby. On the other hand, if the mother has received antibiotic

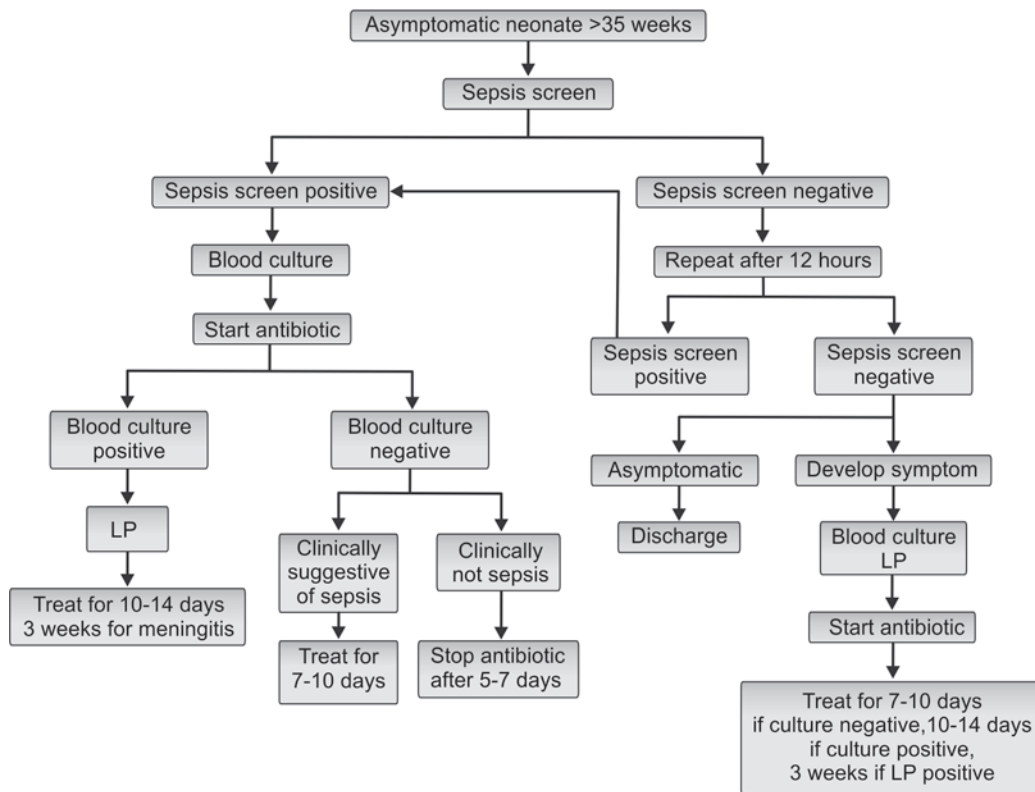
and the sepsis screen and/ or culture is positive then antibiotic is continued as in symptomatic baby and the antibiotic is discontinued after 72 hours if the screening tests and culture is normal (Flow charts 3 and 4).

Flow chart 2: Approach to a symptomatic neonate



Flow chart 3: Approach to asymptomatic neonate <35 weeks gestation with one or more risk factors



Flow chart 4: Asymptomatic neonate 35 weeks gestation or more with one or more risk factors

ANTIBIOTICS IN NEONATAL SEPSIS

The choice of empirical use of antibiotics for neonatal septicemia depends upon many factors, e.g. availability, affordability, community acquired or nosocomial, antibiotic sensitivity pattern of the nursery and the type of infection. In clinical practice for community acquired neonatal sepsis the first line of drug is usually a combination of aminoglycoside, i.e. gentamicin, amikacin or netromicin along with ampicillin or crystalline penicillin. If the condition does not improve, then third generation cephalosporin is added to the aminoglycoside and ampicillin is stopped. In contrast in hospital acquired neonatal sepsis, a combination of aminoglycoside and third generation cephalosporin is the drug of choice. If antibiotic sensitivity pattern is known, then choice of the drug is made accordingly. With the advent of several newer generations of antibiotics, there is a general tendency to use latest drugs, which is not always warranted. Rational use of antibiotics is essential to reduce the long-term effect of emergence of drug resistance and economic burden to the family. There are several antibiotics available and are used routinely in neonatal septicemia. Table 7 depicts the antibiotics and their doses in newborn period.

SUPPORTIVE THERAPY

Apart from antimicrobial therapy, supportive and symptomatic care is of vital importance for the intact survival of these babies.

The supportive therapy includes the following:

- Temperature regulation
- Careful management of fluid and electrolyte, normoglycemia, acid base status and oxygenation.
- Nutritional management
- Control of seizures if occur
- Management of shock if it develops
- Blood and blood component therapy if indicated.
- Early surgical intervention in case of septic arthritis, peritonitis and necrotizing enterocolitis.

NEWER MODALITIES IN THE TREATMENT OF NEONATAL SEPSIS

Intravenous immunoglobulin (IVIG): Some investigators have attributed high rates of sepsis in neonates to low levels of IgG immunoglobulin and have hypothesized that intravenous immunoglobulin therapy in the neonate is an acceptable approach for treatment. Similar to most

Table 7: Antibiotics, antifungal and antiviral agents and their doses in neonates

S.No	Name of the antibiotic	Dose
1	Acyclovir	IV/PO 20 mg/kg/dose q 8 hrly
2.	Amikacin	<ul style="list-style-type: none"> < 29 weeks: 0-7 d 18 mg/kg/dose q 48 h; 8-28 d 15 mg/kg/dose q 36 hr; > 29 d 15 mg/kg/dose q 24 h 30-34 wk: 0-7 d: 18 mg/kg/dose q 36 h; >8 d: 15 mg/kg/dose q 24 hr >35 wk: All: 15 mg/kg/dose q 24 h
3	Amoxicillin	15 mg/kg/dose q 12 hrly
4.	Amoxicillin + Clavulanic acid	15 mg/kg/dose q 12 hrly based on amoxicillin
5.	Amphotericin B	Day 1: 0.5-1 mg/kg/dose infused over 4-6 hrs. 1.5 mg/kg/dose with resistant infections. Total dose: 30-35 mg/kg over 6 weeks
6.	Amphotericin B liposome	IV 1-5 mg/kg/dose q 24 hr over 2 hrs
7.	Ampicillin	25-50 mg/kg/dose <ul style="list-style-type: none"> <29 wk 0-28 d: q 12 h; >28 d: q 8 h 30-36 wk: 0-14 d: q 12 h; > 14 d: q 8 h 37-44 wk: 0-7 d: q 12 h; > 7d: q 8 h > 45 wk: All: q 6 h
8.	Ceftazidime	30 mg/kg/dose over 30 min. <ul style="list-style-type: none"> <29 weeks up to 4 weeks of age q 12 h 30-36 weeks up to 2 weeks q 12 h; >2 weeks q 8 h 37-44 weeks up to 1 week q 12 h; >1 week q 8 h
9.	Cefotaxime	50 mg/kg/dose <ul style="list-style-type: none"> <29 weeks up to 4 weeks of age q 12 h 30-36 weeks up to 2 weeks q 12 h; >2 weeks q 8 h 37-44 weeks up to 1 week q 12 h; >1 week q 8 h
10.	Erythromycin	PO/IV 10 mg/kg/dose <ul style="list-style-type: none"> <7 days q 12 hrly > 7 days q 8 hrly
11.	Fluconazole	IV/PO loading 12 mg/kg; Maintenance: 6 mg/kg/dose <ul style="list-style-type: none"> <30 wk up to 2 weeks q 72 h, > 2 weeks q 48 h 30-36 weeks up to 2 weeks q 48 h; >2 weeks q 24 h 37-44 weeks up to 1 week q 48 h; >1 week q 24 h
12	Flucytosine	20-40 mg/kg q 6 hr
13.	Gentamicin	IM/IV <ul style="list-style-type: none"> < 29 week: 5 mg/kg/dose: 0-7 d: 4 mg/kg/dose: q 48 h; 8-28 d: 4 mg/kg/dose: q36 h; > 29 d: 4 mg/kg/dose: q 24 h 30-34 week: 0-7 d: 4.5 mg/kg/dose q 36 h; >8d: 4mg/kg/dose q 24 h > 35 week: All: 4 mg/kg/dose q 24 h
14.	Imipenem-Cilastatin	20-25 mg/kg/dose q 12 h
15.	Meropenem	20 mg/kg/dose q 12 h. Meningitis: 40 mg/kg/dose q 8 h
16.	Metronidazole	IV/PO 15 mg/kg loading, 7.5 mg/kg infusion dose over 60 minutes. <ul style="list-style-type: none"> <30 week up to 4 weeks q 48 h 30-36 weeks up to 2 weeks q 12 h ; >2 weeks q 12 h 37-44 weeks up to 1 week q 24 h; >1 week q 12 h.
17.	Ticarcillin	75-100 mg/kg/dose IV Infusion <ul style="list-style-type: none"> <29 weeks up to 4 weeks of age q 18 h; > 2 weeks q 12 h 30-36 weeks up to 2 weeks q 12 h; >2 weeks q 8 h 37-44 weeks up to 1 week q 12 h; >1 week q 8 h

18.	Vancomycin	Meningitis: 15 mg/kg/dose Bacteremia: 10 mg/kg/dose <ul style="list-style-type: none"> • <29 weeks up to 2 weeks of age q 18 h; > 2 weeks q 12 h • 30-36 weeks up to 2 weeks q 12 h; >2 weeks q 8 h • 37-44 weeks up to 1 week q 12 h; >1 week q 8 h
19.	Tobramycin	Same as Gentamicin
20.	Piperacillin-Tazobactam	50-100 mg/kg/dose as Piperacillin component <ul style="list-style-type: none"> • <29 weeks up to 4 weeks of age q 12 h; > 4 weeks q 8 h • 30-36 weeks up to 2 weeks q 12 h; >2 weeks q 8 h • 37-44 weeks up to 1 week q 12 h; >1 week q 8 h
21.	Chloramphenicol	Loading dose: 20 mg/kg IV infusion Maintenance dose: <ul style="list-style-type: none"> • Premature < 1 month: 2.5 mg/kg/dose q 6 h • Full term < 1 week: 5 mg/kg/dose q 6 h • Full term > 1 week: 12.5 mg/kg/dose q 6 h
22.	Aztreonam	30 mg/kg/dose IV <ul style="list-style-type: none"> • <29 weeks up to 4 weeks of age q 12 h; > 4 weeks q 8 h • 30-36 weeks up to 2 weeks q 12 h; >2 weeks q 8 h • 37-44 weeks up to 1 week q 12 h; >1 week q 8 h
23.	Clindamycin	5-7.5 mg/kg/dose <ul style="list-style-type: none"> • <29 weeks up to 4 weeks of age q 12 h; > 4 weeks q 8 h • 30-36 weeks up to 2 weeks q 12 h; >2 weeks q 8 h • 37-44 weeks up to 1 week q 12 h; >1 week q 8 h
24.	Linezolid	10 mg/kg/dose Full term and Preterm >7 d: q8 h Preterm < 7 d: q12 h
25.	Quinupristin-Dalfopristin	7.5 mg/kg/dose q12 h

immunoglobins, the transplacental transport of IgG from the mother to fetus begins around 32 weeks gestation and increases until term. Premature infants born prior to 32 weeks gestation have profound IgG deficiencies.

It has been demonstrated that administering immunoglobulin concurrent with antibiotics was more effective in treating neonatal sepsis than administering antibiotics alone. The mortality rate of preterm infants receiving antibiotics supplemented with immunoglobulin was 10 percent (2/20) compared to those receiving antibiotics alone 26 percent (4/15), and no term infants died. Follow-up of the experimental groups at one and five years demonstrated no adverse sequelae from immunoglobulin therapy.⁵⁰ A larger follow-up study in 130 septic neonates comparing intravenous IgM to IgG adjuvant therapy with concurrent antibiotic therapy demonstrated no significant difference in survival between the two formulations while both improved mortality rates compared to nonimmunoglobulin treated groups.⁵¹

There are several published data⁵²⁻⁵⁴ on the use of IVIG in neonatal sepsis both for prophylaxis as well as for treatment in preterm as well as in term babies. The prophylactic benefit of immunoglobulin therapy was assessed by Baker's group in 1989 with a double blinded study of 588 low birth weight neonates. Although, there was no

difference in mortality rate, those neonates transfused with immunoglobulin demonstrated a reduction in the incidence of infection (relative risk of 0.7), fewer days of total hospitalization (62 v. 68d), and fewer days of hospitalization for septic neonates (80 v. 101d).⁵⁵ A recent Cochrane Meta-Analysis by Ohlsson concluded that prophylactic IVIG produced a 3 percent reduction in sepsis and a 4 percent reduction in other incidences of severe infection but did not lead to any difference in mortality rate.⁵⁶

A recent RCT done by INIS Collaborative Group included 3493 infants from 113 hospitals in nine countries and who were receiving antibiotics for suspected and proven bacterial infection. They were randomly assigned to receive two infusions of either polyvalent IgG immune globulin (at a dose of 500 mg per kilogram of body weight) or matching placebo 48 hours apart. The primary outcome was death or major disability at the age of 2 years. There was no significant between-group difference in the rates of the primary outcome, which occurred in 686 of 1759 infants (39.0%) who received intravenous immune globulin and in 677 of 1734 infants (39.0%) who received placebo (relative risk, 1.00; 95% confidence interval, 0.92 to 1.08). Similarly, there were no significant differences in the rates of secondary outcomes, including the incidence

of subsequent sepsis episodes. In follow-up of 2-year-old infants, there were no significant differences in the rates of major or non major disability or of adverse events. They concluded that therapy with intravenous immune globulin had no effect on the outcomes of suspected or proven neonatal sepsis.⁵⁷

In the light of the available data, use of IVIG to prevent or treat neonatal infection is not routinely recommended. However, there may be clinical situations in which a clinician might consider use of IVIG therapy (the sick preterm baby with overwhelming sepsis) or for prophylaxis in a preterm baby with low IgG level and recurrent infection. A dose of 500 to 1000 mg/kg/dose would be appropriate for both situations and the dose should be repeated every 2 weeks till improvement.

Granulocyte colony stimulating factor (G-CSF) and granulocyte-monocyte colony stimulating factor (GM-CSF): Both these agents have been found to be promising in some trials.^{58,59} Recently a multicenter trial by Kuhn et al, including 200 infants, studied the benefit of prophylactic rG-CSF treatment in preterm neonates with neutropenia in preventing nosocomial infections during 4 weeks of treatment. Although rG-CSF increased the number of neutrophils in these patients during the initial two weeks of treatment, this difference did not persist to the conclusion of the study. Kuhn et al concluded that prophylactic rG-CSF did not increase infection free survival four weeks after initiating treatment.⁶⁰ rG-CSF prophylaxis however may prove beneficial in bolstering neutrophil number and preventing infection in some subsets of neonates including those that are small for gestational age and those with early established postnatal neutropenia.⁶¹⁻⁶³ However, in spite of proliferative and functional benefits GM-CSF on the neonatal neutrophil population, rGM-CSF administration does not significantly increase sepsis free survival and there is insufficient evidence to support its use both as a prophylactic and treatment strategy.⁶⁴

White blood cell transfusion: Some scientists have forgone attempts to treat neonatal sepsis by stimulating the proliferation and function of existing neonatal neutrophil precursors and have instead administered adult neutrophils to at risk neonates. The first documented granulocyte transfusion in neonates was performed by Laurenti et al. In their trial, they transfused 20 neonates suffering from systemic *Klebsiella* infections with granulocytes acquired from adults. Results found significant reductions in mortality, 10 percent in transfused groups and 72 percent in non-transfused groups.⁶⁵ A trial by Cairo et al in 1992, where they compared granulocyte transfusion to IVIG transfusion for the treatment of sepsis in neutropenic neonates. This trial including 35 infants found 100 percent survival (21/21) in the granulocyte treated group and 64 percent survival (9/14, $p < 0.03$) in the IV immunoglobulin treated group.⁶⁶ However, the 2003 Cochrane review by Mohan

and Brocklehurst questioned the efficacy of granulocyte transfusions. They determined that the relative risk of eligible trials was not significantly different in all-cause mortality when compared to placebo. They did however agree that the increased protection of granulocyte transfusion over IV immunoglobulin use determined in the 1992 Cairo trial was of borderline statistical significance. The limited statistical significance was attributed to a small number of trials with relatively few study subjects.⁶⁷

Blood exchange transfusion (BET): Double volume BET has been used as a modality for managing sepsis for several decades, but large, well-conducted RCTs are still lacking. The earlier trials were uncontrolled and showed impressive improvements in neutrophil counts, immunoglobulin levels, recovery from sclerema and less mortality compared to historical experiences.^{68,69} In a small RCT from India, conducted on septicemic neonates, there was a non significant reduction in mortality [7/20 versus 7/10; RR 0.5 (95% CI 0.24, 1.03)], but there were significant improvements in total leukocyte count, absolute neutrophil count and neutrophil functions in the BET group.⁷⁰ In another small RCT on sclerematous neonates from the same centre, BET resulted in a significant reduction in mortality [50% versus 95%; RR 0.53 (95% CI 0.34, 0.83)] and significant improvement in immunoglobulin levels.⁷¹ BET may be performed in a case of deteriorating sepsis with sclerema provided the general condition of the baby allows the procedure.

On-line plasma exchange and hemofiltration: As an alternative to exchange transfusion the above modality has been tried in experimental models with encouraging results.

Strategies for treating septic shock in neonates: A number of therapeutic products are being used in the treatment of septic shock, e.g. monoclonal antibodies to tumor necrosis factor (TNF α) and interleukin-1 (IL-1) in animal models. In addition, pentoxifylline, a phosphodiesterase inhibitor has been tried which decreases the production of TNF- α . The role of prostaglandins, ibuprofen, ketoconazole and inhibitors of nitric oxide synthase would need further evaluation in the management of septic shock (Table 8).

PROGNOSIS

Prior to the availability of antibiotics, almost all infants with sepsis died. Outcome data for group B streptococcal (GBS) neonatal sepsis after the introduction of intrapartum antibiotic prophylaxis and the routine use of empirical antibiotic therapy demonstrate an overall fatality rate between 5 and 10 percent. However, mortality is lower in term infants with case fatality rates for early-onset disease, ranging from 2 to 3 percent, and from 1 to 2 percent for late-onset disease. Clinical features associated with mortality in early-onset GBS infection include birth weight less than 2500 g, absolute neutrophil count less than 1500 cells/microL, hypotension, apnea, and pleural effusion.⁷²

Table 8: Newer modalities for treating septic shock

- Antiendotoxin, anti-CD14 monoclonal antibodies.
- Anti-inflammatory cytokines: IL-4, IL-10, TGF-B1, G-CSF.
- Inhibition of TNF- α -gene-transcription: Pentoxifylline, Amrinone, Dobutamine, Chlorpromazine.
- Inhibition of TNF- α gene translation: Corticosteroid.
- Inhibition of TNF and IL-1: Anti-TNF, anti-IL-1 monoclonal antibody.
- Inhibition of IL-1 and TNF receptors: IL-1ra, IL-1 and TNF soluble receptors.
- Inhibition of nitric oxide: Arginine analog (L-NAME and L-nmme), Vit B₁₂, Methylene blue.

The mortality rate appears to be higher in neonates with early-onset *Escherichia coli* (*E. coli*) sepsis, as illustrated by the following studies: In a retrospective review of all the neonatal cases of early-onset *Escherichia coli* (*E. coli*) sepsis at a single Spanish center from 1992 to 2002, the mortality rate for term infants was 4 percent.⁷³ In a retrospective case-control study, cases of *E. coli* sepsis in infants less than seven days of age were identified in selected counties of California, Georgia, and Connecticut from 1997 to 2001. The overall case fatality rate was 16 percent. Over two-thirds of the patients were premature, and separate mortality data were not presented for preterm and term infants. Of the 132 *E. coli* cases, 68 were due to an ampicillin resistant species. It is difficult to ascertain the overall mortality in term and late preterm infants with neonatal sepsis, because there is a subset of septic patients who do not have positive culture results.⁷⁴

SUMMARY

Neonatal infection is a high incidence high-risk disease in India. Accurate diagnosis is difficult because of low sensitivity to even blood culture and other adjunctive indirect tests. Hence, the clinicians must accept the fact that a number of neonates will be started with antibiotic treatment even though they do not have the disease. In order to minimize the therapy for those who are not infected, a careful history, thorough clinical examination and a carefully performed sepsis screening can be used together in the management of neonatal sepsis. A variety of adjunctive therapy may offer potential benefits for neonatal sepsis. Most of the agents are not available and those that are available need further evaluation.

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Intrauterine and Perinatal Infections—An Overview

Ajay Kumar, AK Dutta

Infections acquired *in utero* (Congenital) or in the perinatal period: During the birth process (Intarpartum) or in the postpartum period are significant causes of fetal and neonatal mortality (Table 1). The original concept of TORCH perinatal infections was to group five infections (T: Toxoplasmosis, O: Others usually syphilis, R: Rubella, C: Cytomegalovirus, H: Herpes simplex infection) with similar presentations. This term is now archaic and should not be used.¹ A new acronym is needed to include other

well described causes of *in utero* and perinatal infections like enteroviruses, Varicella zoster, Lyme disease and parvovirus. An inclusive term TORCHES CLAP has been suggested which stands for toxoplasmosis, rubella, cytomegalovirus, herpes simplex virus, enteroviruses, syphilis, chickenpox, Lyme disease and parvovirus. New pathogens are being discovered so it is unlikely that any acronym is going to be permanent.²

Table 1: Infections in intrauterine and perinatal period

Intrauterine viral infections

- Rubella
- Cytomegalovirus (CMV)
- Parvovirus B₁₉
- Varicella-Zoster (VZV)
- Enteroviruses
- HIV
- HTLV-1
- Hepatitis C
- Hepatitis B
- Lassa Fever
- Japanese Encephalitis

Perinatal and neonatal infections

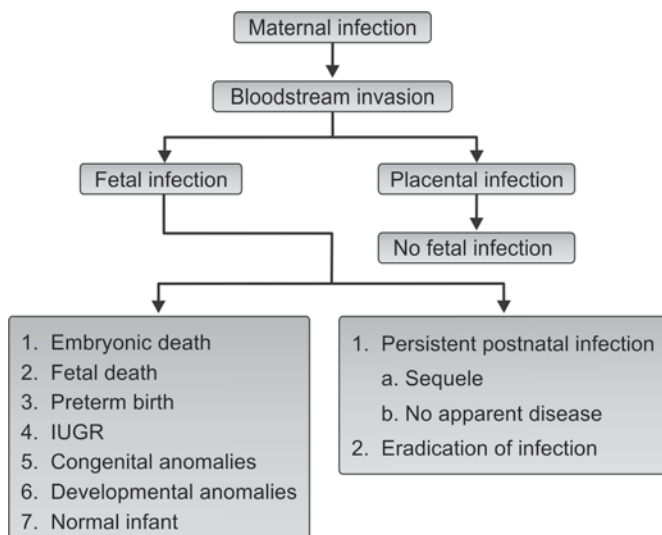
- Viral
 - Hepatitis B
 - HIV
 - HSV
 - Varicella (Chickenpox)
- Bacterial
 - Group B β strep
 - Gonorrhea
 - Chlamydia
 - Syphilis

PATHOGENESIS OF CONGENITAL AND PERINATAL INFECTIONS

The usual way in which the fetus is infected is by transplacental spread after maternal infection when the organism circulates in the mother's blood. These infections acquired *in utero* may be severe enough to cause fetal loss or can result in intrauterine growth restriction, prematurity or chronic postnatal infection. The degree of severity depends upon the gestational age of the fetus when infected, the severity of maternal disease and the virulence of the organism. The pathogenesis of these organisms is unique. They have very low virulence with the result the fetal infection rarely leads to death. Early in the pregnancy the most complex embryogenesis takes place, making the organs like eyes and ears vulnerable. The immature fetus lacks the immunologic mechanisms necessary to completely eliminate an infecting organism. Therefore, a state of immunologic tolerance is established with the result the organism persists in the fetus in the post natal period². (Flow chart 1)

CLINICAL MANIFESTATIONS OF CONGENITAL AND PERINATAL INFECTIONS

Hematogenous transplacental spread may result in death and resorption of embryo, abortion or stillbirth or live birth of a premature or term baby who may or may not be affected.

Flow chart 1: Pathogenesis of hematogenous transplacental infections

INTRAUTERINE GROWTH RETARDATION AND LOW BIRTH WEIGHT

Although low birth weight and small for date infants are associated with many maternal infections, evidence for a causal relationship is only sufficient for rubella VZV infection, toxoplasmosis and CMV infection. The organs of babies dying with congenital rubella syndrome³ or CMV infection contain a decreased number of morphologically normal cells.

DEVELOPMENTAL ANOMALIES AND TERATOGENESIS

CMV, rubella virus and VZV cause developmental anomalies in the human fetus. Coxsackie B3 and B4 are associated with congenital heart disease.²

CONGENITAL DISEASE

Clinical evidence of intrauterine infection may be present at birth or may manifest soon thereafter or years later. In infants with congenital rubella, toxoplasmosis, syphilis, congenital CMV, HSV or enterovirus infection signs of wide dissemination may be evident during the neonatal period. These include jaundice, hepatosplenomegaly and pneumonia. In some infants, the constellation of signs is sufficient to suggest the likely congenital infection (Table 2).

EFFICIENCY OF TRANSMISSION FROM MOTHER TO FETUS

The efficiency of transmission from infected mother to fetus varies among microbial agents and with the trimester

Table 2: Syndromes in neonates caused by congenital infections

Microorganism	Signs
Toxoplasma	Hydrocephalus, diffuse intracranial calcification, chorioretinitis
Rubella virus	Cardiac defects, sensorineural hearing loss, cataracts, microcephaly, blueberry muffin rash, hepatomegaly, interstitial pneumonia, myocarditis, disturbance in bone growth, intrauterine growth retardation
Cytomegalovirus	Microcephaly, periventricular calcification, jaundice, petechie or purpura, hepatosplenomegaly, IUGR
Herpes simplex	Skin vesicles or scarring. Eye scarring, microcephaly or hydranencephaly, keratoconjunctivitis, meningoencephalitis, sepsis with hepatic failure
Treponema pallidum	Bullous, macular or eczematous skin lesions involving palms and soles, rhinorrhea, dactylitis, osteochondritis, periostitis, hepatosplenomegaly and lymphadenopathy
Varicella zoster	Limb hypoplasia, cicatricial skin lesions, ocular abnormalities, cortical atrophy
Parvovirus B 19	Nonimmune hydrops fetalis
HIV	Severe thrush, failure to thrive, recurrent bacterial infection, calcification of the basal ganglia

of pregnancy. *In utero* transmission of rubella and toxoplasma occurs mainly with primary infection, whereas *in utero* transmission of CMV, HIV, and *T. pallidum* can occur in consecutive pregnancies.

The risk of congenital rubella infection in fetus of mothers with symptomatic rubella is 90 percent before 11 weeks of gestation, declines to a low of 25 percent at 23 to 26 weeks and then rises to 67 percent after 31 weeks. Infections in first 11 weeks of gestation are uniformly teratogenic, whereas no birth defect occurs in infants after 16 weeks of gestation⁴.

Frequency of stillbirth and congenital infection during pregnancy was least if the women acquired infection in first trimester (14%), increased in the second trimester (29%) and was highest in the third trimester (59%).⁵

Congenital CMV infection results from primary and recurrent infections. Whitley and Stagno estimated that 1 to 4 percent of women have primary infection during pregnancy, that 40 percent of these women transmit the infection to the fetus, and that 5 to 15 percent of the infants have signs of CMV disease. Congenital infection due to recurrent CMV infection occurs in 0.5 to 1 percent of live births, but less than 1 percent of the infected have clinically apparent congenital disease.^{6,7}

The fetal transmission rate of HIV infection from the infected mothers who received no treatment is about 25 percent. Data are insufficient to identify efficiency of transmission by trimester.⁸

DIAGNOSIS OF INFECTION IN THE PREGNANT WOMAN

Clinical Diagnosis

In many instances, the diagnosis of infection in pregnant women and congenital infection in the newborn can be suspected on the basis of clinical signs and symptoms. Many infectious diseases with serious consequences for the fetus are difficult to diagnose in the mother solely on clinical grounds. Asymptomatic or subclinical infection may be caused by rubella virus, CMV, *T. gondii*, *T. pallidum*, HSV and HIV. The vast majority of women infected during pregnancy with these organisms have no apparent signs of disease. Only 50 percent of women infected with rubella have a rash. Only few proportions of cases of CMV mononucleosis are recognized in pregnancy. Similarly, the number of women with clinical toxoplasmosis is less than 10 percent. The genital lesions associated with HSV infection and syphilis are often not recognized.²

ISOLATION AND IDENTIFICATION OF INFECTIOUS AGENT

The most direct mode of diagnosis is isolation of the microbial agent from tissues and body fluids such as blood, CSF, or urine. Amniotic fluid contains viruses or bacteria shed from the placenta, skin, urine, or tracheal fluid of the infected fetus. This fluid can be obtained earlier during pregnancy and can be used to detect the infecting organism by culture, antigen detection test, or PCR assay. These methods have contributed significantly to the diagnosis of rubella, VZV, CMV, and *T. gondii*.²

Serologic Diagnosis

The serologic diagnosis of infection in pregnant women most often requires demonstration of a significant rise in antibody titers against the suspected agent. If done in early pregnancy, a negative test will tell that women are unprotected against *T. pallidum*, *T. gondii*, and rubella. A positive test will tell that the woman is infected with hepatitis B or HIV. Difficulties in interpretation of serologic test results seldom arise when patients are seen shortly after exposure or at the onset of symptoms. Demonstration of IgA and IgE antibodies is useful in the early diagnosis of infection in the pregnant woman, fetus, and newborn.²

TORCH Screen

The utility of TORCH titres as an effective diagnostic tool has been questioned in the last decade because of overuse

and consistent lack of interpretability and reliability.⁹ Both maternal IgG and IgM antibody titers are performed routinely because IgG frequently persists once patients have been exposed to the pathogen. However, IgM also can be present for prolonged periods, three months to more than one year in acute toxoplasmosis¹⁰ which can create difficulties in interpreting potential fetal exposure during a pregnancy. In contrast to maternal serum, the presence of IgM antibodies in the newborn is more suggestive of congenital infection because these antibodies cannot cross the placenta, although contamination can occur at the time of delivery.

One study examined the cost and number of diagnoses of TORCH infections in 75 infants with intrauterine growth restriction who were screened with TORCH titres, urine cultures for CMV and head ultrasound.¹¹ Three infants had a probable infection diagnosed, one by a positive CMV urine culture and two by ultrasound of the head; none of the infants had a positive IgM antibody for toxoplasmosis, rubella, CMV, or HSV. The costs of the tests for the 75 infants were estimated at \$17,816 for IgM titers, \$5734 for CMV urine cultures, and \$28,165 for head ultrasound. The authors concluded that workup for TORCH infections were not cost-effective in the population of infants with intrauterine growth restriction. A study evaluating maternal TORCH testing found that complete maternal TORCH testing is often unnecessary and concluded that only testing for CMV would be cost effective.¹²

PREVENTION AND MANAGEMENT OF INFECTION IN PREGNANT WOMEN

Prevention of Infection

Pregnant women should avoid contact with persons with communicable diseases, particularly if women are known to be seronegative (e.g. CMV) or have no prior history of the disease (e.g. VZV). Precautions should be taken by pregnant woman if her partner has vesicles of HSV or suspected to be infected with HIV. Pregnant women should avoid eating undercooked lamb, pork or beef. They should avoid contact with cat feces.

Immunization

Routine immunization schedules for infants and children with currently available live vaccines, including measles, poliomyelitis, mumps and rubella should give lifelong protection.

Immunoglobulin

Human immune globulin after exposure to rubella, varicella, measles, or hepatitis A virus may modify clinical signs and symptoms of the disease but has not proved to be consistently effective in preventing disease and viremia in susceptible person. Human serum immune globulin is

of undetermined value in protecting the fetus of a susceptible woman against infection with these viruses. It may be used for rubella for women to whom therapeutic abortion is unacceptable.

Antimicrobial Therapy

Almost without exception, antimicrobial agents administered systemically to the mother pass to the fetus. Pregnant women with recently acquired acute toxoplasmosis, Lyme disease and syphilis should undergo treatment. Women who are colonized with *C. trachomatis* or group B *Streptococcus* may receive treatment under selected circumstances.²

INDIVIDUAL INFECTIONS

Toxoplasmosis

Toxoplasma gondii is a ubiquitous protozoan parasite that infects animals and humans. It is an intracellular parasite with a unique biphasic cycle that consists of a sexual cycle that occurs in felines and asexual cycle that occurs in other animals and humans. The infant is infected transplacentally after the parasite invades the placenta. The risk of transmission to the fetus during an acute maternal infection varies depending upon the gestational age during which the maternal infection occurred. As the gestational age increases, the risk of infection in the fetus increases but the severity of infection decreases. Once acquired, the latent encysted organism will persist for life in the host. Estimates of prevalence of congenital toxoplasmosis based upon serologic screening of neonates or infants range from approximately 1 per 1000 in some areas of Latin America to 1 per 10000 live births in US.¹³

*Congenital toxoplasmosis has four types of clinical manifestations.*¹³⁻¹⁵

- **Subclinical infection:** Most have no clinical manifestations (70 to 90%) on routine physical examination. More specific testing like CSF examination (mononuclear pleocytosis and raised protein), ophthalmic evaluation (macular scar) and CNS imaging (focal cerebral calcification) may reveal abnormalities.
- **Severe disease in neonatal period:** Clinical findings noted are chorioretinitis, abnormal CSF examination, seizures, intracranial infections, jaundice, splenomegaly, hepatomegaly, pneumonitis, hydrocephalus (Fig. 1) and rash.
- **Mild or severe disease in the first month of life:** Chorioretinitis, motor and cerebellar dysfunction, microcephaly, seizures, sensorineural hearing loss, mental retardation.
- **Sequel or relapse of undiagnosed infection later in the infancy, childhood or adolescence.**

The diagnosis of congenital *Toxoplasma* infection in newborn is usually made serologically. Diagnosis in newborn

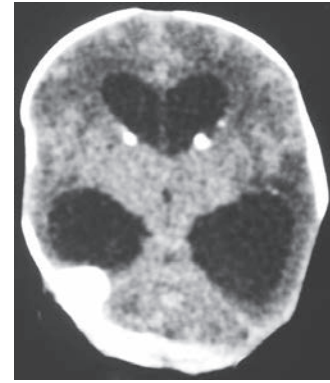


Fig. 1: CT Scan head of a newborn with Congenital Toxoplasmosis showing dilatation of lateral ventricles with intracerebral and periventricular calcifications

relies on the presence of *Toxoplasma* specific IgM detected by ELISA or ISAGA. When the infant's IgM are negative or equivocal IgA and IgE ELISA should be performed.^{16,17} Detection of these antibodies is more sensitive than measuring IgM but specificity is not assured.^{18,19}

*Laboratory methods that involve isolation or demonstration of *T. gondii* include:*²⁰

- **Polymerase chain reaction:** PCR on amniotic fluid is particularly diagnostic of fetal infection. PCR can also be used for CSF, vitreous fluid, urine, peripheral blood, bronchoalveolar lavage fluid, cord blood or placenta.
- **Observation of cysts in placenta**
- **Isolation of parasite from blood or body fluid by mouse inoculation or tissue culture.**

Antenatal screening allows early diagnosis of acute maternal, fetal and neonatal infections and improves outcome. Routine screening throughout pregnancy is performed in France.²¹

Treatment:²¹ Spiramycin is recommended before 18 weeks gestation and until term if the fetus is uninfected by 18 weeks amniotic fluid PCR. This macrolide antibiotic reduces or delays vertical transmission to fetus through high placental levels. However, if transmission occurs disease severity may be unaltered. Pyrimethamine, sulfadiazine and folic acid are recommended for confirmed fetal infections after 18 weeks gestation or when unable to perform amniocentesis and all acute maternal infections after 24 weeks. Fetal infection diagnosed before 17 weeks should be treated with sulfadiazine alone until after the first trimester as pyrimethamine may affect organogenesis.

Therapy is recommended for all neonatal infections regardless of symptoms. As current medications do not eradicate *T. gondii* and primarily act against the tachyzoite form not tissue cysts extended therapy until 1 year of age

is recommended. Pyramethamine and sulfadiazine in combination are recommended till one year of age. Prednisolone is used for active CNS disease or active chorioretinitis, which threatens vision.

CONGENITAL SYPHILIS

It results from transplacental passage of *T. pallidum*. The risk of transmission to the fetus correlates largely with the duration of maternal infection, the more recent the maternal infection, the more likely the transmission to the fetus will occur. During the primary and secondary stages of maternal syphilis the risk of transmission to fetus approaches 100 percent. This risk declines to 10 to 30 percent in mother with late latent syphilis. Transmission through placenta can occur throughout pregnancy.²² The most important risk factors for congenital syphilis are lack of prenatal health care and maternal illicit drug use. Clinical scenarios that contribute to the occurrence of congenital syphilis include lack of prenatal care; no serologic test for syphilis (STS) performed during pregnancy; a negative STS in the first trimester, without repeat test later in pregnancy; a negative maternal STS around the time of delivery in a woman who was recently infected with syphilis but had not converted her STS yet; laboratory error in reporting STS results; delay in treatment of a pregnant woman identified as having syphilis and failure of treatment in an infected pregnant woman.²²

Case Definition

The center for disease control and prevention has given a case definition for congenital syphilis²³ (Table 3).

Clinical Features

Early congenital syphilis: It is arbitrarily defined by the clinical manifestations with onset before 2 years of age.²⁴ Two-third of live-born neonates with congenital syphilis are asymptomatic at birth.^{24,25} Clinical manifestations in untreated neonate appear by 3 months of age. The placenta of these neonates at birth may be large, thick and pale. The umbilical cord is edematous and shows spiral stripes of red and light blue discoloration. It may show the evidence of necrotizing funisitis.²⁶ The newborn may have hepatomegaly, rhinitis (snuffles), red or pink spots on back, buttocks, posterior thighs and soles. The rash progresses to desquamation and crusting. Other manifestations of congenital syphilis include nonimmune hydrops, myocarditis, pneumonia, pseudoparalysis of parrot (failure to move an extremity secondary to pain), nephritic syndrome and CNS involvement.²⁷

Late congenital Syphilis: It is arbitrarily defined by clinical manifestations with onset after two years of age. It develops in approximately 40 percent of infants born to women with untreated syphilis during pregnancy. Manifestations

Table 3: US Centers for disease control and prevention (CDC) surveillance case definition for congenital syphilis

Laboratory criteria for diagnosis

Demonstration of treponema palladium by dark field microscopy, fluorescent antibody, or other specific stains in specimens from lesions, placenta, umbilical cord, or autopsy material

Case classification

Probable

Infant whose mother had untreated or inadequately treated syphilis at delivery, regardless of signs in the infant, or

Infant or child who has a reactive treponemal test for syphilis and any one of the following:

Any evidence of congenital syphilis on physical examination:

- For children 0 to 2 years: Hepatosplenomegaly, rash, condyloma lata, snuffles, jaundice, pseudoparalysis, edema
- For children >2 years: Interstitial keratitis, sensorineural hearing loss, 'saber shins', frontal bossing, Hutchinsonian teeth, mulberry molars, mulberry molars, saddle nose, rhagades, Clutton joints

– Any evidence of congenital syphilis on radiographs of long bones

– A reactive cerebrospinal fluid (CSF) venereal research laboratory (VDRL) Test

– An elevated CSF cell count or protein (without other cause)

Confirmed

Case that is laboratory confirmed

include facial features (saddle nose, short maxilla, protuberant mandible), interstitial keratitis, sensorineural hearing loss, Hutchinsonian teeth (hypoplastic notched widely spaced teeth most commonly central incisors), mulberry molars (maldevelopment of cusps of first molars) and perforation of hard palate. Other manifestations include rhagades (perioral fissures or clusters of scars radiating around the mouth), anterior bowing of the shins (saber shins), enlargement of sternoclavicular portion of the clavicle (Higouminakis sign), painless arthritis of knees (Clutton's joints).²⁷

Diagnosis

It can be made by direct visualization of *T. pallidum* by dark field microscopy or fluorescent antibody staining of infected body fluids or lesions, placenta or umbilical cord.²⁸ Serologic tests can establish a diagnosis of proven/highly probable, at risk or unlikely congenital syphilis. Serologic tests include nontreponemal tests (e.g. Venereal disease research laboratory [VDRL] or rapid plasma reagin [RPR]) and treponemal tests (e.g. microhemagglutination test for *T. pallidum* [MHA-TP] or fluorescent treponemal antibody absorption [FTA-ABS]). Serologic tests for IgG antibodies are problematic because it is not possible to differentiate between passively acquired maternal antibody

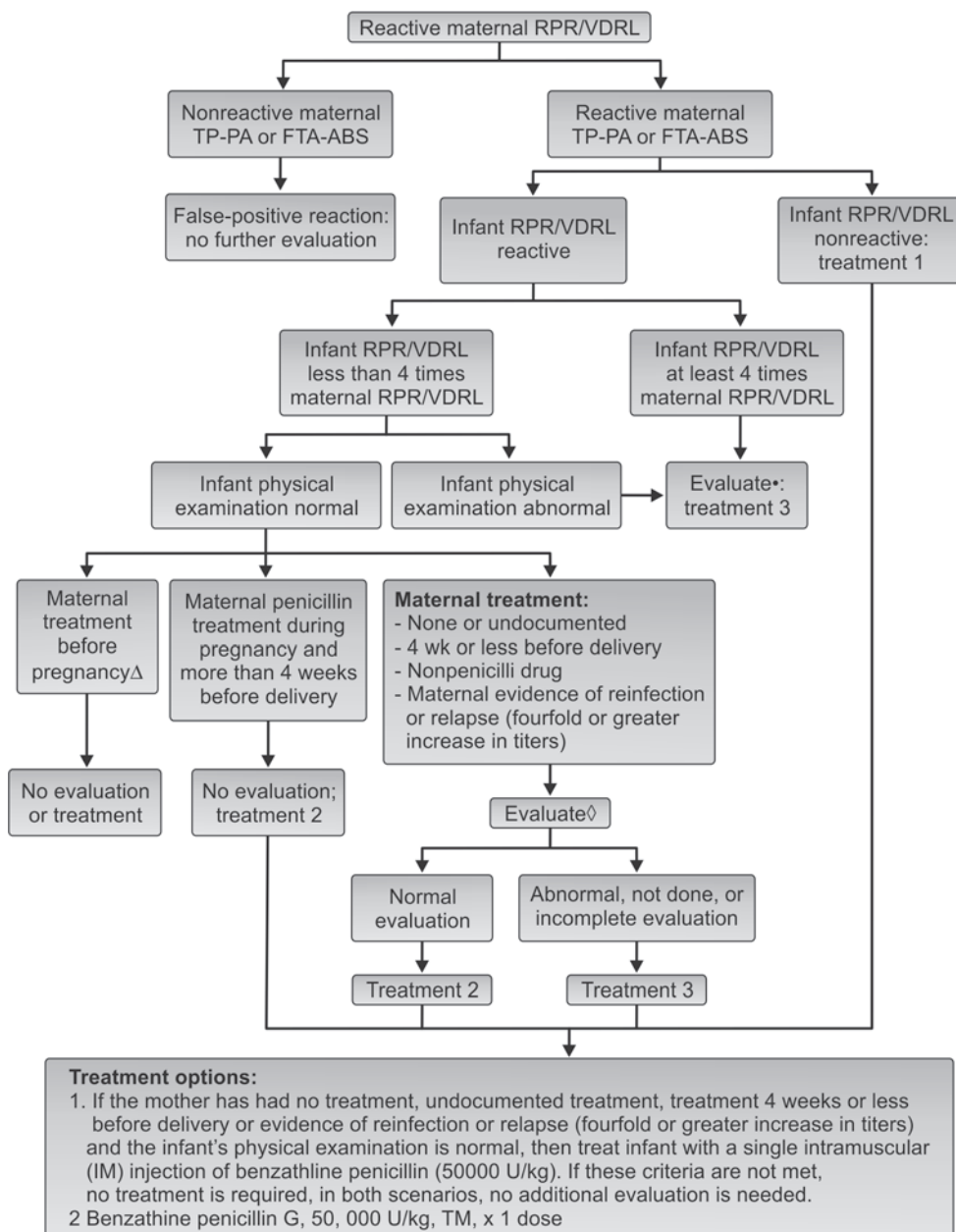
and endogenous antibody produced by the fetus/neonate. The ability to detect IgM antibodies, which do not cross the placenta would confirm fetal infection. Unfortunately, a sufficiently sensitive and specific IgM assay is not currently available for routine use in the assessment of congenital syphilis.²⁹

Maternal treatment history, clinical findings and interpretation of serological tests help to classify the neonate into following broad groups:²³ Flow chart 2.

Proven or Highly Probable Congenital Syphilis

Congenital syphilis is proven or highly probable if the neonate (<1 month of age) has any of the following: An abnormal physical examination that is consistent with congenital syphilis, a serum quantitative nontreponemal serologic titre that is \geq fourfold the corresponding maternal titre, a positive dark field or fluorescent antibody test of lesions, body fluid(s), placenta, or umbilical cord, a reactive serum VDRL/RPR and abnormal CSF, reactive treponemal antibody test after 15 months of age.

Flow chart 2: Congenital syphilis: Evaluation and management



Presumed Congenital Syphilis

Infants <1 month of age who have a normal physical examination and serum VDRL or RPR titres <fourfold the maternal titre are presumed to have congenital syphilis if their mother was not treated or received inadequate/suboptimal therapy.

At Risk for Congenital Syphilis

Infants <1 month of age who have a normal physical examination and serum VDRL or RPR titres <fourfold the maternal titre are at risk for congenital syphilis, even if their mothers were adequately treated.

Unlikely Congenital Syphilis

A diagnosis of congenital syphilis is unlikely if the infant has a normal physical examination and nonreactive VDRL/RPR and the mother was adequately treated during pregnancy and had an appropriate serologic response.

Treatment

Parenteral penicillin is the drug of choice for the treatment of congenital syphilis.³⁰ Penicillin is the only drug with documented efficacy and it has minimal toxicity. Effective treatment of syphilis requires maintenance of a minimal inhibitory concentration (MIC) of 0.03 units/ml of penicillin in serum (or cerebrospinal fluid) for 7 to 10 days. Current regimens are designed to achieve and maintain several times the necessary MIC and to avoid penicillin free intervals during therapy.

PARVOVIRUS INFECTION

Parvovirus transmission results after contact with respiratory secretions, blood/ blood products, or by vertical transmission. The prevalence of infection increases throughout childhood, such that approximately one-half of women of childbearing age are immune and the other half are susceptible to primary infection.³¹ B₁₉ infection during pregnancy can result in fetal complications including miscarriage, intrauterine fetal death and/or nonimmune hydrops fetalis.³² Because of this potential, it is critical to determine the serologic status of the pregnant woman who has a history of significant exposure to the virus or who has any of the classic symptoms of B₁₉ infection.

Pathogenesis

The fetus is especially susceptible to the effects of B₁₉-induced anemia due to its shortened RBC half-life and the expanding RBC volume. The relatively immature fetal immune system is also less able to effectively control virus infection. The ensuing fetal hydrops appears to result from the onset of severe anemia, which in turn causes high output heart failure. Fetal B₁₉ infection can also present with thrombocytopenia.

Diagnosis

Maternal parvovirus infection—IgM antibody capture radioimmunoassay and enzyme-linked immunosorbent assay (ELISA) are sensitive tests, detecting between 80 and 90 percent of patients with clinical B₁₉ infection.³³ Fetal parvovirus infection — Polymerase chain reaction (PCR) is a sensitive method to detect small amounts of B₁₉ DNA. Use of this technique on amniotic fluid is the method of choice to make the fetal diagnosis. Another option is to obtain fetal blood for B₁₉ IgM; however, percutaneous fetal blood sampling, the method used to obtain fetal blood, carries a 1 percent fetal loss rate.³⁴

Treatment

Mild to moderate anemia generally is well tolerated by the fetus and resolves without sequelae. Severe anemia, although uncommon, can lead to hydrops fetalis and death. Because parvovirus-induced anemia is a transient process, determination of fetal hemoglobin is not necessary unless severe anemia is suggested by sonographic signs, such as fetal skin edema, ascites or pleural or pericardial effusions. Doppler assessment of the fetal middle cerebral artery (MCA) peak systolic velocity (PSV) is emerging as an accurate tool for the determination of fetal anemia and is a noninvasive alternative to cord blood sampling.³⁵

When severe anemia is suspected because of an elevated Doppler MCA PSV or signs of hydrops, the fetus requires close monitoring and assessment of fetal hematocrit by percutaneous umbilical vein sampling. Intrauterine fetal blood transfusion usually is performed if severe anemia is confirmed.³⁶ Intravenous immune globulin (IVIG) has been used to treat acute parvovirus in immunodeficient adults and HIV-infected children. However, there is only one case report on its use as a fetal therapy.³⁷ Given the limited available data, the use of IVIG during pregnancy currently is not recommended.

Whenever possible, the management of a woman with a hydropic infant should be undertaken in a tertiary care facility staffed by individuals experienced in the care of sick neonates. As with all high-risk births, delivery of a hydropic infant mandates coordinated efforts by the obstetrician, perinatologist, and neonatal team to optimize pregnancy outcome.

The majority of hydropic infants require respiratory assistance and mechanical ventilation. Ventilation may be compromised by pulmonary hypoplasia, pulmonary edema, air leaks, or by the accumulation of pleural or peritoneal fluid. Abdominal paracentesis and thoracentesis of fetal ascites and pleural effusions may be needed either just prior to delivery or immediately after to facilitate resuscitation. Postnatal management depends upon the gestational age of the infant, other associated conditions (e.g. respiratory distress syndrome) and illness severity.

Infants with severe anemia and cardiovascular instability may benefit from an isovolumetric or partial exchange transfusion with packed red blood cells.

Prevention

Three groups of pregnant women potentially at risk of fetal parvovirus disease are those exposed to an infected household contact, schoolteachers and health care providers. Their status as acutely infected or susceptible can be determined by testing for serum IgG, IgM and PCR. For susceptible or acutely infected women, serial fetal ultrasonography should be done to monitor fetal growth and the possible evolution of hydrops. Serial determinations of maternal serum α -fetoprotein (AFP) may be done (AFP may rise up to 4 weeks before ultrasonography evidence of fetal hydrops), although this use is questioned.³¹

VARICELLA ZOSTER INFECTION

Varicella-zoster virus (VZV) is the virus responsible for varicella (chickenpox) and herpes zoster ("shingles"). VZV is a member of the herpesvirus family.

Congenital Varicella

Most cases of congenital varicella syndrome occur in infants whose mothers were infected between 8 and 20 weeks gestation. However, the overall risk of infection is quite small compared to numerous other viruses acquired during pregnancy. The risk appears to be approximately 2 percent if the infection occurs before 20 weeks.³⁸ Characteristic findings of affected infants include:³⁹

- Cicatricial skin lesions, which may be depressed and pigmented in a dermatomal distribution.
- Ocular defects, such as cataracts, chorioretinitis, Horner syndrome, microphthalmos and nystagmus.
- Limb abnormalities, which often include hypoplasia of bone and muscle.
- Central nervous system abnormalities, such as cortical atrophy, seizures, and intellectual disability (mental retardation).

Neonatal Varicella

It is a serious illness associated with a mortality rate up to 25 percent. Newborns born to mothers who are exposed to VZV or have clinical disease manifestations within two weeks of delivery are at the greatest risk for infection. The risk of infection and the case fatality rate are significantly increased when symptoms of maternal infection occur less than five days prior to delivery.⁴⁰ This interval allows insufficient time for the development of maternal IgG and passive transfer of antibody protection to the fetus. Postnatally acquired varicella that occurs between 10 and 28 days after birth usually is mild. (Fig. 2) However,



Fig. 2: Clinical photograph of neonate with varicella
(For color version see plate 1)

because of their relative immunologic immaturity, newborns are at greater risk for acquiring severe disease than are older infants or children.⁴¹

Prevention

The Advisory Committee on Immunization Practices (ACIP)⁴² recommends administration of VZIG/ VariZIG to newborns

- Whose mothers have signs and symptoms of varicella around the time of delivery (five days before or two days after)
- Premature infants born at >28 weeks of gestation who are exposed during the neonatal period and whose mothers do not have signs of immunity
- Premature infants born at <28 weeks of gestation or who weigh <1000 grams at birth and were exposed during the neonatal period, regardless of maternal history of varicella or vaccination. VariZIG should be administered within 96 hours because its efficacy after this time interval is not known.

Treatment

Acyclovir reduces the risk of mortality in severe varicella.⁴³ Newborns with severe infection should be treated with acyclovir (30 mg/kg per day in 3 divided doses IV) for 10 days. To be effective, antiviral treatment must be started as soon as possible after the onset of symptoms because most viral replication has stopped by 72 hours after appearance of the rash.

CONGENITAL RUBELLA

Congenital rubella infection (CRI) encompasses all outcomes associated with intrauterine rubella infection (e.g. miscarriage, stillbirth, combinations of birth defects, asymptomatic infection) whereas congenital rubella syndrome refers to variable constellations of birth defects (e.g. hearing impairment, congenital heart defects, cataracts/congenital glaucoma, pigmentary retinopathy).⁴⁴

Maternal-fetal transmission of rubella virus occurs via hematogenous spread during maternal viremia, which usually occurs five to seven days after maternal inoculation. After infecting the placenta, the virus spreads through the vascular system of the developing fetus. There are two proposed mechanisms for rubella cytopathology: Virus-induced inhibition of cell division⁴⁵ and direct cytopathic effects.⁴⁶

Clinical Features

Congenital rubella infection (CRI) may lead to fetal death *in utero*, premature delivery or congenital defects. CRI is a chronic infection and has a broad spectrum of clinical manifestations that may manifest throughout life. In neonates the manifestations of congenital rubella infection include IUGR, meningoencephalitis, hearing loss, cloudy cornea (Fig. 3), interstitial pneumonia, cardiac defects, hepatosplenomegaly, jaundice, hepatitis, radiolucent bone lesions (Fig. 4), petechiae and blueberry muffin lesions (Fig. 5), adenopathy, hemolytic anemia and

thrombocytopenia.⁴⁷ Delayed manifestations of rubella occur in about 20 percent of children with symptomatic congenital rubella infection. These manifestations include hearing loss, endocrine disorders (diabetes, hypothyroidism and growth hormone deficiency), eye problems

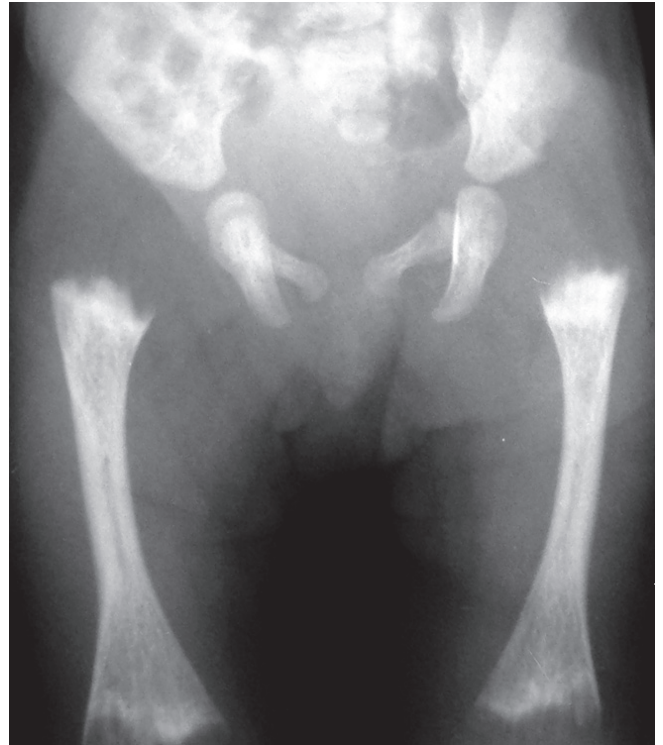


Fig. 4: Moth eaten appearance of bones in a neonate with congenital rubella

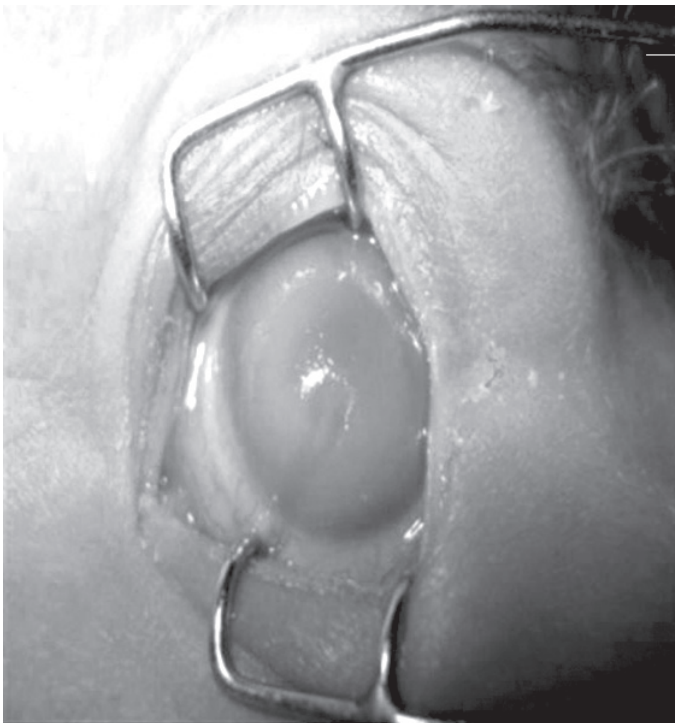


Fig. 3: Cloudy cornea due to glaucoma in a neonate with congenital rubella syndrome (For color version see plate 1)



Fig. 5: Clinical photograph of a newborn with congenital rubella showing blue berry muffin rash (For color version see plate 1)

(retinopathy, cataract, glaucoma), vascular effects (renal artery stenosis, hypertension), progressive panencephalitis and immune defects.⁴⁸

After fetal infection rubella virus persists throughout gestation and for months postnatally. At one year of age as many as 20 percent of infants with CRS shed virus in the pharynx.⁴⁹

Diagnosis

The presence of certain defects or laboratory data consistent with CRS satisfies the Centres for Disease Control and Prevention's clinical case definition (Table 4). Cases of CRS are classified as “suspected,” “probable,” “confirmed,” or “infection only,” depending upon clinical findings and laboratory criteria for diagnosis.⁵⁰

Table 4: Case definition and classification criteria for congenital rubella syndrome (CRS)

Clinical case definition

An illness, usually manifesting in infancy, resulting from rubella infection *in utero* and characterized by signs or symptoms from the following categories:

Category A: Cataracts/congenital glaucoma, congenital heart disease (most commonly patent ductus arteriosus or peripheral pulmonary artery stenosis), hearing impairment, pigmentary retinopathy

Category B: Purpura, hepatosplenomegaly, jaundice, microcephaly, developmental delay, meningoencephalitis, radiolucent bone disease

Laboratory criteria (any one of the following)

Isolation of rubella

Demonstration of rubella-specific immunoglobulin M (IgM)

Infant rubella antibody level (immunoglobulin G, IgG) that persists at a higher level and for a longer time than expected from passive transfer of maternal antibody (i.e. rubella titer that does not drop at the expected rate of a twofold dilution per month)

Polymerase chain reaction (PCR) positive for rubella virus

Classification Criteria

Suspected	A case with some compatible clinical findings but not meeting the criteria for a probable case A case that is not laboratory confirmed and that has either: – Any two complications from category A above, or
Probable	– One complication from category A and one from category B above and Lacks evidence of any other etiology
Confirmed	A clinically consistent case that is laboratory confirmed
Infection only Δ	A case that demonstrates laboratory evidence of infection but without any clinical symptoms or signs

Lab Diagnosis

Although the diagnosis of CRS is suspected clinically, it is confirmed with laboratory tests. Lab evaluation should be performed before the child reaches one year of age after which it is difficult to establish a diagnosis of congenital rubella infection.⁵¹ The confirmation can be done through isolation of rubella virus and serology.⁵⁰

Virus Isolation

Rubella virus is most frequently isolated from nasopharyngeal secretions, although it can also be cultured from blood (including cord blood), placenta, urine and cerebrospinal fluid.

Serology

Serologic confirmation of CRS consists of demonstration of rubella-specific IgM antibody or infant IgG rubella antibody level that persists at a higher level and for a longer time than expected from passive transfer of maternal antibody.

Management

Supportive care and surveillance and are the cornerstones of management for congenital rubella syndrome (CRS). At the time of diagnosis, a comprehensive evaluation should be performed to determine the extent of disease severity. The evaluation should include thorough neurologic, cardiac, ophthalmologic and audiologic examination; complete blood count; long-bone radiographs; and usually examination of cerebrospinal fluid. Acute management involves provision of supportive care and treatment of the clinical manifestations as necessary. Long-term management involves continued support and interventions for complications (e.g. sensorineural hearing loss, cataracts, cardiac defects) and monitoring for progression or late manifestations (e.g. hearing loss, endocrine problems).⁵²

CYTOMEGALOVIRUS INFECTION

Cytomegalovirus (CMV) is a ubiquitous virus that commonly infects people across the spectrum of all ages, races, and ethnic groups and those from a variety of socioeconomic, cultural and geographic backgrounds.⁵³

Congenital

Approximately 1 percent (0.2 to 2.5%) of newborns are born congenitally infected with CMV. Most of these newborns appear normal and are asymptomatic but 5 to 15 percent of congenitally infected newborns will have symptoms at birth. Both maternal primary and recurrent infection during pregnancy can result in congenital infection of the infant but the rate of transmission is far higher for mothers with primary infection (40 versus <1% transmission). Infants born congenitally infected with CMV as a

result of a primary maternal infection also are much more likely to have symptoms at birth and suffer sequelae.⁵⁴

Perinatal

Infants may be perinatally infected with CMV via contact with maternal cervicovaginal secretions during delivery or from breast milk ingestion after delivery. Preterm infants appear to be at greatest risk of acquiring the virus from breast milk.

Clinical Features

As many as 90 percent of newborns who are congenitally infected with CMV are asymptomatic at birth. However, as many as 15 percent of these apparently unaffected children can experience progressive hearing loss that most often is unilateral but occasionally may be bilateral.⁵⁵ Approximately 10 percent of congenitally infected newborns will have symptoms at birth. Somatic manifestations include: small size for gestational age, hepatosplenomegaly, petechiae and purpura of the skin and jaundice at birth.⁵⁶ At least two-thirds of the newborns with symptomatic congenital CMV infection will have neurologic involvement, including microcephaly, seizures, abnormal neurologic examination and feeding difficulties may be seen.⁵⁷

Although often asymptomatic, perinatal infection with CMV can produce a variety of clinical symptoms. A sepsis-like syndrome occurs most commonly and is associated with hepatosplenomegaly, abnormal blood counts with lymphopenia, neutropenia and thrombocytopenia, abnormal transaminases and pneumonitis.⁵⁸

Diagnosis

The diagnosis of congenital CMV infection or disease is accomplished by isolation of the virus in urine or saliva samples collected within the first three weeks of life. Detection of CMV DNA in the urine and serum of newborns also using polymerase chain reaction (PCR) techniques may be used to diagnose congenital CMV infection but these methods are less available, more expensive, and often less reliable than is traditional cell culture.⁵⁹ Prenatal diagnosis by viral culture or DNA detection of the virus in amniotic fluid or by CMV IgM antibody determination of fetal blood also has been reported and may be especially useful in the symptomatic fetus.⁶⁰ Serology for CMV IgG antibody determination (TORCH titers) is not helpful because most of the general population has CMV antibody and a positive result may only reflect passive transfer of maternal antibody to the infant. The presence of CMV IgM antibody in the newborn suggests congenital infection may be present. However, confirmatory viral culture still must be performed because both false-positive and false-negative serologic results occur.⁶¹

Treatment of neonates with congenital or perinatal CMV disease remains controversial but may be considered

in certain patients. Newborns who are likely to benefit immediately from antiviral therapy with ganciclovir include those with viral sepsis-like syndrome caused by CMV pneumonitis or severe and refractile thrombocytopenia, sight-threatening retinitis.⁶² Newborns who may benefit long-term from antiviral therapy include those with sensorineural hearing loss and microcephaly.

One report of a randomized clinical trial of ganciclovir (6 mg/kg per dose administered intravenously for six weeks) in newborns with severe congenital CMV disease and neurologic involvement showed apparent protection against hearing loss or progression of the infection and improved head circumference growth for the first 6 to 12 months of life.⁶³ Valganciclovir, an orally available form of ganciclovir, also has been used in the treatment of congenital CMV infection but data are not yet available for its use in infancy.⁶⁴

HERPES SIMPLEX

The incidence of neonatal HSV infection is estimated to be between 1 in 3000 and 1 in 20,000 births.¹ Neonatal HSV has three distinct periods of acquisition: Intrauterine, perinatal and postnatal.⁶⁵

Intrauterine

Occurs rarely (estimated incidence of 1 in 250,000 deliveries).

Perinatal

The majority (85%) of neonatal HSV infections are acquired perinatally. HSV is acquired perinatally when HSV infection, either symptomatic or asymptomatic, is present in the genital tract of the pregnant woman at the time of delivery. Factors that may influence perinatal transmission include the type of maternal HSV infection (primary versus recurrent), maternal HSV antibody status, duration of ruptured membranes, use of fetal scalp monitors and mode of delivery (cesarean versus vaginal).⁶⁶ However, most neonates with HSV disease are born to mothers without a history of HSV infection or other identifiable risk factors.⁶⁷

Postnatal

Approximately 10 percent of neonatal HSV infections are acquired postnatally.⁶⁶ Postnatal acquisition of neonatal HSV occurs when a caretaker with active HSV infection, such as herpes labialis, has close contact with the newborn infant.

Neonatal HSV

Can be broadly classified into three categories for therapeutic and prognostic considerations.

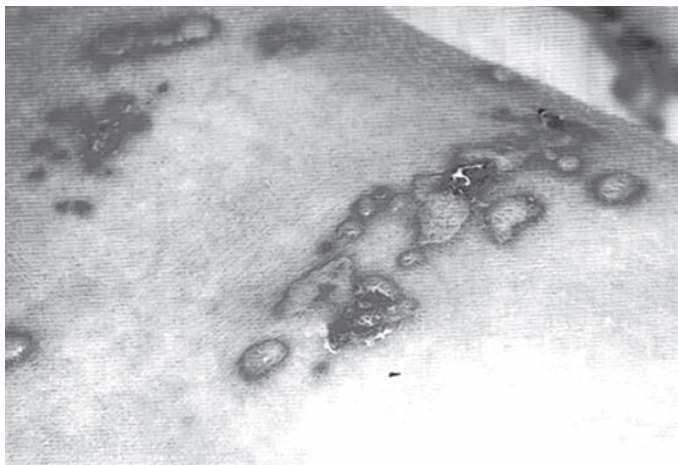


Fig. 6: Clinical photograph showing cluster of vesicles in a child with congenital herpes infection (*For color version see plate 1*)

Skin, Eye and Mouth

Vesicles typically appear on the sixth to ninth day of neonatal life. A cluster of vesicles often develops on the presenting part of the body, where extended direct contact with virus may occur (Fig. 6). Vesicles occur in 90 percent of infants with localized mucocutaneous infection and recurrent disease is common. Furthermore, significant morbidity can occur in these infants despite the absence of signs of disseminated disease at the time of diagnosis; up to 10 percent of infants later show neurologic impairment and infants with keratoconjunctivitis can develop chorioretinitis, cataracts and retinopathy.¹

CNS Disease

Approximately, one-third of neonates with HSV present with encephalitis in the absence of disseminated disease, and from 40 to 60 percent of these infants do not have mucocutaneous vesicles. These infants usually become symptomatic at 10 to 14 days of life with lethargy, seizures, temperature instability, and hypotonia. Mortality is approximately 15 percent with treatment and approximately two-thirds of surviving infants have impaired neurodevelopment.¹

Disseminated Infection

This is the most severe form of neonatal HSV infection. It accounts for approximately 22 percent of all infants with neonatal HSV infection. Symptoms usually begin within the first week of neonatal life. Clinical findings include seizures, shock, respiratory distress, disseminated intravascular coagulation (DIC), and pneumonitis. A typical vesicular rash may be absent in as many as 20 percent of infants. Mortality is around 57 percent. Forty percent of the infants who survive have morbidity.¹

Diagnosis

Viral Culture

Isolation of HSV by viral cell culture is the definitive laboratory method of establishing the presence of an active HSV infection in the neonate. Isolation of HSV from surface sites of the neonate, such as skin lesions, eye or conjunctivae, mouth or oropharyngeal secretions and stool or rectum, is significant particularly if obtained 24 to 36 hours after birth. Neonates with disseminated disease may have HSV isolated from their blood. Neonates with HSV hepatitis or necrotizing enterocolitis may have HSV isolated from duodenal aspirates, ascites fluid, or liver tissue. HSV may be isolated from tracheal aspirates in neonates with HSV pneumonia and isolation of HSV from the CSF or brain tissue is diagnostic of CNS involvement.⁶⁸

PCR Testing can be done on CSF, blood and amniotic fluid. The detection of HSV DNA in the cerebrospinal fluid (CSF) of a neonate confirms the diagnosis of central nervous system (CNS) involvement. CSF HSV PCR is more sensitive than viral culture.⁶⁹ In neonates with severe sepsis syndrome associated with disseminated intravascular coagulation, hepatitis or thrombocytopenia, the presence of HSV DNA in the blood or plasma confirms the diagnosis of disseminated neonatal HSV disease and provides the opportunity for early initiation of antiviral therapy.⁷⁰

DFA and EIA permit rapid detection of HSV antigens in skin and mucous membrane lesions.^{71,72} DFA has high specificity for HSV infection and typing of the HSV antigens may be done directly on material on the slide. However, DFA is not as sensitive as culture in many patients and accuracy depends on obtaining an adequate specimen containing cells from scrapings of the base of mucocutaneous lesions. EIA is primarily used to screen asymptomatic or pregnant women for HSV genital infection. Both false positive and false negative results may occur and combination with cell culture is recommended to optimize accuracy. The performance of rapid EIA in the diagnosis of neonatal HSV infection is not well established, highlighting the need for cell culture to confirm the diagnosis of HSV in neonates.⁷²

Serology

Combined HSV 1 and 2 serology is of little value, because many women are infected with HSV 1. Obtaining type-specific antibody from the mother or the infant may help determine whether there was maternal exposure to either and prognosis. Additionally, specific IgM may not be detected for up to 3 weeks in neonates. However, the number of different viral antigen-specific antibodies produced seems to correlate with the extent of disseminated disease, and the presence of certain antigen-specific antibodies may have long-term prognostic value.

Treatment

Acyclovir

Recommendations include treating infants with disease limited to the skin, eye and mouth disease with 20 mg acyclovir/kg every 8 hours for 14 days and those with CNS or disseminated disease for at least 21 days or longer if the CSF PCR remains positive. Infants with ocular involvement should have an ophthalmologic evaluation and consider topical ophthalmic agents (1% trifluridine, 0.1% iododeoxyuridine, or 3% vidarabine) in addition to parenteral therapy.¹

Prevention

The principal problem in developing strategies for the prevention of HSV transmission is the inability to identify maternal shedding of virus at the time of delivery. Viral identification requires isolation in tissue culture, so any attempt to identify women who may be shedding HSV at delivery would require antenatal cervical cultures. Until more rapid techniques such as a screening PCR are made available for the identification of HSV, the only clear recommendation that can be made is to deliver infants by cesarean section if genital lesions are present at the start of labor. The efficacy of this approach may diminish when membranes are ruptured beyond 4 hours. Nevertheless, it is generally recommended that cesarean section be considered even with membrane rupture of longer durations, although data showing efficacy beyond 4 hours are lacking. Infants inadvertently delivered vaginally in the setting of cervical lesions should be isolated from other infants in the nursery, and cultures should be obtained from the oropharynx/nasopharynx and conjunctivae. If the mother can be identified as having recurrent infection, the resultant neonatal infection rate is low and parents should be instructed to consult their pediatrician when a rash or other clinical changes (lethargy, tachypnea, poor feeding) develop. Weekly pediatric follow-up during the first month is recommended. Infants with a positive culture from any site or the evolution of clinical symptomatology should immediately have cultures repeated and antiviral therapy started. If caesarean delivery is performed after 24 hr or baby is vaginally delivered Acyclovir may be initiated without waiting for culture or DFA results.¹

ADVANCES IN CONGENITAL/PERINATAL INFECTIONS

During the past 20 years, a number of scientific and sociological changes have altered the scope of TORCH infections. Incidence of these diseases has changed significantly because there are better preventive measures available for diseases like Rubella and Varicella. The use of new therapeutic drugs has altered the picture of CMV and toxoplasmosis. Ganciclovir is showing promise as a drug to prevent

those with severe CMV infection from developing the progressive deafness and other sequelae that characterize the disorder. Blood products are now routinely tested for the virus and the use of seronegative blood permits the infection to be avoided in premature infants. Treatment for toxoplasmosis *in utero* and during the first year of life has been shown to significantly improve outcomes.

Advances in molecular diagnostics have enabled the development of faster, more precise methods to detect the presence of pathogens. DNA probes and PCR are able to identify pathogens when cultures and serologic tests are slow, difficult or inconclusive. Toxoplasmosis, for example, can be quickly detected in the amniotic fluid, allowing for earlier treatment of the fetus. Finally, the growing use of the Internet to access information has changed how health professionals educate themselves and the public. Websites that make available authoritative information and practical advice exist for a number of congenital infections and can be invaluable to parents.⁷³

CONCLUSION

The nature of TORCH infections has changed dramatically as a result of new vaccines, new pathogens, more sophisticated diagnostic testing and greater public awareness of the need for early prenatal care. In the future, we will have new organisms to consider, new vaccines to prevent these diseases and more effective treatments. The impact of the “new genetics” may enable the identification of those at risk for these infections even before conception.

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Necrotizing Enterocolitis

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Necrotizing enterocolitis (NEC) is one of the most common gastrointestinal emergencies in newborn infants. In NEC, the small (most often distal) and/or large bowel gets injured, develops intramural gas and may progress to frank necrosis with perforation. Although the disease was identified more than a century ago, Schmid and Quaiser were first to coin the term NEC and the first comprehensive description of the disease was given by Berdon and colleagues in the 1960s. Despite the progress made in neonatology in the last few decades, NEC still baffles neonatologists' world over with unproven pathogenesis and no definite management and preventive guidelines being agreed upon. Not only the disease is associated with increased mortality but morbidity in terms of bowel strictures, short gut syndromes and poor neurodevelopmental outcome is also high. With increasing survival of premature babies, the population at risk for NEC is increasing. Spontaneous intestinal perforation although earlier was classified as NEC is increasing being identified as a separate entity.

EPIDEMIOLOGY

Due to improved NICU practices, routine antenatal steroids and surfactant use, the survival of ELBW babies is increasing and hence the population at risk for NEC is also ever increasing. Term babies constitute 10 percent of all cases. In most series, the incidence of NEC is reported at 1 to 5 percent of NICU admission or 0.5 to 5 per 1000 livebirths. Both the incidence of necrotizing enterocolitis and its fatality rates increase in inverse proportion to birth weight and gestational age. In the published NICHD neonatal network cohort (1999–2001), about 7 percent of 11,072 VLBW infants developed proven necrotizing enterocolitis (\geq stage II), with about half undergoing surgery.¹ In this cohort, rates were inversely related to birth weight,

with necrotizing enterocolitis affecting 11.5 percent of infants weighing 401 to 750 g, 9 percent of infants 751 to 1000 g, 6 percent of 1001 g. Almost similar rates have been reported by Vermont Oxford Network and Canadian neonatal network. The rates have remained stable over time across most neonatal networks, the only exception being study by New South Wales and Australian Capital Territory Neonatal Intensive Care Unit Study group (NSW ACT NICUS) reporting a reduction in the incidence of NEC from 12 percent in 1986 to 1987 and 1992 to 1993 to 6 percent in 1998 to 1999 for all infants born in New South Wales² at 24 to 28 weeks' gestation and the researchers noted that this decline occurred despite increasing VLBW admissions and survivors at NICUs. Mortality and surgery rates remained stable. Although encouraging, this is the only large study to report a decline in the rate of the disease in VLBW preterm infants, although a smaller, single-center report from the United States also reported a decline in the incidence of NEC in infants with birth weights between 500 and 800 g. Mortality and surgery rates remained stable. National Neonatal Perinatal Database 2003 from India has indicated the risk of NEC to be 0.2 percent. This low incidence is because only 3.4 percent of the babies included in the database were less than 1500 g and ELBW babies constituted only 0.7 percent of the population.

There is no definite sex predilection for NEC but the mortality is more common in the male VLBW babies. Black infants are at greater risk of NEC primarily because of the increased prematurity rates in this population. This reported racial disparity in deaths from the disease remained significant even after controlling for birth weight and other characteristics, and needs further investigation. There is no racial data in Indian population.

Mortality rates in NEC range from 15 to 30 percent. Although most cases of necrotizing enterocolitis are

managed medically, an estimated one-third of the infants undergo surgery. Mortality in surgical cases approaches 50 percent and is highest for the smallest, least mature infants. Most cases of necrotizing enterocolitis are sporadic, with no clear seasonal distribution, but outbreaks do occur. Observations made during these epidemics suggest that they are infectious outbreaks. No one infectious agent has been linked to epidemic necrotizing enterocolitis.

The age of onset of NEC is directly related to the birth weight and gestation age. NEC is uncommon in term infants, in whom it usually appears within 2 to 5 days after birth. The average age of onset has been reported to be 20.2 days for babies born at less than 30 weeks' estimated gestational age (EGA), 13.8 days for babies born at 31 to 33 weeks' EGA, and 5.4 days for babies born after 34 weeks' gestation. In an Indian study reported from PGIMER Chandigarh India, age of presentation was 4.9 ± 4.8 days, however, the population consisted of more mature babies with mean weight 1667 ± 577 g and mean gestation age 33.2 ± 2.6 weeks.³

PATHOLOGY

The predominant anatomic lesion in NEC is coagulative or ischemic necrosis. Necrosis is the direct result of ischemia. The usual site for NEC occurrence is the ileocolic region and sometimes the terminal ileum is the only part of the intestine affected. Necrosis involves the small and the large intestine in about 50 percent of cases and is divided equally according to continuous or discontinuous involvement.

The inflammatory process in NEC starts in the venules. The location and extent of the affected areas (often multiple) are random, and they are not related to the arterial supply (Fig. 1). NEC is characterized by necrosis which is out of proportion to the degree of inflammation with micro abscesses and crypt abscesses being relatively uncommon. These findings are reverse of what one would expect to see in the infectious colitis. Pneumatosis intestinalis which is hallmark of the disease develops largely as a result of fermentation of intraluminal contents by the

bacteria. Gas bubbles which may be grossly visible in the intestinal wall are reported to involve the entire colon and are more common in the term infant than in premature infant.⁴ Perforation tends to occur at the junction between normal and necrotic bowel, but it can occur amidst the devitalized bowel and can occur at more than one spots.

Microscopic examination shows mucosal edema and hemorrhage representing coagulative necrosis with presence of acute and chronic inflammatory cells. Pneumatosis is located in the submucosal region and between muscle layers. Subserosal pneumatosis is not seen microscopically because the gas is evacuated before fixation can be accomplished. Thrombi are widespread but bacteria are scanty in the wall. In rapidly progressive lesions, necrotic lesions can be seen in other organs like liver, spleen, adrenals and kidneys. Reparative changes, including epithelial regeneration, granulation tissue, and fibrosis are common in recovering NEC. The development of scar tissue and fibrosis, if circumferential may progress to stricture formation. This development is especially common in distal colon and may present several months after the initial disease has resolved.⁵

RISK FACTORS AND PATHOPHYSIOLOGY

Despite extensive research, the disease still seems to be incompletely understood. Prematurity and feeding seem to be most consistent correlates of the disease. Classic triad of pathological events consists of: (1) Intestinal ischemia 2) Colonization by pathological bacteria (3) Protein substrate in the intestinal lumen (Flow chart 1). Presence of any two is sufficient enough to produce the disease. The other pathogenetic mechanisms for the disease include immaturity in neonatal vasculature, immune function, motility and barrier function (Flow chart 1). NEC is more likely to appear following quantitative extremes (i.e. severe ischemia, highly pathogenic flora, or marked excess of substrate) and develops only if a threshold of injury, sufficient to initiate intestinal necrosis, is exceeded. This may be the reason why most babies in NICU do not develop the disease.

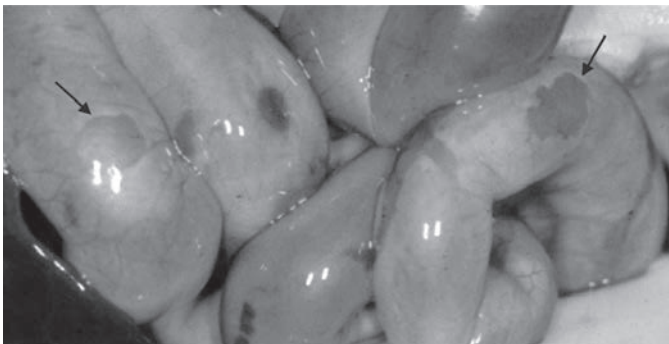
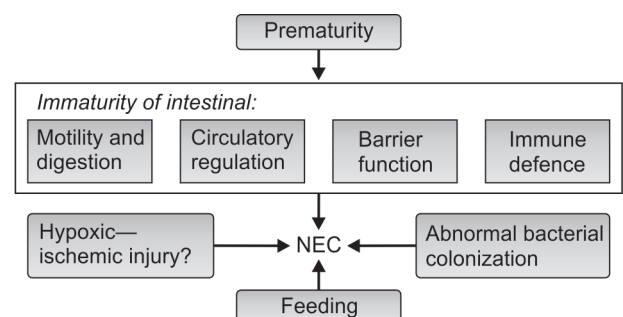


Fig. 1: Postmortem appearance of intestine in severe NEC with arrows indicating coagulative necrosis of whole of mucosa, submucosa, muscularis layer

Flow chart 1: Pathogenesis of NEC



Immature Intestinal Motility

Gut motility begins by second trimester but starts maturing by third trimester, although this can be hastened by early feeding. IUGR babies have less motility than the AGA babies and this could be partially responsible for the increased incidence in IUGR babies. In addition to impaired intestinal motility, premature infants have not yet developed the ability to digest and absorb nutrients, and incompletely digested molecules could contribute to intestinal injury. An intrinsic immaturity of the enteric nervous system delays transit and may lead to poor clearance of bacteria and subsequent bacterial overgrowth. Peristalsis also serves as an important component of epithelial barrier integrity. Peristalsis limits the amount of time during which antigens are able to interact with the apical surface of the enterocytes and also speeds the process by which antigen-antibody complexes are eliminated.⁶ Thus, impaired digestion of nutrients, coupled with delayed transit time, could result in injury of intestines with immature host and barrier defences.

Immature Intestinal Defence Mechanisms and Barrier Functions

Preterm babies have reduced amount of antimicrobial peptides defensins (α and β) and cathelicidins. These antimicrobial peptides have bioactivity against a wide range of microbes, including bacteria, viruses, fungi, protozoa, and spirochetes, and the immature intestine may be vulnerable to such pathogens.

Mucin produced by intestinal epithelial cells has many functions like lubrication, mechanical protection and protection against gastric and duodenal secretions. The level of mucin secreted increases with increase in the gestational age making these preterm babies more prone to intestinal inflammation. Developmental expression of mucin genes changes throughout the intestine and seems to mimic adult pattern expression between 23 and 27 weeks' gestation.

Intestinal epithelia are joined by tight junctional complexes, which form by 10 weeks' gestation. By selectively controlling the movement of small ions across the epithelial monolayer, enterocytes use Cl^- ions and water secretion (secretory diarrhea) to flush unwanted pathogens or toxins from the intestinal lumen. Since fetal intestinal secretion and absorption mature gradually, under the influence of amniotic fluid, from 26 weeks' gestation to full-term, pathogens might not be efficiently washed from the intestinal lumen in preterm infants.

Abnormal Bacterial Colonization

Since necrotizing enterocolitis does not occur in utero, intestinal bacteria might have a role in its pathogenesis, especially if abnormal colonization occurs. Pathogenic host-bacterial interactions have been well characterized—a

family of pattern recognition receptors (PRRs) transmits signals from microbial-associated molecular patterns (MAMPs) to induce proinflammatory and proapoptotic and antiapoptotic responses in host cells. Commensal bacteria can inhibit inflammatory pathways. Premature infants are especially susceptible to intestinal colonisation by pathological bacteria because of their daily exposure to nosocomial flora and the likelihood of exposure to antibiotics on admission to NICUs.

Immature Intestinal Circulatory Regulation

The occurrence of NEC in the setting of congenital heart disease, postbypass surgery or HIE in-term babies suggests a role for ischemia hypoxia model in the pathogenesis of NEC. The incidence of NEC is most common in the premature cyanotic heart disease and hypoplastic left heart syndrome. The most common suggested mechanism is the diving reflex where in the blood supply to the brain, heart and adrenals are maintained at the cost of blood supply to lesser vital organs like GIT.

Blood supply of the intestine in premature babies is dependent on balance between two main factors—ET-1 (endothelin) and NO (endogenous nitric oxide). ET-1 is a peptide mainly produced by endothelium and acts on the vasculature of intestine through two receptors—ETA and ETB. Activation of ETA receptors, which are predominantly located on vascular smooth muscle cells, leads to a profound and sustained contraction. Activation of ETB receptors located on endothelial cells leads to nitric oxide (NO)-mediated vasodilatation, whereas activation of ETB receptors located on vascular smooth muscle cells leads to vasoconstriction. Under basal conditions, ETA mediated vasoconstriction is more pronounced effect than ETB mediated vasodilatation. ET-1 is constitutively produced by its production can be increased by multitude of cytokines. ET-1 and its receptors are expressed in greater quantity in the premature babies as this peptide is strongly linked to angiogenesis in such subjects.

NO is produced during the enzymatic conversion of L-arginine to L-citrulline by a family of NO synthetases, including the endothelial isoform of nitric oxide synthase (eNOS) and is the primary vasodilating molecule for intestinal vasculature. Role of NO is gestation dependent with more vasodilatation occurring in response to the NO at lesser gestation. In newborn, under steady state, the balance favours vasodilatation due to an increased constitutive and stimulated production of NO. This serves to ensure an increased, therefore oxygen delivery, to the newborn intestine to meet the metabolic demands of early postnatal life. In pathologic states, endothelial dysfunction alters the balance favoring ET-1-mediated vasoconstriction and likely contributes to the compromise of blood supply of the gut.

In NEC, the balance of intestinal circulation is tilted in favor of vasoconstriction due to increased expression

of ET-1 in response to various cytokines like IL-1 β and reduced synthesis of NO due to reduced activity of eNOS.

L-arginine which is a precursor to the NO synthesis is found in lesser quantity in NEC. Supplementation with L-arginine has been found in experimental model of NEC to have lesser injury especially if started prophylactically than once the injury has occurred. In a double-blinded RCT, L-arginine supplementation to infants less than 28 weeks gestation significantly decreased the incidence of NEC.⁷ Possible mechanisms for benefit include increased NO production due to increased substrate availability and the fact that arginine is the precursor for the production of other amino acids such as glutamine and glutamate, both of which are important in maintaining physiologic intestinal processes. The finding that L-arginine supplementation decreases the incidence of NEC in premature human infants certainly warrants further study via a multicenter randomized controlled trial.

Growth Factors and Pathogenesis of NEC

Epidermal growth factor (EGF) acts on the enterocyte receptor (EGFR) which is primarily located on the basolateral surface of enterocytes resulting in trophic, maturational, and healing effects on intestinal mucosa. EGF increases with increasing gestational age. Maternal milk is source of EGF in the postnatal period. There is some experimental data suggesting that level of EGF expression is directly related to the development of NEC. Enteral supplementation with EGF before the injury significantly decreased the incidence and severity of experimental NEC. One of the postulated mechanisms for protective role of breast milk in NEC could be related to presence of EGF in breast milk as compared to the formula milk. Supplementation of EGF in experimental mouse model has been reported to decrease the incidence of NEC,⁸ downregulate the production of inflammatory cytokines, and decrease apoptosis at the site of injury. EGF is recently used by Sullivan and co-workers⁹ in a randomized, double-blind, prospective trial with recombinant EGF 1-48 (rEGF) in small group of premature neonates with evidence of NEC stages II or III. The investigators reported that repair of intestinal epithelium was seen at 4, 7, and 14 days as inferred by rectal biopsy specimens. Heparin-binding epidermal-like growth HB-EGF factor is a member of EGF family and uses the EGFR signaling pathway to stimulate cell growth and differentiation. Again in experimental models of NEC and neonatal shock syndrome, HB EGF has been shown to increase the proliferation of epithelial cells and increase in intestinal blood flow. G-CSF supports growth and proliferation of neutrophil precursors. GCSF receptors are present on nonhemopoietic tissue like gut in neonates as well. Amniotic fluid in utero and human milk in the postnatal period provide significant concentration of GCSF. Canpolat and co-workers¹⁰ administered enteral

G-CSF to preterm infants diagnosed with stage I NEC for 5 days. They reported prevention of disease progression with shorter time required for resolution of clinical symptoms, duration of therapy, and length of hospital stay when compared with controls. Presence of EPO in human milk suggests that this might also have some beneficial effect also this has not been extensively studied as of now.

RISK FACTORS AND PREVENTION OF NEC

Antenatal Steroids

The data regarding the antenatal steroids and incidence of NEC is conflicting. Cochrane systematic review on use of antenatal steroids shows an overall reduced incidence of NEC in addition to reduction in neonatal deaths. However, two large retrospective studies have shown increased risk of NEC with antenatal exposure possibly as a result of increased survival of babies with less pulmonary morbidity. Despite the possibility of an increased risk of NEC with the use of antenatal steroids, single course of antenatal corticosteroids to accelerate fetal lung maturation in women at risk of preterm birth is still recommended because of the effects on other outcomes.

Patent Ductus Arteriosus

Patent ductus has been implicated in the pathogenesis of NEC because of the diastolic steal of blood to the lungs. Prophylactic ligation of the PDA within 24 hours of birth results in decreased incidence of NEC. The effect of prophylactic treatment with indomethacin on NEC is variable. However, symptomatic treatment of PDA with indomethacin is associated with increased risk of NEC presumably secondary to decreased splanchnic blood flow.

Antibiotics for Premature Rupture of Membranes

Results of the ORACLE trial has suggested that use of amoxicillin is associated with increased risk of NEC and hence for PROM the antibiotic of choice should be erythromycin alone.¹¹

Maternal Cocaine Use

It has been associated with increased risk of NEC probably because of decrease of intestinal blood flow.

H₂ Blocker Use

In a large case control study from NICHD, use of H₂ blocker has been associated with increased risk of NEC.¹

Fluid Restriction

Excess fluid has been implicated in the pathogenesis of NEC. A systemic review and meta-analysis indicates that restricted water intake significantly increases postnatal weight loss and significantly reduces the risk of NEC.¹²

Blood Transfusion

Low quality evidence has shown an association between neonatal blood transfusion and the development of NEC.¹³ Withholding enteral feeds for a few hours during a blood transfusion may have theoretical benefits, but there is no published evidence to support this practice.

Oral Antibiotics

Because of the role of bacteria in the pathogenesis of NEC, oral antibiotics have been tried to prevent NEC. Meta-analysis¹⁴ has reported that the administration of prophylactic enteral antibiotics resulted in significant reduction in NEC without any impact on mortality. The possible harmful effects of prophylactic antibiotics including the development of bacterial resistance and alteration of the natural microflora make it difficult to recommend this strategy for prevention of NEC.

Oral Immunoglobulins

One of the mechanisms by which breast milk is protective for NEC is presence of immunoglobulins in the milk which inhibits the growth of pathogenic bacteria. IgA, being a secretory immunoglobulin, might be expected to be more efficacious in protecting the neonatal gastrointestinal tract than the more readily available IgG. A Cochrane review on the oral supplementation of immunoglobulins to prevent NEC involving three trials did not show any specific benefit.

Congenital Heart Disease

Among term babies congenital heart disease is an important risk factor for developing NEC. Factors associated with an elevated risk of NEC in infants with heart disease include premature birth, hypoplastic left heart syndrome (OR 3.8), truncus arteriosus (OR 6.3), and episodes of poor systemic perfusion or shock (OR 6.5).¹⁵ Heightened suspicion is warranted in newborns with these risk factors. Outcome of babies with NEC in CHD patients is better with decreased risk of perforation, need for a bowel operation, strictures, need for a stoma, sepsis, and short bowel syndrome compared with the noncongenital heart disease group.

Probiotics

When compared to term infants, VLBW infants at risk of NEC have abnormal fecal colonization, demonstrate a paucity of normal enteric bacterial species, and have delayed onset of bacterial colonization. Probiotic bacteria are live microbial supplements that colonize the gastrointestinal tract and potentially provide benefit to the host. Potential mechanisms by which probiotics may protect high risk infants from developing NEC and/or sepsis include increased barrier to migration bacteria and their products across the mucosa, competitive exclusion

of potential pathogens, modification of host response to microbial products, augmentation of IGA mucosal responses, enhancement of enteral nutrition that inhibit the growth of pathogens, and up-regulation of immune responses. A meta-analysis of 11 trials involving 2176 babies showed a 30 percent reduction in the incidence of NEC and there was also a reduction in the incidence of death amongst VLBW babies. No significant adverse effects were reported. Some authors have concluded that it is unethical to compare probiotics with placebo given the degree of benefit, however, further understanding of probiotics in terms of selection, dosing, duration, and short and long-term effects is needed to decide the optimum strain, dose etc.¹⁶

Prebiotics

Prebiotics are nondigestible dietary supplements, such as long chain carbohydrates or mucins, which promote proliferation of beneficial commensal bacteria. Preliminary studies show increased *Bifidobacterium* stool colonization and decreased pathogenic bacterial colonization in preterm infants fed with formula containing prebiotics besides having effect on host immune system. Because prebiotic supplements do not contain live microorganisms, they carry less risk of infection than probiotic therapies. However, prebiotic administration has been associated with unwanted (but reversible) side effects such as flatulence, bloating and diarrhea. At present there is no consensus on use of prebiotics for prevention of NEC.

Postbiotics

Prebiotics are bacterial metabolites such as butyric acid, a short-chain fatty acid produced by commensal bacteria in the colon through anaerobic catabolism of complex carbohydrates and acts as major energy source for colonic enterocytes and has an incompletely understood role in intestinal growth, inflammatory suppression, apoptosis. Butyrate has been administered with limited success in human inflammatory bowel disease, but there are as yet no studies in neonates.

Other experimental therapies include acidification of gastric pH by acidification of the diet, adding PUFA (which is a precursor to the vasodilatory and cytoprotective cytokines) to the diet of preterm babies. Erythropoietin treated preterm babies have been shown to be having lesser incidence of NEC as compared to the control group. EPO also acts as a trophic factor in the gut whether given enterally or parentally. These therapies although promising has to be clinically validated.

Feeding and NEC

Only 10 percent of the cases of NEC occur in nonfed babies and aggressive feeding regimens have been implicated in the pathogenesis of NEC. Different studies have

been performed regarding the feeding type, volume, rapidity of increase in feeds, etc. and NEC.

Feeding Volume and NEC

Two randomized, prospective trials including an Indian study have assessed infants with feeding volume increments of 30 mL/kg/d¹⁷ and 35 mL/kg/d¹⁸ compared with a control group whose feedings were increased by 15 mL/kg/d. Infants receiving the larger incremental volumes reached full feeding volumes earlier than the control infants without increasing the risk of NEC. Meta-analysis of the trials suggests that there is no increased risk of NEC with rapidly increasing feed increments. The confidence interval, however, is too wide suggesting that the proof is not entirely convincing, hence in ELBW babies, we tend not to increase more than 20 to 25 mL/kg/day.

These results are in conflict with those of Berseth and colleagues,¹⁹ who compared infants randomly assigned to daily increases in feeding volumes with infants whose feeds were held at a minimal volume for the first 10 feeding days. This study demonstrated a significant increase in NEC in the group with advancing volumes, and the study was closed early because the incidence of NEC was 10 percent in the advancing volume group versus 1.4 percent in the minimal volume group. The enteral feeds in the study were started only on day 10, which is not the routine practice across NICUs and hence, the study cannot be interpreted in light of current practices.

Method of Feeding

McGuire²⁰ performed a meta-analysis to compare transpyloric versus intragastric tube feedings. The incidence of NEC was similar between the two feeding methods among

the 8 studies evaluated, as were growth and time to establish full enteral feedings. Infants fed transpylorically experienced significantly higher mortality, and the authors concluded that the routine use of transpyloric tube feeding is not warranted, given the lack of evidence for benefit compared with the increased risk.

Donor Human Milk versus Formula

That breast milk is protective for NEC, whether the same benefit is extended by using donor human milk as compared to the formula milk is preterm babies has been analyzed in a meta-analysis of four trials²¹ which suggest that NEC is three times less likely to occur in the donor human milk group with NNT being.²⁰

Feeding after the Diagnosis of NEC

Conventional practice has been to delay introduction of feeds for a substantial time after the diagnosis by two recent reports have questioned the rationale. A recent study²² has looked at the feeding of babies with established NEC. These investigators reinitiated enteral feedings in infants when portal gas was absent for three consecutive days on abdominal radiographs. When compared with historical controls who were refeed 10 days after diagnosis, these study infants initiated feedings sooner (median 4 days, range 3 to 14 days) and reached full enteral feedings sooner (9 days vs 19 days; $P < 0.001$), had less catheter-related sepsis and shorter hospital stays. This data suggests that probably in some subsets of babies with NEC, feeds could be introduced earlier than is the current practice, precluding the need for TPN. A similar study in NEC Stage II cases showed that fasting for less than 5 days after diagnosis was associated with lesser catheter related sepsis

Table 1: Modified Bell's staging of NEC

Stage	Systemic signs	Intestinal signs	Radiographic signs
IA Suspected NEC	Temperature instability, apnea, bradycardia, lethargy	Gastric retention, abdominal distension, emesis, heme-positive stool	Normal or intestinal dilation, mild ileus
IB Suspected	Same as above	Grossly bloody stool	Same as above
IIA Definite, mildly ill	Same as above	Same as above, plus absent bowel sounds with or without abdominal tenderness	Intestinal dilation, ileus, pneumatosis intestinalis
IIB Definite, moderately ill	Same as above, plus mild metabolic acidosis and thrombocytopenia	Same as above, plus absent bowel sounds, definite tenderness, with or without abdominal cellulitis or right lower quadrant mass	Same as IIA, plus ascites
IIIA Advanced, severely ill, intact bowel	Same as IIB, plus hypotension, bradycardia, severe apnea, combined respiratory and metabolic acidosis, DIC, and neutropenia	Same as above, plus signs of peritonitis, marked tenderness, and abdominal distension	Same as IIA, plus ascites
IIIB Advanced, severely ill, perforated bowel	Same as IIIA	Same as IIIA	Same as above, plus pneumoperitoneum

than the control group (0 vs 29 percent) without increase in other complications.²³

CLINICAL FEATURES

Are extremely variable with generalized and local signs both being present. The severity of symptoms varies according to the progression of the disease. The onset of NEC can be sudden or insidious. In the sudden form, abrupt clinical deterioration occurs, which is indistinguishable from sepsis syndrome. Age at presentation is inversely related to gestational age at birth, with full term infants often presenting in the first few days of life. Median age at presentation is between 2 to 3 weeks of age. Neonates most commonly present with feeding intolerance, delayed gastric emptying, abdominal distension or tenderness (or both), occult or gross blood in the stool, lethargy, apnea, respiratory distress, or poor perfusion. Because early signs of this disease are nonspecific, sepsis may be suspected before necrotizing enterocolitis.

GI signs can include any or all of the following:

- Increased abdominal girth
- Visible intestinal loops
- Obvious abdominal distention and decreased bowel sounds
- Change in stool pattern
- Hematochezia
- A palpable abdominal mass
- Erythema of the abdominal wall.

Systemic signs can include any of the following:

- Respiratory failure
- Decreased peripheral perfusion
- Circulatory collapse
- With insidious onset, the clinical signs may be mild, whereas patients with fulminant disease can present with severe clinical abnormalities.

In 1978, Bell and colleagues proposed a system for the uniform clinical staging of infants with necrotizing enterocolitis. They classified infants as having stage I (suspect), stage II (definite), or stage III (advanced) disease. These criteria were subsequently modified by Walsh and Kliegman (Table 1). Guidelines for management of necrotizing enterocolitis are based on diagnosis according to these modified criteria.

Increased gastric aspirate are often considered a significant risk factor for the disease. However, the overlap amongst the values for the control and the study group is so huge that this cannot be used as a single marker for stopping feeds. Most of studies showing association of increased gastric residues to the development of NEC have shown increase occurred 1 to 3 days before the development of NEC and for the rest of the days the volume of aspirates was no different. The connotation to this is that in any baby who is otherwise well and has an increased gastric aspirate in first week of life should not be a reason for withholding feeds unless the aspirates are persistently

high. Increased abdominal girth of more than 2 cm is 66 percent sensitive antecedent to stage III NEC.²⁴

DIFFERENTIAL DIAGNOSIS

Sepsis with ileus, in both term and preterm patients, can mimic NEC. Both present with systemic signs of infection and abdominal distension. The absence of pneumatosis on plain radiographs argues against NEC, but does not rule it out but in any case the treatment for both conditions is essentially the same. In VLBW infants, inspissated meconium syndrome results in distended intestinal loops. However, these babies typically present with obstructive signs without evidence of sepsis. Isolated gastric perforation can result in pneumoperitoneum. Gastric perforation may be associated with administration of indomethacin or corticosteroids. Iatrogenic gastric perforation from feeding tubes occurs rarely. Although patients who have gastric perforation present with pneumoperitoneum, they are not as systemically ill as patients who have NEC. Patients who have Hirschsprung enterocolitis or severe gastroenteritis may present with pneumatosis.

DIAGNOSIS

Laboratory Diagnosis

Neutrophilia with or without left shift is seen in less severe NEC, with neutropenia observed more commonly in severe NEC and this is associated with poor prognosis. G-CSF use in patients with neutropenia and sepsis including NEC has shown improved survival in babies but the effect was not sustained when the meta-analysis excluded the nonrandomized trials.

Infants with severe NEC develop thrombocytopenia with incidence of 65 to 90 percent. Lower platelet counts have been reported to be associated with greater disease severity. In NEC, platelet counts may fall rapidly (within hours) a finding that supports consumption rather than decreased production and for this reason the therapeutic response to platelet transfusions is commonly short-lived. Indications for transfusion should be based on the presence of clinical bleeding, potential risks of bleeding, as well as the severity of thrombocytopenia. Worsening platelet count may be one indication for surgery.

Anemia is multifactorial in origin. Hemolytic anemia is common with NEC. Red blood cell morphology is consistent with thrombotic microangiopathy and includes teardrops, schistocytes, spherocytes, and acanthocytes. Hemolysis is related to T-cell crypt antigen activation which is seen in almost one-third of the patients. T-crypt antigen is a naturally occurring antigen found on human erythrocytes, normally concealed by a layer of N-acetylneuraminic acid, unless exposed by bacterial or other neuraminidases. When blood donors have antibodies to T crypt antigen, transfusing infants with T-crypt antigen activation may worsen the clinical course of NEC.

Hence, if possible one should ask blood bank for T-antigen negative blood. In addition to hemolysis, blood loss anemia is seen. Iatrogenic anemia may contribute to the problem, since frequent blood sampling is mandatory.

Coagulation abnormalities are common in NEC as the premature babies are endowed by lower levels of coagulation protein and with severe disease there are rapidly consumed and result in features suggestive of DIC. Treatment continues to be supportive, with administration of clotting factors.

Hypонатremia secondary to the tissue sequestration of sodium and third space fluid loss along with acidosis indicating decreased tissue perfusion are important hallmarks of the disease.

SEROLOGICAL TESTS

CRP a relatively sensitive but nonspecific marker for NEC and hence should not be used in isolation for diagnosis of NEC. Serial C-reactive protein could be useful in the management of the disease. Persistently high C-reactive protein indicated developing complications, such as stricture or abscess, or the need for surgical intervention.

Investigators have attempted to identify specific markers that would allow early diagnosis and treatment of NEC. Intestinal FABP are small (14 kDa) proteins that constitute up to 2 percent of the cytosolic protein of mature enterocytes and is raised in serum after any intestinal injury including NEC. Although seems promising, but the data currently is available from three studies including only 42 subjects and the specific cut off to differentiate NEC from other disease is not clear.

Imaging

The imaging modalities that are used in neonates during the active phase of NEC include plain abdominal radiography and abdominal sonography, other modalities like CT and MRI have not been found to be useful in clinical practice.

Plain Radiography

This is currently the modality of choice for diagnosis and staging of NEC. We recommend performing abdominal radiographs every 8 hours during the acute phase of suspected or diagnosed NEC beside anytime a clinical deterioration occurs. The interval can increase if the baby is showing signs of recovery. The plain radiograph should include two views—vertical beam with the patient supine and horizontal view with patient supine called the cross table view. Both vertical and horizontal beam views are required for follow-up in the first 48 hours following diagnosis, as the vast majority of perforations occur in this time frame. After this, vertical beam views alone may suffice unless there is specific concern for perforation. In normal neonates, gas is most often present through most

of the small and large bowel resulting in gas pattern called the “mosaic” appearance.

INTESTINAL DISTENSION

Bowel distension may be focal or generalized depending on the extent of the disease and is a result of ileus and partial obstruction. This sign is the earliest and may precede the development of clinical signs of NEC by few hours and the degree of dilatation usually correlates well with the clinical severity of the disease. Persistence of dilatation suggests failure of response to medical therapy or deterioration. An ominous sign is the change from generalized dilatation to an asymmetric distribution where dilatation is confined to a more localized area of the abdomen. It is even more worrisome if the asymmetric pattern persists and the dilated loops maintain the same appearance as fixed loops on follow-up plain abdominal radiographs. Prone and decubitus positions are helpful in differentiating a normal dilated intestine from an ischemic noncompliant segment. This suggests the development of full-thickness necrosis and may precede clinical deterioration including signs of peritonitis. For these reasons, the degree and pattern of bowel dilatation are the most important signs for early diagnosis and for follow-up. However, bowel distension is a very nonspecific sign.

Pneumatosis Intestinalis

Although not pathognomic, intramural gas is most commonly seen in NEC in premature infants. The incidence of intramural gas varies from 20 to 98 percent in various studies. Intramural gas is most commonly present in the distal small bowel and large intestine and hence it is most commonly seen in the lower right quadrant (Fig. 2), although it can affect any part of the gut. The amount of

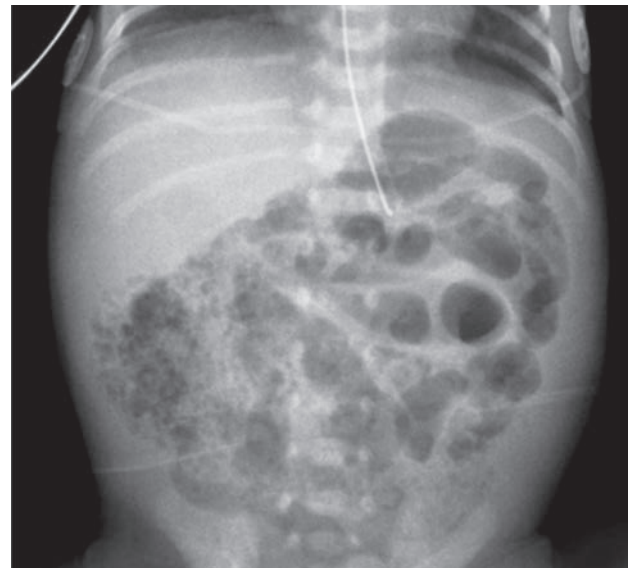


Fig. 2: Soap bubbly pattern due to intramural gas in the right iliac fossa

intramural gas present does not always relate to the clinical severity of NEC and disappearance of intramural gas does not always correlate with clinical improvement.

Intramural gas may be diffuse or localized and appears as linear or cystic radiolucencies and represents an intramural hydrogen gas resulting from bacterial fermentation. The linear lucencies often appear curvilinear; they represent intramural gas in the subserosa and appear as black lines on the radiograph, which can occasionally be confused with overlapping bowel loops filled with gas. A clue to differentiating intramural gas from overlapping loops is the white lines that often accompany the black lines of intramural gas. The white lines represent the mucosa and submucosa, which are lifted off the serosa and are contrasted by the subserosal intramural gas and the intraluminal gas. A search for white lines rather than the black lines may often be more fruitful in helping one confirm the presence of intramural gas. Cystic form has a granular or foamy appearance and frequently is confused with fecal material. It represents gas in the submucosal layer of the bowel.

Portal Venous Gas

It is an extension of intramural gas that enters the veins of the bowel wall and passes into the portal venous system. This is reported to be present in 30 percent cases of confirmed NEC. It appears as branching, linear, radiolucent vessels (Fig. 3) that may extend from the region of the main portal vein toward the periphery of both hepatic lobes. Portal venous gas must be differentiated from gas in the biliary tree, which is uncommon in the neonatal period and is more centrally located in the larger ducts, in contrast to portal venous gas, which may extend more peripherally.

Diminishing Bowel Gas

Also described as asymmetric loops of intestine, which suggest an abnormal motility pattern. In the presence of

ischemia, the reported poor motility allows affected loops of bowel to be filled with fluid, resulting in diminished amount of visualized bowel gas compared with other areas of normal intestine where gas is propelled by peristaltic waves.

Free Abdominal Air

Free gas in the peritoneal cavity results from bowel perforation (Fig. 4), which most commonly occurs in the distal ileum and proximal colon. The view obtained with the horizontal beam is particularly useful for detecting small amounts of gas. On the cross-table lateral view, free gas may appear as triangular lucencies between loops of bowel anteriorly just beneath the abdominal wall or as small bubbles or linear gas collections anterior to the liver. On the supine view, large amounts of gas may give rise to the “football” sign, where the gas outlines the whole of the peritoneal cavity, the undersurface of the diaphragm, and the falciform ligament (the lacing of the football). Smaller amounts of free gas may give rise to lucency below the diaphragm without giving rise to the full-blown football sign. Even on the supine view, smaller amounts of free gas may be detected when both sides of the bowel wall are outlined (Rigler’s sign).

Ultrasonography

When to perform abdominal US during follow-up and how often has not been established. In those neonates who respond promptly to medical therapy, abdominal US probably has no role. However, it may play a significant role in two groups of patients. The first group includes those neonates in whom the evolution of changes at plain abdominal radiography is not in keeping with the clinical course, and the second group includes those who are deteriorating clinically but have no evidence of pneumoperitoneum at plain abdominal radiography.

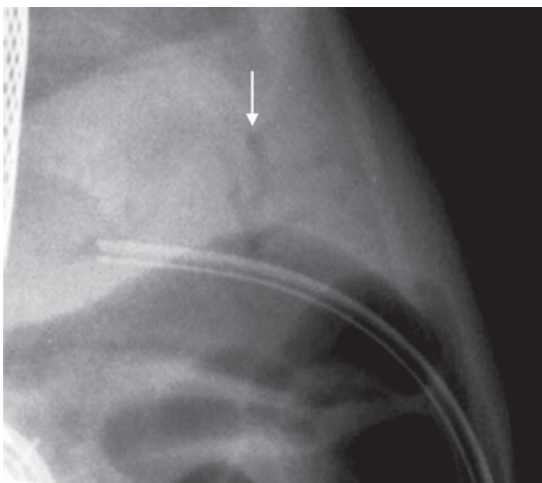


Fig. 3: Portal venous gas

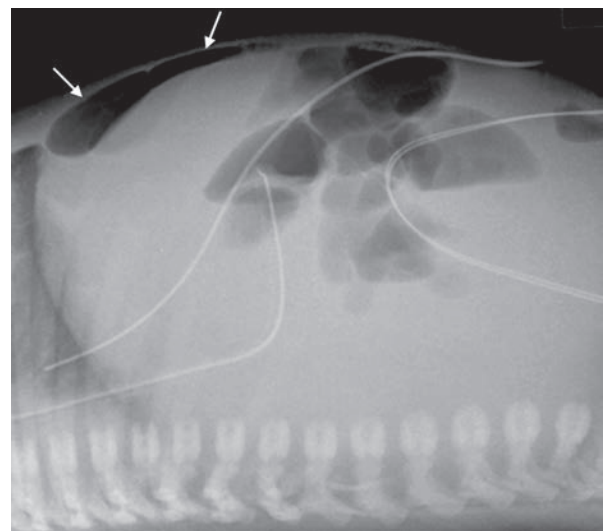


Fig. 4: Pneumoperitoneum

Abdominal US depicts intramural gas as hyperechoic foci in the bowel wall. Large amounts of intramural gas may give the wall a speckled or granular appearance, which can be confused with dense calcification. However, the latter usually has a much sharper posterior acoustic shadow than intramural gas. Portal venous gas may be seen in the main portal vein and its major branches as intraluminal echogenic foci moving with the blood flow. In the smaller intraparenchymal portal branches, portal venous gas is seen as hyperechoic foci that, when sufficient enough, form a linear, branching pattern. Free abdominal air would present as hyperechoic foci with dirty shadowing either between the anterior surface of the liver and the abdominal wall, between bowel loops, or floating on free peritoneal fluid just deep to the abdominal wall. Accumulation of free intraperitoneal fluid can be seen in neonates with more severe NEC with or without perforation and presence of low-level echoes or septations within the fluid is more suggestive of perforation, as they suggest the presence of pus or intestinal contents. Another major advantage of abdominal US is the ability of this modality to directly assess arterial perfusion of the bowel wall, as this is not possible with plain abdominal radiography which may help in determining the viability of the bowel. Kim et al²⁵ have suggested that monitoring with abdominal US may also be helpful in determining the most appropriate time to reinitiate and advance feeding, and it may also be

used to differentiate recurrent NEC from other causes of bowel distension.

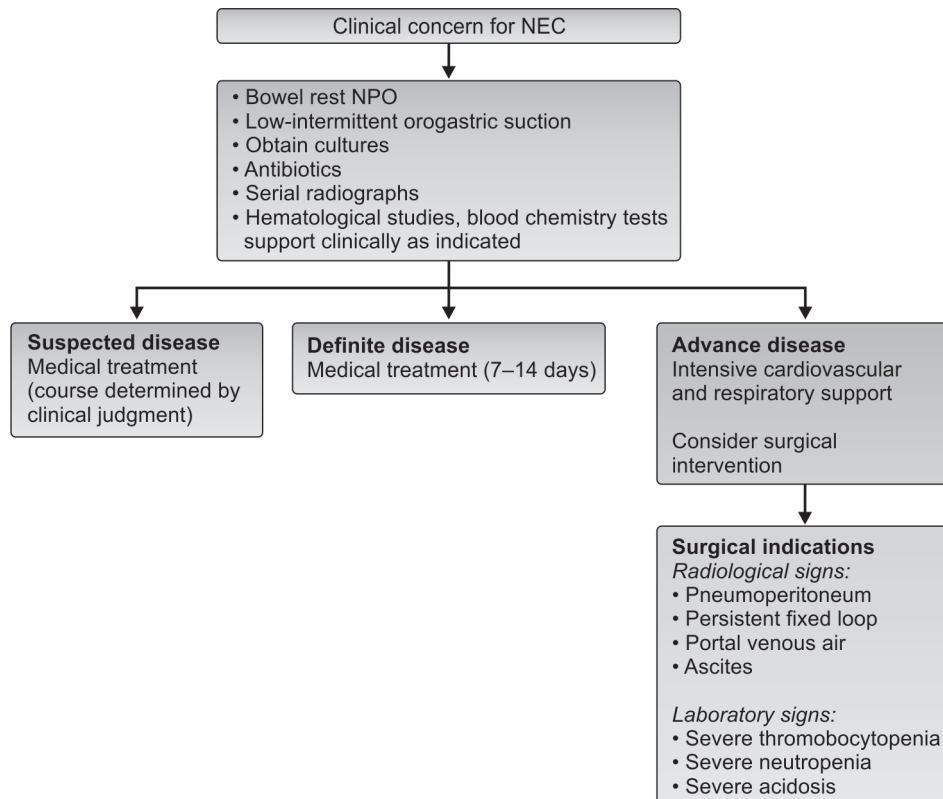
MANAGEMENT (FLOW CHART 2)

Medical Management

The goal of medical management is to stabilize the infant and prevent progression of an early form of NEC to the more advanced stage of the disease. When the diagnosis is suspected, stoppage of feeding and decompression of the gut by nasogastric suction (10–12F tube) is initiated. Nasogastric decompression is important to prevent reduction in intestinal blood flow. A complete blood count, serum electrolytes, and blood gases are obtained along with blood culture. Most require some mechanical ventilatory support. If necessary, tracheal intubation is preferred to continuous positive airway pressure to prevent aerophagia and subsequent greater bowel distention. Many patients will be hypovolemic and require fluid resuscitation and correction of acid base imbalance. If there is evidence of coagulopathy, administration of platelets, fresh-frozen plasma, or cryoprecipitate may be indicated. Inotropes may be required if circulation still is not improved despite fluid resuscitation.

Choice of antibiotic therapy may be guided by patterns of resistance in the individual unit. In addition, VLBW infants are at risk for bacteremia from coagulase-negative

Flow chart 2: Clinical decision making in NEC



Staphylococcus. Accordingly, empiric treatment with vancomycin and a third-generation cephalosporin is appropriate in some cases. Such babies are at increased risk of fungal sepsis because of broad spectrum antibiotic usage and PICC lines. Amphotericin, administered either empirically or following proven culture, may be necessary later in the course of treatment. Routine addition of clindamycin to the antibiotic regimen does not reduce the frequency of intestinal gangrene or perforation and may be associated with an increase in late stricture formation.²⁶ Anaerobic cover with metronidazole may be necessary in cases of perforation.

Close clinical and laboratory monitoring is essential in the management of patients with NEC. Serial physical examination including transillumination to detect pneumoperitoneum and frequent radiological examinations every 6 to 8 hours should be carried out along with blood gas and electrolyte estimations. Over next 24 to 48 hours, the disease may stabilize, improve or progress to advanced stages.

If the disease stabilizes, then most centers would not start feeding babies for 7/14 days after a stage II/III disease respectively, although this as discussed earlier has been questioned in two recent studies. When the feeding is resumed, it is reinstituted preferably with breast milk and advanced slowly. If there is any suspicion of recurrence of NEC after introducing oral feeds, a nasogastric tube is replaced and feeds restarted after a week of hyperalimentation. In case the baby still does not tolerate feeds, then an oral contrast study should be done to rule out the presence of stricture.

Surgical Treatment of NEC

The primary goal of surgical therapy is to improve the patient's condition after medical therapy has failed by removing ischemic and necrotic diseased intestine and/or the spilled intraperitoneal fluid and stool collections resulting from intestinal perforation. If the surgery is required to be done in NEC, then it is mostly required in first 5 days of the initial diagnosis.

Indication for considering surgical option includes:

- Pneumoperitoneum is considered as an absolute indication for surgery. However, sensitivity of pneumoperitoneum is 48 percent in detecting intestinal gangrene.
- Abdominal paracentesis is considered by some authors to be useful indicator for need for surgery. If the free flowing fluid tapped from the abdomen is brown or hemorrhagic with bacteria seen on gram stain, the tap is considered positive for gangrenous bowel, and surgery is indicated.
- Fixed mass on palpation indicating an intraperitoneal abscess or an aggregate of coalesced and infarcted loops of intestine. Apart from this other relative indication are fixed dilated loop on a radiograph, cellulitis of the abdominal wall.

- Worsening despite medical management indicates the intestinal ischemia is progressing to frank gangrene and forms a relative indication for operation.
- Portal venous gas as an indication for need for surgery is controversial.

Traditional surgical management of intestinal necrosis relies on the principles of controlling the source of peritoneal contamination by laparotomy, exploration of the intra-abdominal viscera, and excision of the involved, necrotic intestine. Generally, accepted principles in the operative management of perforated NEC have emerged from numerous institutional, retrospective reviews of surgically treated infants. These management guidelines include: (1) Aggressive perioperative resuscitation, often including inotropic support; (2) Expedient and minimal operative behavior with attempts at limiting physiologic insult; (3) Evaluation of the entire intestine with resection of only necrotic or perforated bowel; (4) Diverting enterostomy proximal to intestine of questionable viability; and (5) Preservation of the ileocecal valve if possible.

Surgical options include: (1) Laparotomy involving resection of the involved intestine with either a enterostomy formation or a primary anastomosis. An intermediate option is laparotomy with intestinal resection and delayed anastomosis 48 to 72 hours later; (2) Primary peritoneal drainage for perforated NEC may help to resuscitate and treat a critically ill infant.

Laparotomy and intestinal resection with enterostomy—is the procedure of choice for isolated perforations less than 20 cm in length. In perforated NEC however, there are multiple areas of necrosis with intervening viable bowel. In such situations, a proximal defunctioning enterostomy is done, which is closed electively later on. There is no agreement on time, weight or age at which an enterostomy should be closed. Major factors used to determine the timing of final surgery are time from original operation, stoma output and rate of the weight gain. In general, enterostomy is closed in 4 weeks to 4 months in otherwise thriving neonates.

Laparotomy and intestinal resection with enterostomy: Advantages of this method include avoidance of morbidity due to enterostomy complications, reduction of postoperative morbidity and a shorter hospital stay. The involved segments of intestine are excised and a primary anastomosis is performed, with routine lavage of the abdominal cavity. This method may be preferred in cases of multiple perforation where a much proximal enterostomy would lead to serious problems with fluid and electrolytes issues and failure to thrive. The major contraindications to resection and primary anastomosis are poor intestinal perfusion and residual macroscopic disease. Disadvantage of this technique is that sometimes the length of bowel resected may be larger than the damaged bowel.

Until resection with enterostomy versus primary anastomosis in perforated NEC is compared in a prospective,

randomized clinical trial, a definitive, evidence-based conclusion for procedure superiority cannot be made.

An intermediate option for physiologically unstable infants with perforated NEC is laparotomy with excision of involved intestine and delayed anastomosis 48 to 72 hours later. This “clip and drop-back” technique has been reported to be useful in selected infants with peritonitis associated with extensive intestinal necrosis and may be useful particularly in infants with proximal jejunal disease. Initial operative management goals are to excise necrotic intestine and preserve remaining viable intestine while preventing further contamination by placing either surgical clips or staples on the remaining bowel ends. Bowel continuity is restored 2 to 3 days later during a period of relative physiologic stability with delayed primary anastomosis using standard technique. This approach avoids the need for diverting enterostomy and its associated complications.

An alternative technique for extensive bowel involvement with multiple perforations called patch, drain and wait was developed by Moore. In this technique perforations are closed by transverse sutures, two transabdominal drains (Penrose) are placed and close observation and monitoring is employed, while providing TPN. A potential benefit is preservation of the bowel length, although multiple fistulas occur frequently, requiring additional surgery.

Peritoneal Drainage

It was first introduced in 1977 by Ein and involves placing one or two Penrose drains into the peritoneal cavity in the right and left lower quadrants under local anesthesia. Drains are removed over 7 to 10 days unless there still is meconium or purulent discharge. If no improvement occurs or the patient's clinical condition continues to deteriorate over 24 to 48 hours, a laparotomy should be performed.

Primary peritoneal drainage may be useful in the resuscitative phase of perforated NEC; urgent bedside reduction of abdominal distention by drainage reduces mean airway pressure and improves oxygenation index in critically ill neonates with NEC. This is contrary to established surgical principles in the management of intra-abdominal sepsis. Possible reasons why this procedure may be effective in small preterm babies may be premature infants have a limited ability to compartmentalize intra-abdominal infection; therefore, complete drainage of the abdominal cavity with a single drain may be effective. Additionally, models of fetal wound healing have demonstrated a lack of significant scar formation, and may account for intestinal remodeling and healing clinically observed with peritoneal drainage.

The advantages of primary peritoneal drainage include being relatively inexpensive, can be performed at the bedside, can be done under local anesthesia and

survivors can avoid morbidity associated with enterostomy. The disadvantages of this method include it is difficult to measure the severity of the disease, possibility of missing alternative diagnosis like volvulus which may present similarly and drainage may be ineffective in managing patients with circumferential necrosis as these patients would either develop a fecal fistula to the drain site or complete bowel obstruction. An Indian study had suggested that only those babies who are severely acidotic at presentation and in shock would need surgical laparotomy and rest can be managed by peritoneal drainage.²⁷

Comparison of peritoneal drainage with laparotomy in perforated NEC: There is no clear consensus on the optimal surgical management of premature infants with perforated NEC. Moss²⁸ and colleagues performed a meta-analysis of ten studies with 475 patients comparing primary peritoneal drainage versus laparotomy. There was no statistically significant survival advantage between primary peritoneal drainage versus laparotomy. Assignment of treatment group was biased substantially by gestational age and birth weight; the mean birth weight of infants subjected to primary peritoneal drainage was 931 g compared with 1615 g in the laparotomy group ($P = 0.0004$). Because of the difference in the population studied it is not possible to conclude whether primary peritoneal drainage or laparotomy offered better survival in infants with perforated NEC. We have to wait for the results of the multicenter trial by NICHD to get a clear answer on this subject.

OUTCOME AND COMPLICATIONS

Over the years, the survival of neonates with NEC has increased progressively and varies from 65 to 85 percent in different series. Mortality rate is dependent on birth weight and associated co-morbidities and severity of multiorgan failure present before the surgical intervention.

Postsurgical complications occur in approximately half of all the patients undergoing surgery for NEC. Immediate postoperative complications include stoma stenosis, retraction or prolapse, wound infection, and intra-abdominal abscess. Cholestasis can develop in such babies due to prolonged fasting and long-term parenteral nutrition. Recurrent NEC may occur in 4 to 6 percent of the bases. The antecedents to recurrence have not been fully described but 70 percent of patients with recurrence can be treated conservatively.

Long-term intestinal complications include strictures, malabsorption, short gut syndrome. Incidence of strictures varies from 10 to 36 percent and is more common after medical management than surgical. The most common site for stricture formation is colon (70%), with the most common colonic site being splenic flexure (20%). Multiple strictures are more common after surgical management. It is advisable to perform a contrast enema before contemplating closing an enterostomy. Malabsorption, may result

from decreased absorptive area, bacterial overgrowth, bile salt depletion (in case of ileal resection). Short gut syndrome is the most serious long-term complication and incidence is estimated at 20 percent.

NEURODEVELOPMENTAL OUTCOME AND NEC

VLBW baby survivors of NEC have a poor neurodevelopmental outcome as compared to VLBW babies without the NEC. In a recent meta-analysis on this topic involving 7843 children,²⁹ out of which of whom 821 had NEC. Neurodevelopmental impairment occurred in 45 percent of children who had had neonatal NEC, compared to 35 percent of children who had been VLBW or ELBW but did not have NEC, with an odds ratio of 1.58 (1.25 to 1.99). Overall the surgical NEC group was 2.34 times more likely to have neurodevelopmental impairment than the medical NEC group (95% CI 1.51 to 3.60, $p = 0.0001$). Factors causing poor neurodevelopment outcome in premature infants are complex. However, specifically related to NEC is the lack of adequate postnatal nutrition for the growth of brain and damage to existing cerebral tissue due to infection or inflammation, respiratory insufficiency, hypotension, acidosis, fluctuations in glycemic control, disseminated intravascular coagulation. In particular, infection and sepsis, which may result from intestinal perforation and/or gangrene, have been highlighted as independent risk factors. Surgery for NEC also causes a cytokine surge which could be responsible for white matter damage. Poor outcome may be independently associated with surgery, with or without NEC. Twenty-eight percent of surviving ELBW infants who required surgery of any sort had a poor sensorineural outcome.

Spontaneous Intestinal Perforation

It is an entity which is increasingly being identified in preterm population different from NEC. Incidence varies from 2 to 8 percent amongst the VLBW babies with male to female ratio being 3:1. This condition generally affects babies with gestational age less than 30 weeks or IUGR babies. When SIP does occur in the near-term or term infant, the defect usually appears in the colon, and the infant's prognosis is better. Five factors have been proposed as potential etiologies or risk factors for SIP:

- Altered GI tract perfusion or ischemia/hypoxia
- Thinning or absence of the intestinal muscularis, the smooth muscle layer of the intestinal wall
- The increased pressure transmitted to the GI tract by mechanical ventilation
- Specific medications, such as indomethacin and dexamethasone
- Infection with coagulase-negative *Staphylococcus* (CONS) or *Candida*.

Histological criteria for SIP include perforations of one or two locations that involve less than 5 cm of bowel. Patients with SIP have "muscular defects such as patchy

thinning or interruption of both the circular and longitudinal layers". In contrast, in NEC, the tissue shows ischemic damage and hemorrhage.

The onset of SIP is often insidious, and the patient is clinically stable. A blue-black discoloration of the abdominal wall is a common finding probably secondary to staining of the underlying tissues by meconium in the peritoneal fluid. Additional signs and symptoms of SIP include abdominal distention, delayed first stool after the third postnatal day, and leukocytosis. Many infants, however, present with no symptoms at all.

Peritoneal air or even a gasless abdomen on X-ray can be the first or only sign of intestinal perforation. Evidence of pneumatosis or portal venous air on X-ray is considered pathognomonic of NEC and not SIP. In the case of a gasless abdomen on X-ray, an abdominal ultrasound can be performed to confirm particulate matter outside the intestines. A gasless abdomen in a perforated patient may seem counterintuitive, but it is possible in a premature patient who may be intubated or have immature swallowing, which decreases the amount of air in the intestinal tract.

Two main treatments exist for intestinal perforation—peritoneal drainage and laparotomy with resection. Like in case of NEC, there is no consensus as to the most appropriate mode of intervention. Those who advocate laparotomy feel that an isolated stable perforation could progress to a more seriously compromised intestinal segment with significant clinical deterioration. Through early surgical intervention, they hope to avoid the potential for deterioration and the need for surgery when the patient is in a more compromised state. Those who advocate the initial peritoneal drainage feel most cases can recover without need for laparotomy and most clean perforations can seal on their own. As of now there are no RCTs to suggest that which method is better and choice and comfort of the operating surgeon and the facilities at the place of surgery should decide the best option.

SUMMARY

NEC is still an enigmatic disease for clinicians worldwide involved in the care of newborns. The incidence and the mortality due to this disease has not changed in last couple of decades. Pathogenetic mechanisms have to be better understood to be able to provide better treatment modalities. Epigenetic mechanisms if they exist also need to be understood as to why only few babies develop NEC and some may get away in the same environment. There is an urgent need to conduct trials to resolve many undecided issues in the management like which surgical option is the best. Close long-term neurodevelopmental follow up of patients treated for NEC is important and families of such patients should be consulted appropriately before surgery regarding the risk for neurological and developmental outcome.

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Surgical Emergencies in the Neonate

Rajeev Kulshreshtha

Surgical emergencies in the neonates can be anticipated on routine antenatal maternal ultrasonography in large majority of the cases. Some of the important findings on maternal ultrasonography, which provide clue to the post-natal surgical emergencies are as follows:

- Polyhydramnios
The important lesions associated with polyhydramnios are:
 - Esophageal atresia.
 - Intestinal obstruction.
 - Abdominal wall defects.
 - Congenital diaphragmatic hernia.
- Oligohydramnios
 - Renal dysgenesis or agenesis (Potter's disease).
These babies have associated pulmonary hypoplasia which leads to postnatal respiratory distress.
- Meconium ascites.
- Free floating bowel loops in amniotic fluid, indicates abdominal wall defects.
- Large head is suggestive of hydrocephalus.
- Absence of the fusion of the vertebral arches indicating spina bifida.
- Distended bladder and upper urinary tracts is suggestive of posterior urethral valves.
- *Fetal ascites*: It is usually associated with posterior urethral valves.
- Large mass in the sacral region of the fetus indicating sacrococcygeal teratoma. Important postnatal surgical emergencies in a neonate can be broadly grouped as follows:
 - Respiratory distress
 - Gastrointestinal tract lesions
 - Large skin defects
 - a. On the back:
 - i. Spina bifida

- b. On the front
 - i. Omphalocele
 - ii. Gastroschisis
 - iii. Exostrophy bladder
- Retention of urine: Posterior urethral valves
- Acute scrotum
 - i. Torsion testes
 - ii. Strangulated inguinal hernia

RESPIRATORY DISTRESS

Presenting Features

Presenting features of respiratory distress in a neonate are as follows:

- Restlessness in an otherwise asymptomatic baby.
- Tachycardia: Heart rate more than 160/mt.
- Tachypnea: Respiratory rate more than 60/mt.
- Tachypnea associated with subcostal/intercostals recession.
- Color change from normal pink to dusky and later cyanosis.
- Grunting, apnea or gasping respiration: The presence of these indicates very serious situation.
- Associated signs are apex beat shifted to right, scaphoid abdomen, excessive salivation or frothing at mouth or nostrils or abdominal distention.

Respiratory distress is evaluated as follows:

- Clinical sign and symptoms of respiratory distress.
- Blood chemistry: Hematocrit, blood sugar, serum calcium and blood gas analysis.
- X-ray chest upright view including abdomen.

The respiratory distress can be graded as minor, moderate and severe depending on clinical sign, symptoms and investigations. Tachypnea associated with subcostal and intercostal recession is considered as moderate. Tachypnea associated with grunting, color changes or

Table 1: Pediatric Respiratory Distress Scoring System

Score	0	1	2
Respiratory			
Rate (Per Minute)	< 60	60–80	> 80
Cyanosis	Absent	Not present with 40% oxygen	Present with 40% oxygen
Subcostal recession	Absent	Mild	Moderate
Grunting	Absent	Audible with stethoscope	Audible without stethoscope
Air entry	Clear	Decreased	Absent

apnea is considered as severe. Alternatively respiratory distress scoring may be used. (Table 1) Each sign is given a score. Score 6 to 8 is considered as severe distress.

If respiratory distress is minor, then history and investigations are done to confirm the diagnosis and plan appropriate management. If the distress is moderate or severe first respiratory distress is managed as follows: History and investigations are done after resuscitation.

General Management of Respiratory Distress

- Neonate is placed under radiant warmer or incubator, without clothes for close observation. Body temperature is maintained. Hypothermia and hypoxia precipitates metabolic acidosis.
- Minimum handling of the baby, so as to reduce oxygen requirements. Increased handling results in increased basal metabolic rate with increased oxygen demands.
- Gentle oropharyngeal suction with pressure of 10 cm of water is done. Patent airway is maintained.
- Humidified oxygen (40%) is given in oxygen hood. Oxygen is never given by face-mask or nasal catheter in a neonate. PaO_2 is maintained between 60 to 80 mm Hg.
- Oral feeds are stopped. Intravenous fluids and antibiotics are started.
- Nasogastric tube is passed. It decompresses stomach thus decreases abdominal distention resulting in reduced splinting of the diaphragm, which facilitates respiration. NG tube prevents vomiting, which avoids aspiration of gastric contents.
- Baby maybe kept in prone, head low position. This position reduces apnea, shortens gastric emptying, and prevents aspiration. However, if baby requires resuscitation then supine position is preferred.
- Blood gas studies, serum calcium, blood sugar and hematocrit is done and repeated at regular intervals.
- Vital signs including respiratory and cardiac status is monitored very carefully.
- If ventilatory support is required, it should not be delayed.

Management of some important surgical conditions causing respiratory distress is as follows:

CHOANAL ATRESIA

Congenital blockage of posterior nares is termed as choanal atresia. It maybe uni or bilateral. Blockage maybe due to membrane or by bone. Bilateral choanal atresia presents with respiratory distress.

Up to the age of 3 to 4 months, baby is compulsive nose breather. In bilateral choanal atresia if mouth is closed or baby is feeding, respiratory distress starts and the baby may become cyanotic. Either the baby cries or if an airway is put in the mouth, distress disappears dramatically.

Bilateral choanal atresia is a rare anomaly. The incidence is 1 in 60,000 live births.

Diagnosis is confirmed by:

- Inability to pass 6 F red rubber catheter through nose into oropharynx.
- Radiopaque dye is instilled in the nostril. A lateral X-ray of the face is taken. Presence of dye in nostrils only and absence of dye in the oropharynx confirms the diagnosis.

Treatment is as follows:

- Initially airway in the oral cavity is effective.
- If the blockage is membranous, it is ruptured through nostrils.
- If the blockage is bony, it is removed via transpalatal route.

ESOPHAGEAL ATRESIA

Congenital discontinuity of esophageal lumen is known as esophageal atresia. This maybe with or without fistulous communication with trachea.

Incidence of esophageal atresia varies from 1 in 2500 to 1 in 4500 in live births. Both the sexes are equally affected.

Antenatal Diagnosis

Antenatally esophageal atresia is diagnosed on routine maternal ultrasonography, which reveals polyhydramnios associated with inability to detect fetal stomach. High resolution scan can identify distended upper atretic esophageal pouch with repeated swallowing and regurgitation efforts.

Classification

Esophageal atresia is classified in the following types:

- Type I.* Esophageal atresia with no tracheal communication (8–10%).
- Type II.* Esophageal atresia and proximal esophageal pouch communicating with trachea.
- Type III.* Esophageal atresia and distal esophageal pouch communicating with trachea, which is usually at the carina. This is the most common type (87–90%).

- Type IV.* Esophageal atresia and both proximal and distal pouches of esophagus communicates with trachea.
- Type V.* No esophageal atresia, but esophagus communicating with trachea.
It is also called as H Type fistula (1–2%).
- Type VI.* There is only esophageal stenosis and no fistulous communication with trachea.

Diagnosis

At Birth

In view of the antenatal diagnosis on maternal ultrasonography, the diagnosis is confirmed at birth by passing, a sterile 6 to 8 F red rubber catheter orally. If it gets arrested at 10 cm from gum margin, it indicates the diagnosis of esophageal atresia, which is confirmed by X-ray chest combined with abdomen, in an erect posture with catheter *in situ*.

- If the catheter lies in the upper pouch and there is no abdominal gas shadow, it indicates esophageal atresia, Type I (Fig. 1)
- If catheter lies in upper esophageal pouch with distended stomach and abdominal gas shadows, it indicates esophageal atresia, Type III (Fig. 2).

After Birth: Presenting Features

If antenatal maternal ultrasonography is not done and diagnosis is not established by passing the catheter immediately after birth, the late presenting features are:

- Excessive salivary secretions and frothing at nose and mouth.
- Signs and symptoms of respiratory distress due to aspiration pneumonia, followed by apneic attacks and cyanosis.
- On giving oral feeds, there is acute episode of coughing, choking, and cyanosis.

Associated Anomalies

Infants with esophageal atresia have a 48 to 55 percent incidence of associated anomalies. The coexisting anomalies are highest in the group of esophageal atresia without tracheoesophageal fistula.

(Type I, 58%) The most common associated anomalies are cardiac (40%) and of the genitourinary tract.

Preoperative Management

The surgical correction of esophageal atresia is done after full resuscitation, and never as an emergency procedure. The specific management includes:

- Proximal esophageal pouch is decompressed by continuous slow suction. Double lumen Replogle catheter is best suited for this purpose. This is necessary to avoid accumulation of secretions in upper pouch, which may lead to aspiration pneumonia. In between intermittent suction is also done.
- Baby is nursed in prone or lateral horizontal position, which permits easy access for suction and monitoring the vital signs of the baby.
- Appropriate investigations are done to confirm the diagnosis and to detect associated anomalies.



Fig. 1: Plain X-ray of chest and abdomen: Type I esophageal atresia



Fig. 2: Plain X-ray of abdomen and chest: Type III esophageal atresia

Timing of Surgical Correction

Immediate Primary Repair

The indications are:

- No pulmonary complications, viz. severe pneumonia.
- An arterial PaO_2 more than 60 mm Hg in room air.
- Not associated with major congenital malformations which are incompatible with life.
- Distance between proximal and distal esophageal pouch less than 2.5 cm.

Delayed Surgical Intervention

The indications are:

- Associated with pneumonia, sepsis or complex cardiac malformation.
- Severe prematurity.
- The gap between proximal and distal pouch is more than 2.5 cm.

Treatment of cardiac anomaly takes precedence over correction of esophageal atresia. Primary repair can be done after treatment of pneumonia or sepsis.

Staged Operation

The indications for staged operation are:

- If primary repair cannot be done due to reasons mentioned in delayed surgical repair.
- Failed primary repair.
- Long gap between two esophageal pouchs, viz. in type I esophageal atresia, where gap is usually more than 3 to 4 cm.

Stages of surgical correction are:

- Left cervical esophagostomy and feeding gastrostomy immediately after birth.
- Thoracotomy and ligation of tracheoesophageal fistula after 2 to 3 weeks of stage I.
- Replacement of the gap between proximal and distal esophagus by isolated vascularized segment of colon or by gastric tube is done at 6 to 8 months of age.

Postoperatively baby is managed as per the standard guidelines. Feeds through transanastomotic tube maybe started after 48 to 72 hours following X-ray chest. Barium study is done 8 to 10th postoperative day (Fig. 3). If there is no leak, tube is removed and baby is given oral feeds. Postoperative esophageal dilatations are started three weeks after primary repair, if necessary.

Complications

Early

- Pneumothorax
- Anastomotic leak—Diagnosed by appearance of saliva in the chest drainage tube and collection of fluid in X-ray chest.

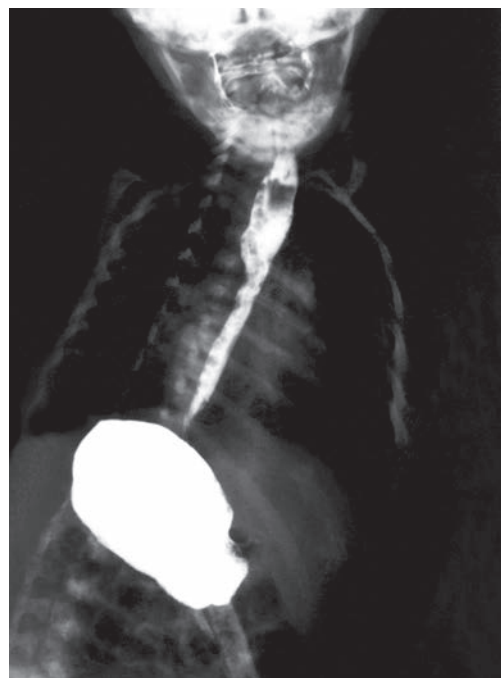


Fig. 3: Contrast study done on 8th postoperative day following primary repair of esophagus

- Recurrence of fistula.
- Pulmonary atelectasis or infection.

Late

- Anastomotic stricture.
- Gastroesophageal reflux (GER).
- GER occurs in about 50 to 55 percent cases initially it is managed conservatively. However in about 5 to 8 percent cases fundoplication maybe necessary.
- Tracheomalacia.

Tracheomalacia is a structural and functional weakness of trachea, resulting in partial respiratory obstruction in approximately 10 to 12 percent cases. Presenting features are:

- Difficulty in feeding due to respiratory problems.
- Cyanotic attacks and/or apneic episodes.
- Peculiar barking cough.

Treatment is conservative, only in some selected cases aortopexy maybe necessary.

CONGENITAL DIAPHRAGMATIC HERNIA

Congenital diaphragmatic hernia (CDH) is defined as herniation of the intestine into chest through a congenital defect in the diaphragm. Diaphragmatic hernia are of two types:

- *Bochdalek hernia:* Herniation of the bowel in the chest is through the posterolateral defect in the diaphragm. This is the most common type of CDH.

- *Morgagni's hernia*: Herniation is through the anterior defect in the diaphragm.

Incidence of CDH varies from 1 in 2200 to 1 in 5000 livebirths. The incidence is much higher in stillborn. 85 percent Bochdalek type CDH occurs on left side. Less than 1 percent are bilateral. Female baby is affected twice as common as male. Cardiac and neural tube defects are most common associated anomalies.

Pathophysiology

Developing fetal lung is compressed by herniated abdominal viscera in the chest, which leads to pulmonary maldevelopment and lung hypoplasia resulting in:

- Reduction in alveolar surface for gaseous exchange.
- Decreased and abnormal pulmonary vasculature. There is muscular hyperplasia in small pulmonary arteries.
- Exaggerated abnormal response of abnormal pulmonary vasculature to hypoxia, hypercarbia and acidosis resulting in right to left shunting through ductus arteriosus and foramen ovale.

The net outcome of the lung hypoplasia and abnormal pulmonary vasculature in CDH is:

- Hypoxia and hypercarbia.
- Metabolic acidosis.
- Persistent fetal circulation (PFC).

Antenatal Diagnosis

Antenatal diagnosis of CDH is possible as early as 15th week of gestation on routine antenatal maternal sonography. The readily detectable features are:

- Presence of abdominal viscera in the chest.
- Polyhydramnios.



Fig. 4: Plain X-ray chest and abdomen with nasogastric tube in stomach: Left sided congenital diaphragmatic hernia

- Mediastinal displacement.
- Absence of intra-abdominal stomach bubble.

Presenting Features

Presenting features are marked respiratory distress, which include:

- Tachypnea, dyspnea, sternal recession, expiratory grunt and cyanosis.
- Scaphoid abdomen.
- Breath sounds are absent or diminished on affected side of the chest.
- Apex beat is shifted to the right side in the commonly present left sided CDH.

Investigations

- X-ray chest combined with abdomen in erect posture is usually the only investigation required to confirm the diagnosis. It will demonstrate presence of stomach and intestines in the chest and the mediastinal shift, along with paucity or absence of gas shadows in the abdomen. Diaphragmatic margin is absent (Figs 4 and 5).
- Contrast study is usually not done. It maybe done when right-sided CDH is suspected.
- Ultrasonography identifies and measures the diaphragmatic defect.

Differential Diagnosis

Differential diagnosis of CDH include the following:

- Congenital cystic adenomatoid malformation of the lungs.
- Pulmonary cystic lesions.



Fig. 5: Right sided CDH

- Staphylococcal pneumonia with cysts.
- Pneumothorax.

To differentiate above conditions from CDH an X-ray chest and abdomen erect posture with nasogastric tube placed in the stomach is taken. In CDH, the nasogastric tube lies in the chest, while in other conditions it lies in the abdomen.

Management

Current trends of management are delayed surgical approach, instead of an early and immediate surgical intervention, which was earlier considered as important factor in survival.

Preoperative Management

- As soon as the baby with CDH is admitted, size 6 or 8 F sterile nasogastric tube is passed to decompress the stomach to facilitate respiration.
- Routine neonatal care including intravenous fluids, antibiotics, temperature maintenance, monitoring of vital signs and management of hypoglycemia, metabolic acidosis are continued.
- To maintain adequate tissue perfusion without causing pulmonary overload, large volumes of crystalloid maybe necessary.
- Oxygen should not be given by nasal catheter or by face mask, as significant amount of oxygen will enter stomach causing its distension, which will further compromise respiration. Oxygen should be given through oxygen hood.
- If there is respiratory distress and hypoxia, endotracheal intubation must be done and ventilatory support must be started immediately.
- Ventilatory requirements in CDH:
 - Hypoplastic lungs require higher pressure for inflation, but higher pressures can rupture the alveoli causing pneumothorax. Therefore, if with ventilatory support, there is sudden deterioration in oxygen saturation levels, pneumothorax must be suspected and immediate intercostal chest drain under water seal must be put in. The pneumothorax can occur on either side of the chest.
 - To maintain relatively low ventilatory pressure to avoid pneumothorax, following are necessary:
 - i. High oxygen concentration.
 - ii. Rapid respiratory rate.
 - iii. Low tidal volumes.
 - Though conventional mechanical ventilation is usually started. However if it is ineffective, High Frequency Ventilation (HFV) may be given.
 - Objectives of the ventilatory support are to maintain postductal:
 - i. pO_2 above 40 to 50 mm Hg
 - ii. pCO_2 less than 30 mm Hg
 - iii. pH above 7.5

The aim of the preoperative management is to prevent hypoxia, thus preventing persistent fetal circulation (PFC) and persistent pulmonary hypertension (PPH).

Operation

Congenital diaphragmatic hernia (CDH) is not considered as a dire emergency where immediate operation is required. Current trend is preoperative resuscitation, with basic aim to correct hypoxia, hypoperfusion, and metabolic acidosis. This is associated with much improved survival.

After resuscitation, baby is operated. Repair of the diaphragmatic hernia is done through abdominal approach.

Postoperative Management

Ventilatory support is continued, by using low tidal volume, low inspiratory pressure and high respiratory rate. Aim is to minimize barotraumas, while maintaining normal pH and pCO_2 . Hyperventilation has been recommended, but permissive hypercapnea is gaining wider popularity. Usually the infant is weaned off the ventilator between 48 and 72 hours.

Complications

- During surgery abdominal viscera maybe injured or adrenal gland maybe included in the suture while closing the defect of the diaphragm.
- Damage to ipsilateral hypoplastic lung by overenthusiastic resuscitation resulting in overinflation, rupture and pneumothorax. This can happen even on contralateral side.
- Persistent respiratory insufficiency due to PPH or PFC.

Future Management Strategies

Fetal Surgery

In some centers in USA this is being done successfully. Repair of the diaphragmatic defect is done in the fetus and pregnancy is allowed to continue.

PLUG (Plug the Lung until it Grows)

Trachea of the fetus is plugged. Accumulation of secretions in the lungs pushes the herniated abdominal contents back into abdomen. Lungs grow normally. This procedure is still in the experimental stage.

CONGENITAL LOBAR EMPHYSEMA

Hyperinflation of a lobe or a segment of the lung resulting in compression or atelectasis of the adjacent normal lung and displacement of mediastinum characterizes congenital lobar emphysema (CLE). Sometimes, the hyperinflated lung may herniate across the midline. Hyperinflated lung does not participate in the normal gaseous exchange in the lungs, resulting in respiratory insufficiency.

The approximate incidence reported in various reports is 1 in 5000 to 7000 live born babies.

Left upper lobe is most commonly affected (45%) followed by right middle lobe (30%), right upper lobe (21%) and both lower lobes in about 1 to 2 percent cases.

Etiopathogenesis

Bronchial cartilage of the affected lobe is abnormal, causing partial airway obstruction. The bronchial cartilage maybe either absent, hypoplastic or dysplastic.

Macroscopically affected lobe is markedly distended and fails to collapse. On microscopic examination there is overdistention of alveoli and alveolar ducts. There is variable degree of fragmentation and rupture of alveolar walls.

Pathophysiology

Due to abnormal bronchial cartilage, the bronchi remains collapsed during passive process of expiration and the air, which entered the lobe during the active process of inspiration, remains trapped inside. With each breath the affected lobe distends with trapped air. Overdistention of the lung results in respiratory distress which gradually increases in intensity.

Presenting Features

The baby appears normal at birth. The characteristic features of congenital lobar emphysema usually occur at about 3 to 4 weeks of age after birth. The symptoms are relentlessly progressive after onset.

Investigations

- *X-ray chest:* Plain X-ray chest confirms the diagnosis in large majority of the cases. It reveals:
 - Overdistention of one lobe with reduced vascular and bronchial markings.
 - Mediastinal shift and herniation of emphysematous lung on other side.
 - Atelectasis of the adjacent lobe.
- CT scan: Confirms the findings of X-ray chest.

Treatment

Conservative management is contraindicated. Surgical treatment is lobectomy of the affected lobe.

PNEUMOTHORAX

Accumulation of the air in pleural space is defined as pneumothorax. Pneumothorax under pressure when there is one-way valve effect, i.e. air can enter pleural space but cannot escape out is defined as tension pneumothorax. It is a rapidly fatal condition in the neonates.

Overall incidence is 0.5 to 2 percent in all neonates. The incidence is higher in low birth weight babies. Incidence of pneumothorax is as high as 38 percent in babies

of hyaline membrane disease who are on mechanical ventilation.

Symptoms

Severity of symptoms is directly proportional to tension within mediastinum or in pleural cavity. The common presenting features are:

- Sudden onset of respiratory distress. Tachypnea, dyspnea, tachycardia, retraction of chest wall and cyanosis occurs rapidly.
- Respiratory distress is followed in rapid succession by apnea, bradycardia and cardiac arrest.

Diagnosis

Chest X-ray in upright position confirms the diagnosis. In newborn, narrow beam of fiberoptic light can indicate presence of pneumothorax (Fig. 6A and B).



Fig. 6A: Pneumothorax demonstrated by fiberoptic light. The other baby is with normal chest for comparison (*For color version see plate 1*)

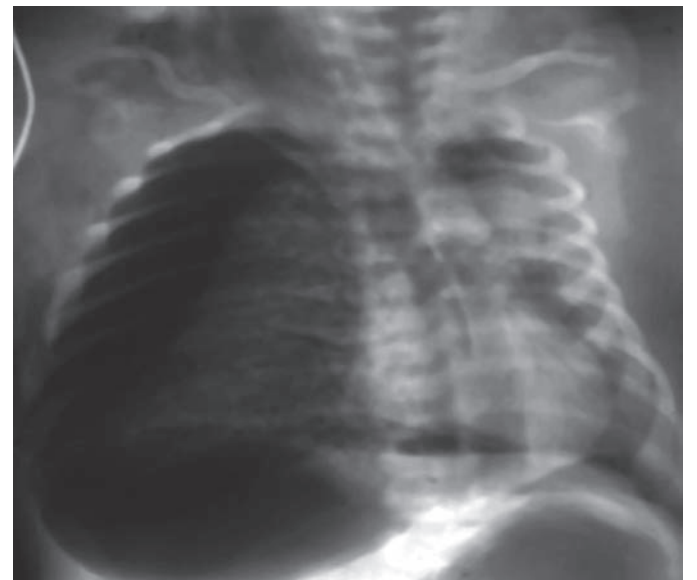


Fig. 6B: Plain X-ray of chest: Pneumothorax

Treatment

- Intercostal chest tube in pleural cavity with under water seal drainage must be done immediately. The intercostal chest tube is inserted in 3rd or 4th intercostal space in anterior axillary line to avoid injury to enlarged thymus in neonates.
- In tension pneumothorax, if the baby is in impending danger of cardiac arrest, a needle maybe inserted in the chest to convert tension pneumothorax into open pneumothorax to be followed by intercostal chest tube insertion.

GASTROINTESTINAL TRACT LESIONS

Emergencies caused by GIT lesions may present with following signs and symptoms:

Abdominal Distention

- Intestinal obstruction
- Pneumoperitoneum
 - Perforation of bowel
Perforation of bowel: Perforated stomach is associated with large amount of intra-abdominal air. At times it is necessary to aspirate air from abdomen to relieve respiratory distress prior to definitive surgery.
 - Pulmonary air leak
Pulmonary air leak due to increased intrapleural pressure at the time of first breath after the birth of baby results in pneumothorax. The leaked air may dissect into peritoneal cavity, especially in the babies who are on mechanical ventilation.

Vomiting

- Bilious vomiting
Intestinal obstruction. The dictum is, if the baby has bilious vomiting, it is considered as intestinal obstruction until proved otherwise.
- Non-bilious vomiting
Some of the important causes of non-bilious vomiting are:
 - Gastroesophageal reflux.
 - Sepsis with ileus.
 - Decreased bowel motility: Prematurity, antenatal maternal sedation, hypothyroidism.
 - NS lesion: Intraventricular hemorrhage.
 - Lesions above ampulla of Vater.
 - Upper duodenal stenosis.
 - Annular pancreas (rare).

Failure to Pass Meconium

- Anorectal malformation.
- Hirschsprung's disease.

- Meconium plug syndrome.
- Meconium ileus.

Failure to Pass Stool after Initial Passage of Meconium

- Volvulus
- Malrotation
- *Ileal atresia:* Baby may pass small amount of grayish-green meconium once or twice after birth, but later there is absolute constipation.

Hematemesis or Blood in Stool

- Neonatal necrotizing enterocolitis.
- Stress ulcers in stomach.
- Coagulation disorders.

NEONATAL INTESTINAL OBSTRUCTION

Intestinal obstruction is one of the most common surgical emergencies in the neonates. Surgical causes of the intestinal obstruction in the neonates can be broadly divided according to site of obstruction as follows:

Duodenum

- Duodenal atresia or stenosis.
- Malrotation of the intestine.
- Annular pancreas.

Jejunum and Ileum

- Atresia or stenosis.
- Meconium ileus and peritonitis
- Neonatal necrotizing enterocolitis.

Colon

- Hirschsprung's disease.
- Meconium plug syndrome.

Presenting Features

Vomiting

Bilious vomiting is indicative of intestinal obstruction in the babies, until proven otherwise.

Failure to Pass Meconium

- Meconium is normally passed within 6 to 8 hours after birth. Delayed or failure to pass meconium within 24 hours or more after birth is suggestive of intestinal obstruction. In Hirschsprung's disease there is either delayed passage of meconium or it is passed after suppository or per rectal examination.
- In intestinal atresia, baby may pass meconium once or twice after birth, but it is small in amount and is pale or light green in color.

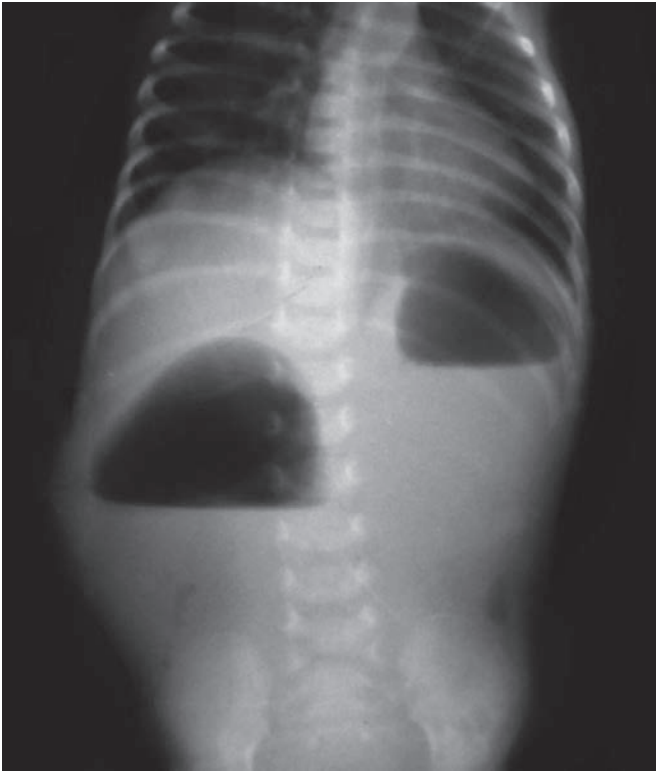


Fig. 7: Duodenal obstruction: Characteristic double bubble shadow in X-ray of abdomen



Fig. 8: Jejunal atresia: X-ray of abdomen shows triple bubble shadow

Abdominal Distention

Abdominal distention depends on the site of obstruction. It is minimal or absent in duodenal obstruction. Abdominal distention is maximum in low intestinal obstruction viz. ileal atresia or Hirschsprung's disease.

Investigations

X-ray Abdomen

Plain X-ray abdomen taken in upright position is very essential and gives vital clues for the diagnosis. In some cases it is diagnostic. Some of the observations are as follows:

- *Fluid levels:* Double bubble shadow is diagnostic of duodenal obstruction. Three bubbles are highly suggestive of jejunal atresia, while multiple fluid levels indicate ileal obstruction specially if there is one large fluid level along with multiple fluid levels (Figs 7 and 8).
- *Pattern of bowel loops:* For example, step ladder pattern in mechanical obstruction.
- *Presence of free air:* Indicate bowel perforation.
- *Intramural gas indicates:* Neonatal necrotizing enterocolitis.

Contrast Enema

It is done when clinical features are suggestive of Hirschsprung's disease.

Ultrasonography

Ultrasonography of the abdomen is useful if there is any mass lesion or free fluid in the abdomen.

Complications

Failure to recognize early signs and symptoms and delay in the management leads to following complications, which significantly increases the morbidity and mortality.

- Respiratory distress due to progressive abdominal distention.
- Dehydration and electrolyte imbalance.
- Aspiration pneumonia.
- Apnea.
- Hypoglycemia.
- Metabolic acidosis.
- Hypothermia.
- Shock.

Peripheral circulatory failure indicates bowel perforation with peritonitis, gangrene of intestine, septicemia or prolonged hypovolemia due to inadequate fluid resuscitation.

Management

- First step is to stop oral intake.
- *Nasogastric aspiration:* 8 or 10 F sterile nasogastric tube is placed in position in the stomach and aspiration of accumulated gastric fluid is done regularly.
- *Intravenous fluids:* IV access must be established immediately. Maintenance and correctional IV fluid is started.
- *Electrolyte imbalance:* Serum electrolytes are monitored regularly and electrolyte imbalance is corrected accordingly.
- *Blood volume:* Restoration of blood volume is mandatory. Hematocrit is monitored frequently. Intravenous fluid, plasma or blood may be transfused depending on the requirement.
- *Metabolic acidosis:* Blood gas analysis is done and metabolic acidosis is corrected.
- *Antibiotics:* Broad spectrum prophylactic antibiotics are started and are given intravenously.
- *Adequate ventilation:* If necessary supplemental oxygen or assisted ventilation may be given.

Baby with intestinal obstruction should not be operated until fluid deficit, electrolyte imbalance and metabolic disorders have been corrected and blood volume is fully restored. After complete resuscitation, exploratory laparotomy should be done and causative lesion is corrected. Survival largely depends on adequate and effective pre and postoperative care.

ANORECTAL MALFORMATIONS

Absence of anus in the perineum is traditionally known as imperforate anus (Fig. 9). Now this anomaly is termed as anorectal malformation (ARM), as in a significant percentage of cases, distal rectal end communicates either with urinary tract in the male babies, genital tract in the female babies or opens on the perineal surface with a fistulous tract in either of them. The reported incidence of ARM is 1 in every 2,000 to 4,000 live births.



Fig. 9: Imperforate anus (For color version see plate 2)

Antenatal sonographic findings indicative of ARM are:

- Dilated bowel loops.
- Intraluminal calcification of meconium, when a rectourinary fistula is present.
- Absence of anal ultrasonographic characteristics in the perineum, at 25 to 30 weeks of gestation.

ARM is classified as supralelevator (high) or translevator (low) anomaly depending on whether rectum terminates above or below the levator ani muscle complex. Supralelevator anomaly may communicate with urethra in male and genital tract in female baby.

Associated Anomalies

Genitourinary Anomalies

Incidence of associated genitourinary (GU) anomalies varies from 25 to 60 percent.

The incidence is more in high ARM.

Sacrum

Sacral deformities are frequently associated with ARM. The various associated sacral anomalies are:

- Hemisacrum.
- Absent sacral vertebrae: If more than two sacral vertebrae are missing, it may be associated with incontinence.

Anomalies of Vertebral Column

- Hemivertebra
- “Tethered” cord

Other Associated Anomalies

Cardiac, musculoskeletal and esophageal atresia are other associated anomalies.

Management

The first step in the management is to confirm the diagnosis and to decide whether protective colostomy is required or not.

Management in the Male Baby

Postnatal history and clinical examination provide important clues to the diagnosis:

History: In the male baby, history of the passage of meconium in the urine along with absence of normal opening in the perineum, indicates ARM with rectourethral fistula. No further investigations are required. As an initial management protective colostomy is done.

Clinical Examination

- Presence of anocutaneous fistula, anterior anus or any fistulous opening in the perineum with passage of meconium confirms low anomaly. Anoplasty is done.



Fig. 10: Invertogram: Supralelevator anomaly



Fig. 11: Invertogram: Translevator anomaly

- If there is no information on clinical examination or urine analysis, then investigations are done to confirm the diagnosis.

Investigations

- Rice invertogram or cross table lateral X-ray, which determines the level of termination of blind rectal pouch. Following are prerequisites of invertogram:
 - Invertogram should be done at least 12 to 14 hours after birth.
 - Baby should be kept hanging upside down for at least 2 to 3 minutes.
 - Hips are kept straight so that both the femurs do not obstruct the pubic bone.
 - The true lateral view is taken.
 - X-ray beam is focused at greater trochanter.
- After obtaining invertogram or cross table lateral X-ray following landmarks are identified:
 - *P-C Line*: A line is drawn from center of pubic bone to last piece of sacrum.
 - *I Point*: The lower most comma shaped tip of ischial bone is marked as “I” point.
- Following are evaluated on invertogram:
 - Level of gas in the blind rectal pouch (Figs 10 and 11):
 - i. If above P-C Line: It indicates low anomaly
 - ii. If below P-C line: It indicates high anomaly
 - *Sacral anomaly*: Sacrum is evaluated for any anomaly. If less than two segments of sacrum are present, it is strongly suggestive of fecal incontinence.
 - *Bowel loop pattern*: There may be a very large air fluid level in the pelvis suggestive of short colon syndrome (Fig. 12)

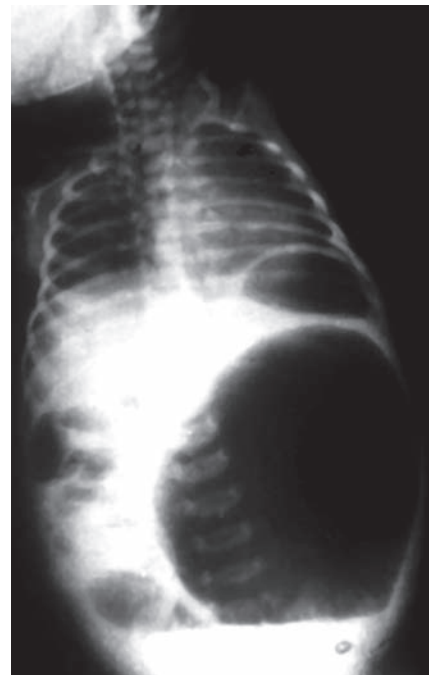


Fig. 12: X-ray of abdomen demonstrating very large air fluid level characteristic of pouch colon syndrome

- *Associated anomaly*: Identify any associated vertebral, cardiac, or chest anomaly.
- Ultrasonography, CT scan or MR imaging: Either of these investigations may be done to determine the distance between rectal pouch and perineal skin. After confirming the level of rectal pouch following is the surgical management in the male baby:

- *Low anomaly*: When bowel to perineal skin distance is less than 1 cm or distal bowel gas shadow is above P-C line in invertogram, then anoplasty is done.
- *High anomaly*: When bowel to perineal skin distance is more than 1 cm or gas shadow is below P-C line, protective colostomy is the first step. Later investigations are done and PSARP is planned.

Management in the Female Baby

Clinical examination determines the type of anorectal anomaly. Usually investigations are not necessary to confirm the diagnosis.

Three Openings in the Perineum

If clinical examination reveals three openings in the perineum, it indicates low anomaly. The surgical options are:

- Ano-cutaneous fistula or anterior perineal anus: Anoplasty is done.
- Vestibular anus: Either of the following procedure may be done:
 - Anal transposition, or
 - Protective colostomy followed by mPSARP.

Two Openings in the Perineum

Openings seen are of urethra and vagina. It is an uncommon anomaly. In these cases, protective colostomy is done followed by PSARP.

One Opening in the Perineum

One opening in the perineum confirms the diagnosis of cloacal malformation. A protective colostomy, usually in the proximal transverse colon is done. Later the baby is fully investigated. Surgical procedure depends on the exact malformation, which differs from one patient to another.

COLOSTOMY

Protective colostomy is done as divided colostomy in the distal part of the descending colon or in proximal part of the sigmoid colon.

Investigations to be done after Colostomy

- To evaluate length of distal bowel and identify the presence of fistula with urinary tract:
 - Distal cologram:
 - Cystourethrogram:
- To evaluate associated urinary tract anomalies:
 - Intravenous urogram or contrast enhanced CT scan to identify renal anomalies
 - MCU to confirm the presence or absence of megaureter, vesicoureteric reflux, or any other bladder or ureteric anomaly.

- Renal scan (DTPA or MAG3) maybe done to quantify renal functions and anomalies.
- To evaluate other associated malformations. If clinical symptoms or examination suggests cardiac or anomaly of any other organ, then appropriate investigations are done.

Posterior Sagittal Anorectoplasty

After complete investigations posterior sagittal anorectoplasty is done at 4 to 6 months of age as a definitive procedure.

HIRSCHSPRUNG'S DISEASE

Hirschsprung's disease is the congenital absence of the ganglion cells both in the muscle layers (Auerbach's plexus) and in the submucosa (Meissner's plexus), with presence of hypertrophic nerve trunks in the distal bowel, beginning with aganglionic segment and including the internal sphincter. The aganglionic segment extends proximally to varying distances. This anomaly results in functional obstruction with dilatation and hypertrophy of the proximal ganglionic segment.

The incidence of Hirschsprung's disease ranges from 1 in 4000 to 1 in 7000 live births. Male to female ratio is 4:1 but, long segment aganglionosis is more common in female babies.

Pathology

The characteristic feature of Hirschsprung's disease is absence of ganglion cells in both submucosal (Meissner's plexus) and Intermuscular (Auerbach's plexus) layers, associated with marked increase in nerve fibers extending into submucosa. The process of aganglionosis is always continuous and uninterrupted. There are no skip lesions.

Proximal to aganglionic segment, there is transitional zone, in which ganglion cells are few in number, hypertrophied nerve fibers are present and colonic motility is abnormal.

In the normal ganglionic intestine a balance exists between contractile and relaxation activity, which keeps smooth muscle finely controlled. In aganglionic segment this fine balance is disturbed, which results in increased smooth muscle tone.

Presenting features in the neonates are:

- Delay of more than 24 hours in passage of first meconium after birth.
- As acute intestinal obstruction: There is history of delayed passage of meconium after birth or baby did not pass meconium after birth, followed by abdominal distension and bilious vomiting. Per rectal examination reveals empty rectum, but withdrawal of finger results in passage of meconium and gas. Abdomen becomes soft and vomiting stops. The cycle repeats again after some interval.

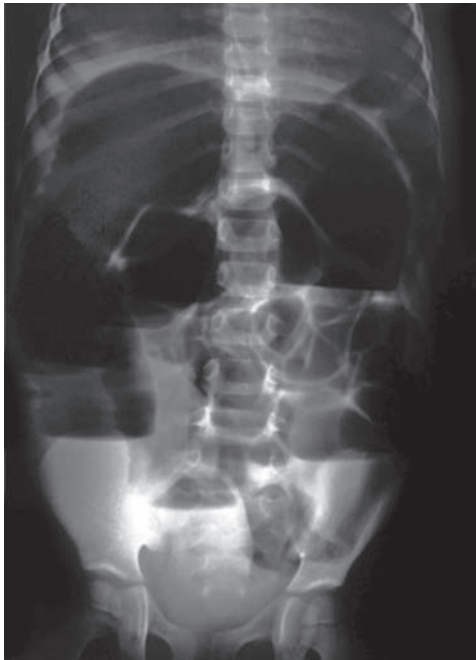


Fig. 13: Hirschsprung's disease: X-ray of abdomen demonstrating distended proximal colonic loops

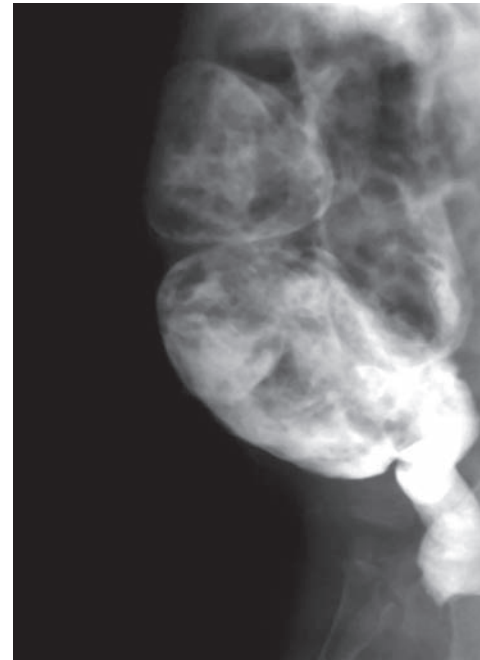


Fig. 14: Hirschsprung's disease: Barium enema

Investigations

Plain X-ray abdomen in erect posture:

- In the neonates: It is difficult to differentiate between small and large bowel in the neonates.
 - X-ray could be normal if bowel is deflated specially after passing stool or after per rectal examination.
 - Dilated proximal colon may be seen (Fig. 13).
 - Multiple fluid levels: Indicates intestinal obstruction. It could be because of Hirschsprung's disease.

Contrast enema

- It is done in an unprepared colon.
- Barium diluted with normal saline is used.
- Oblique views are taken to visualize whole length of the colon.
- 24 hours postevacuation films must be taken.
- The findings are:
 - Normal caliber distal colon with hugely dilated proximal colon (Fig. 14).
 - Presence of retained barium in 24 hours post evacuation film is very strongly suggestive of Hirschsprung's disease.

Management in the neonates is as follows:

Uncomplicated

After resuscitation and investigations to confirm the diagnosis, colostomy is done. Site of colostomy depends on the extent of aganglionosis.

- Transverse colostomy is done, if aganglionosis extend up to rectosigmoid junction.

- Terminal colostomy is planned in long segment cases. The colostomy is done in the ganglionic colon, just proximal to transitional zone.

Complicated

- There is acute intestinal obstruction or bowel perforation. The management is rapid resuscitation and emergency laparotomy and colostomy.
- *In enterocolitis:* Management is very aggressive and includes intravenous fluids, blood or fresh frozen plasma. Broad-spectrum antibiotics, warm saline irrigation of colon and rectum.

After stabilization of clinical condition, colostomy is done in the ganglionic segment. Definitive surgery is done at the age of 4 to 6 months. There are various techniques for definitive pull through. The basic aim of all the surgical procedures is:

- Excision of aganglionic segment.
- Posterior internal sphincterectomy.
- Anastomose the ganglionic segment to anal canal.

There are various techniques both as single or multistage, through abdomino-perineal approach or as endorectal-procedure. The procedure can be done through laparoscopic assistance also.

LARGE SKIN DEFECTS

Omphalocele and Gastroschisis

Omphalocele and gastroschisis represent abdominal wall defects in the newborn. Combined incidence of both is approximately 1 in 2000 live births.

Congenital Hernia of the Cord

When diameter of the hernia of the umbilical cord is less than 4 cm and the umbilical ring defect is less than 2.5 cm. It is defined as congenital hernia of the cord. It contains only loops of intestine.

It is different from umbilical hernia, in which the protrusion is covered by skin. In congenital hernia of the cord protrusion, containing bowel loops, is covered by transparent membrane.

Primary surgical closure is the treatment of choice, which includes replacing the intestinal loops back into the peritoneal cavity, excision of the sac and primary closure of the peritoneum, muscles and the skin. The prognosis is excellent.

Omphalocele (Exomphalos)

Omphalocele is the herniation of the intra-abdominal contents through the umbilical ring. The herniated contents are covered by translucent, avascular membrane, which consists of amnion, Wharton's jelly, and yolk sac membrane from out to inside (Fig. 15).

The umbilical cord is inserted on top of the sac. The umbilical vessels radiate out on the wall of the sac. The size of the defect varies from 5 to 12 cm. The contents of the sac are usually loops of small and large intestine. In approx 12 to 28 percent liver is also in the sac. Rectus muscles are situated at the margin of the defect.

Antenatal Diagnosis

It is possible to diagnose omphalocele and gastroschisis antenatally by:

- Maternal ultrasonography.
- Maternal serum alpha-fetoproteins: It is raised in both conditions.

Amniocentesis and chromosomal analysis should be done in omphalocele to detect associated anomalies as early as 10th week of gestation.

By using transvaginal ultrasonography, omphalocele is detected by presence of membranous sac and liver protruding from abdomen. Gastroschisis is diagnosed by presence of free-floating loops of intestine in the amniotic fluid.

Associated congenital anomalies are present in 35 to 78 percent of babies with omphalocele.

Complications

- Rupture of the sac. Rupture of the sac maybe before birth, during labor or after birth (Fig. 16).
- Infection and sepsis.
- Hypothermia and hypovolemia may result from evaporative water losses.

Management

Preoperative Management

- Examination of the sac: Whether the sac is intact, or ruptured. Evaluate the size and contents of the sac.
- Nasogastric tube is passed and NG aspirations are done regularly to prevent vomiting and aspiration of gastric contents. It also decompresses the stomach thus facilitates respiration and prevents dilatation of the intestines.
- Intravenous fluids and antibiotics are started.
- Hematocrit, serum electrolytes, blood sugar and arterial blood gases are done.
- Chest and abdominal X-rays are done.

Non-operative Management

Indications of non-operative management are:

- Large omphalocele with intact sac and no associated anomalies.
- Large omphalocele, with intact sac but associated with severe life-threatening cardiac anomaly, the correction of which is more urgent.
- Associated anomalies, which interfere with primary repair of omphalocele.



Fig. 15: Omphalocele (For color version see plate 2)



Fig. 16: Omphalocele (Ruptured sac)
(For color version see plate 2)

0.25 percent solution of mercurochrome in alcohol or betadine lotion is applied over the sac 6 to 8 hourly till solid Escher forms. Epithelialization takes 10 to 12 weeks and results in ventral hernia, which can be repaired later at the age 2 to 3 years.

Operative Management

Operative management is either primary closure or staged repair.

Primary Repair

Small or medium sized omphalocele can easily be repaired by primary closure.

If the defect is large, or cardiac or respiratory monitoring suggests impending problems later, either a staged repair maybe done or silastic mesh maybe used in the repair.

Staged Repair

Indications are:

- Primary closure is not possible due to above mentioned complications.
- Large omphalocele with ruptured sac.
- Large omphalocele containing liver.
- The various procedures for staged repair are as follows:
 - Skin flap closure over intact sac.
 - Skin flap closure.
 - Prosthetic “Silo” closure.

GASTROSCHISIS

There is a full thickness defect in the anterior abdominal wall, which is approx. 2 to 5 cm on the right side of the umbilical cord.

Gastroschisis has following characteristic features. There is no sac, nor there is any remnant of the sac.

- Defect in the anterior abdominal wall is about 2 to 5 cms, on the right side of normally situated umbilical cord. The defect is separated from the cord by a bridge of skin.
- Bowel loops are eviscerated, which are dilated, walls are thickened and edematous. Bowel loops are covered by fibrinous adhesions. Stomach or colon maybe eviscerated, but liver never herniates (Fig. 17).
- Abdominal cavity is small and appears empty.
- Associated major malformations are infrequent.
- Prematurity is very common (60–65%).

Gastroschisis is a rare condition. Exact incidence is not known.

Associated Anomalies

- Non-rotation or malrotation of the gut is frequently associated.

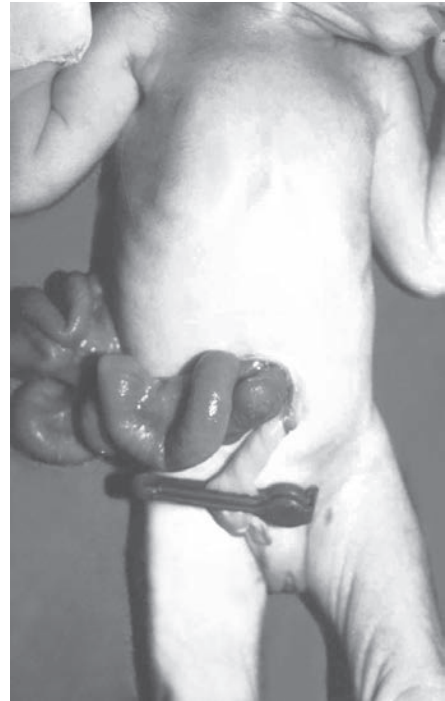


Fig. 17: Gastroschisis (For color version see plate 2)

- Ischemia or gangrene of the parts of the intestine, because of small defect in the abdominal cavity due to which blood supply maybe compromised.
- Cryptorchidism (18-47%).

Antenatal Diagnosis

Gastroschisis can be easily diagnosed antenatally by ultrasonography due to following characteristic features:

- Normally placed umbilical cord.
- Absence of sac or covering membrane
- Free floating eviscerated intestinal loops, through abdominal wall defect.
- Thickening of bowel loops.
- Absence of major associated anomalies.

Management

Preoperative Management

- Due to eviscerated bowel loops there is excessive evaporative losses resulting in hypovolemia and hypothermia. Therefore:
 - Eviscerated bowel loops are covered with warm moist saline packs and wrapped in a polythene sheath so as to prevent evaporation or maybe simply placed in polythene bag.
 - Intravenous fluids are given in the dose of 150 to 200 ml/kg/day so as to compensate losses from the exposed bowel loops in the initial phase.
 - Body temperature is maintained.

- Nasogastric tube is passed and aspirations are done to decompress stomach.
- Warm saline rectal washes are given to evacuate meconium.

Operative Management

Primary Closure

Primary closure is possible in large majority of the cases. It is done in the same way as omphalocele.

Primary repair should be done as early as possible after birth, if possible even immediately after birth.

With modern techniques of neonatal intensive care and aggressive pre and postoperative management the babies with gastroschisis and omphalocele have an excellent survival rate.

EXSTROPHY OF THE BLADDER

Exstrophy bladder is an uncommon congenital malformation. The reported incidence is 1 per 30,000 to 50,000 live births. Male children are affected 2 to 5 times more than the female.

Presenting Features

The classic bladder exstrophy in male children is represented by:

- Absence of the anterior abdominal wall in the suprapubic area.
- Low placed or absent umbilicus.
- Absence of the anterior wall of the urinary bladder.
- Posterior wall of the bladder everts out due to intra-abdominal pressure.
- Open urethral plate, i.e. dorsum of the penis is open with cleft of the glans (epispadias). Prepuce is present only on ventral surface.
- Wide separation of the pubic symphysis with separation of rectus abdominis muscles.
- Penis is short and wide, as both the corpora are attached to widely separated pubic rami. There is dorsal chordee.

In female children besides abdominal and bladder wall defects, there is bifid clitoris and separation of labia. The vagina is short and anteriorly displaced.

Following anomalies are commonly associated with exstrophy bladder:

- Musculoskeletal anomalies.
- Due to pubic symphysis diastasis, there is external rotation of the hip, which alters the gait of the child.
- Vertebral anomalies.
- Anterior displacement of the anus, there may be rectal prolapse also.

Antenatal diagnosis is possible. Exstrophy bladder is strongly suspected if after 14 weeks of gestation urinary bladder is not demonstrated.

Investigations

No investigations are required to diagnose the condition. However, ultrasonography, renal scintigraphy and intravenous urography evaluate upper urinary tract.

Management

There are two major options in the surgical treatment of exstrophy of bladder:

- Primary reconstruction
- Urinary diversion
 - Primary reconstruction is a staged procedure, which is as follows:
 - 1st Stage:* “Turn In” or bladder closure
Preferably it is done within 72 hours after birth, as newborn is still under the influence of maternal hormone relaxin. During this period pelvic ring can be closed effectively without osteotomies.
 - 2nd Stage:* Epispadias repair
It is performed between 12 to 18 months of age.
 - 3rd Stage:* Bladder neck reconstruction
It is done at 3 to 5 years of age. Antireflux procedure is done simultaneously at the time of bladder neck repair.
 - 4th Stage:* Augmentation cystoplasty
If required, it should be done at the age of 8 to 10 years. The main indication is, if the capacity of the bladder is small but bladder neck functions are adequate.

Complications

- Wound dehiscence
- Urethral stricture
- Recurrent UTI
- Stitch abscess
- Urinary incontinence
 - Diversion of urine: It is not done in the neonates. Indications for urinary diversion:
 - Very small bladder with hypertrophied mucosa at birth.
 - Inadequate bladder capacity after bladder neck reconstruction.
- Failure to gain continence after primary reconstruction. There are following options for urinary diversion:
 - Colonic or ileal conduit.
 - Ureterosigmoidostomy: It is not a procedure of choice due to late complications.

SPINA BIFIDA

Spina bifida is defined as failure of the fusion of vertebral arches with or without protrusion of the meninges and dysplasia of the cord.

Spina bifida can be classified as spina bifida occulta and spina bifida cystica, which is associated with protrusion of the meninges with or without dysplasia of the cord.

The emergency situation is in following cases of spina bifida cystica:

- Meningocele with very thin sac about to rupture or ruptured sac. Rupture is within 4 to 6 hours after birth.
- Meningomyelocele: If there is CSF leak or neural plaque is exposed on the surface of the sac.
- Myelocele with leaking CSF presented within 4 to 6 hours after birth.

However, the surgical interference is deferred in following situations where spina bifida is associated with:

- Gross paraplegia
- Incontinence of urine and feces
- Large hydrocephalus
- Severe kyphosis or scoliosis
- Associated with complex congenital malformations, incompatible with life.

RETENTION OF URINE

Posterior Urethral Valves

Mucosal or membranous folds present in the posterior urethra, which act as one way valve, i.e. obstruct the flow of urine in antegrade direction, while allowing retrograde flow are termed as posterior urethral valves. These folds are not present in the normal urethra.

The classification by Young et al who described three types of valves is still valid. The three types are:

Type I

Ninety five percent of all PUV are Type I. There is a ridge on the floor of urethra continuous with verumontanum anteriorly. It divides into two processes, which are directed upward and forward and is attached to urethra in its entire circumference.

Valves are membranous, which maybe thin or thick and rigid. Degree of obstruction caused by the valves varies considerably.

Type II

This originates at verumontanum and passes along the posterior urethral wall towards bladder neck. These valves do not cause obstruction.

Type III

It is actually a membrane, lying transversely across the urethra. A small perforation is present in the center. It causes obstruction in both antegrade and retrograde direction. These valves are rarely present (2–3%).

Entire urinary tract proximal to PUV is affected in varying degrees depending on the severity of urethral obstruction. Urinary obstruction starts antenatally early in

the second trimester after normal differentiation of the urinary tract is complete and continues till birth and later.

Because of the obstruction in the posterior urethra there are secondary changes, which are as follows:

Prostatic urethra

Important changes are:

- Dilatation and elongation of posterior urethra
- Verumontanum is distorted.
- Ejaculatory duct maybe dilated with reflux of urine into vas deferens.

Bladder neck

- Bladder neck is hypertrophied and displaced anteriorly, but is often open.
- Usually bladder neck changes resolve once the valves are ablated and obstruction is relieved.

Urinary bladder

Secondary changes on the urinary bladder due to PUV are:

- There is hypertrophy and hyperplasia of the detrusor muscle.
- High intraluminal pressure.
- Increased residual urine.
- High pressure voiding.

Ureters

Raised intravesical pressure as a result of PUV, results in vesicoureteric reflux (VUR).

Kidney

- Hydronephrosis
Hydronephrosis is due to:
 - VUR
 - Obstruction: High pressures within bladder are transmitted to ureters and kidneys directly through hydrostatic pressure.
 - Due to abnormal ureteral bud which results in dysplastic kidney and dilated collecting system.
- Renal damage:
Renal damage is due to two components:
 - Renal dysplasia.
 - Obstructive uropathy.

Presenting Features

Posterior urethral valve presents with wide variety of symptoms, ranging from minor voiding disorders to complete retention of urine with metabolic problems and/or renal failure.

Presenting features in neonates vary according to severity of PUV. Neonate may present with:

- Severe respiratory distress due to pulmonary hypoplasia secondary to oligohydramnios due to decreased fetal urine production. Large majority of neonates with pulmonary hypoplasia and PUV die soon after birth.

- Intrauterine growth retardation, refusal to accept feeds, and vomiting. These symptoms indicate systemic illness due to nephropathy.
- Retention of urine, weak stream or dribbling of urine.
- Fever and sepsis due to UTI.

On examination, there is palpable mass in the abdomen, which may be distended bladder or hydronephrotic kidney.

Investigations

Antenatal

Antenatally PUV are diagnosed during routine maternal ultrasonography.

The critical time of detection of PUV is 24 weeks after gestation. U/S evaluation done before 24 weeks may not detect PUV. The ultrasonographic findings are:

- Bilateral hydroureteronephrosis.
- Dilated bladder with thick walls.
- Dilated posterior urethra and hypertrophied ladder neck.
- Increased renal echogenicity at mean age of 28 weeks of gestation is suggestive of obstructive uropathy. Echogenicity is normal in nonobstructive dilatation.

Postnatal

Ultrasonography: Routine abdominal ultrasonography confirms the findings of antenatal ultrasonography and if done through perineal approach, provide better confirmatory findings:

Voiding cystourethrogram (VCUG): It is the most reliable diagnostic investigation.

Renal Scintigraphy

DTPA or MAG -3 renal scan is done to assess differential renal functions.

Laboratory Evaluation

To evaluate renal functions and electrolyte status.

- Blood urea and serum creatinine levels are elevated.
- Metabolic acidosis.
- Hyperkalemia: If present it indicates a real threat.
- Urine examination: Routine and cultures to detect infection.

Management

The first priority is to relieve the urinary obstruction. A urethral catheter is passed under strict aseptic conditions. Urine is sent for routine examination and for cultures.

In severe case of PUV with pulmonary hypoplasia catheter drainage is the only management till pulmonary status improves.

In majority of the neonates, PUV are associated with following clinical problems:

- Uremia
- Dehydration and electrolyte imbalance
- Metabolic acidosis
- Infection
- Nutritional problems

Baby is resuscitated by intravenous fluids, electrolyte and acid base correction with broad-spectrum antibiotics.

Following options are available for the treatment of posterior urethral valves.

Ablation of Valves

Due to availability of modern pediatric instruments primary ablation of posterior urethral valve is routinely done as primary procedure. Valve ablation can be done by:

- *Cystoscope:* Pediatric cystoscope size 6 or 8 is passed per urethra. Bugbee electrode is used to fulgurate the valves. Valves are fulgurated at 11 and 4'o clock position.
- *Whitaker Hook:* It is a 6 Fr instrument, which has a crocheting hook on the end. It is passed in the urethra. It may be used either blindly or under fluoroscopic control to hook and disrupt the valves.
- *Nd-Yag Laser:* The Nd-Yag laser can fulgurate valves.

Urinary Diversion

The indications of urinary diversions are:

- Very sick baby
- Primary valve ablation is not possible either due to clinical condition of the baby or due to nonavailability of the proper instrument.
- There is gross bilateral vesicoureteric reflux.

Vesicostomy is the procedure of choice. Ninety percent patients improve and condition stabilizes even with VUR.

Long-term Results

Recent advances in the diagnosis and management have dramatically improved the survival. The mortality, which was approx. twenty five percent in 1960's is virtually nil now. However, patients with most severe form of disease are either still born or die soon after birth due to severe respiratory distress, as a result of associated pulmonary hypoplasia. These children do not present for the treatment of posterior urethra valves.

25 to 35 percent babies treated in the neonatal period develop end stage renal failure and may require renal transplantation. There is another group of babies, who do not develop end stage renal failure, but they also do not have enough renal functions to permit normal growth and development.

ACUTE SCROTUM

Torsion Testes

Seventy percent cases of torsion testes in neonates occur prenatally. Torsion is extravaginal, i.e. the twist occurs outside the attachment of tunica vaginalis.

The presenting features are:

- In prenatal torsion, the testes is nontender, firm, indurated, swollen with a slightly bluish cast.
- In postnatal torsion, testes is swollen and is extremely tender on palpation.
- Scrotal skin maybe erythematous or edematous.
- Transillumination is negative.
- Cremaster reflex is negative.

Diagnosis is made by clinical suspicion and physical examination. Ultrasonography employing Doppler flow studies can be useful.

Differential Diagnosis Includes

- Torsion of appendix of testes.
- Strangulated inguinal hernia.
- Scrotal hematoma following birth trauma secondary to breech delivery.

Epididymo-orchitis is never considered as a diagnosis in the neonates.

Treatment

Immediate surgical exploration of the affected scrotum should be done.

- If testes are necrotic: Excision of the gangrenous testes is done. Contralateral orchidopexy must be done.
- If torsion is recent:
 - Tunica vaginalis is opened.
 - Color of testes is noted.
 - Detorsion should be done.
 - If color improves, orchidopexy on both sides is done.

STRANGULATED INGUINAL HERNIA

Inguinal hernia is present in 5 percent premature babies weighing less than 1500 gm and in 30 percent weighing less than 1000 gm. It is more common in small for gestational age babies and in male. Incidence of strangulated hernia is very high in this group of babies.

Neonatal Blood Component Therapy

Anupam Sachdeva, Samridh Nagar, SP Yadav, Vasant Chinnabhandar

Rapid advances in medical care are continuously pushing the boundaries at which preterm neonates can be salvaged. With these increased rates of survival blood components tailored specifically to satisfy the needs of these very low birth weight (VLBW <1500 g) and extremely low birth weight (ELBW <1000 g) should be available.

WHY ARE THE GUIDELINES FOR NEONATAL TRANSFUSION NEEDED?

- Sick neonates are one of the most heavily transfused groups.¹
- Most neonatal transfusion practice remains opinion based and there is a diversity of opinion and practice.²⁻⁶
- The administration of blood products conveys a finite risk of transmitting potentially serious infections and is not without risk and cost.^{7,8}
- The most dynamic changes occur during the perinatal period and early infancy.

Blood Transfusion Practice Unique to the Newborn

- A child is not a miniature adult and a neonate is not a miniature child
- Neonatal physiology
- Neonatal immunology and compatibility testing
- Neonatal vascular access
- Small volume packs.

Unique Aspects of Neonatal Physiology

Infant Size and Blood Volume

Full-term newborns have a blood volume of approximately 85 ml/kg; preterm low-birth weight newborns have an average blood volume of 100 ml/kg. As survival rates continue to improve for infants weighing 1000 g or less at birth, blood banks will increasingly be asked to provide

blood components for patients whose total blood volume is less than 100 mL. The need for frequent laboratory tests has made replacement of iatrogenic blood loss the most common indication for transfusion of low-birth preterm neonates.⁹ However, the previous practice of replacing blood mL for mL is now giving way to replacement as needed to maintain a target hematocrit in certain clinical situations.

Newborns do not compensate for hypovolemia as well as adults. After ten percent volume depletion, a newborn diminishes the left ventricular stroke volume, without increasing the heart rate. To maintain systemic blood pressure, peripheral vascular resistance increases and this, combined with the diminished cardiac output, results in poor tissue perfusion, low tissue oxygenation, and metabolic acidosis.¹⁰

Erythropoietin Response

Erythropoietin response to hypoxia in newborns differs from that of adults and older children. In older children and adults, oxygen sensors in the kidney recognize diminished oxygen delivery and release EPO into the circulation. In the fetus, the oxygen sensor that stimulates EPO production is believed to be the liver, which appears to be programmed for the hypoxic intrauterine environment. This hypo-responsiveness to hypoxia protects the fetus from becoming polycythemic. Eventually, EPO production shifts from the liver to the kidneys, a developmental change thought to be regulated by time of conception, not birth, and possibly not beginning until term. After birth, it is the most immature infants who produce the least amount of EPO for any degree of anemia; this may reflect the absence of the developmental shift of erythropoietin production from the liver to the kidneys.¹¹ Circulating EPO levels are lower, for a given hematocrit, in preterm neonates.¹¹

Erythroid progenitor cells in the hypoproliferative bone marrow of these preterm infants show normal intrinsic sensitivity to EPO; clinical trials are in equivocal to evaluate treatment of the anemia of prematurity with recombinant human erythropoietin.¹² Sick preterm neonates who receive many transfusions shortly after birth have reduced circulating levels of fetal hemoglobin.

Cold Stress

Hypothermia in the newborn causes exaggerated effects, including increased metabolic rate, hypoglycemia, metabolic acidosis, and a tendency towards apneic episodes that may lead to hypoxia, hypotension, and cardiac arrest. Exchange transfusion with blood at room temperature may decrease a newborn's rectal temperature by 0.7 to 2.5°C, therefore, blood for exchange transfusion should be warmed. The usual method is to use an in-line warmer. Blood should not be warmed under a radiant heater (either large or small volumes), but small volumes of blood are sometimes placed in a temperature-controlled incubator, where there are safeguards against excessive warming. When transfusions are given to infants in the phototherapy unit, the tubing should be introduced through the side port, because red cells in tubing that enter the top port maybe hemolyzed.¹³

Immunologic Status

Infants have an immature humoral immune system, and any antibodies present derive almost entirely from the maternal circulation. Transplacental transfer of immunoglobulin and other proteins is independent of molecular size; IgG (150 kDa) is transferred much more readily than albumin (64 kDa). In humans, maternal IgM does not reach the fetus and IgA is not readily transferred, although low levels have been found in the newborn.

All four subclasses of IgG are transported across the placenta, but the rate varies between individual mother-fetus pairs. Early in pregnancy, IgG probably passes from mother to fetus by diffusion, and concentration in fetal serum is low for all subgroups. Between 20 and 33 weeks of gestation, fetal IgG levels rise markedly, apparently due to maturation of a selective transport system that involves, in part, specific protein receptors on the membrane of placental cells.¹⁰

IgG₁, the predominant subclass in maternal blood, crosses the placenta first and is transported in greatest quantity. Cord blood has higher antibody concentrations than maternal blood. Catabolism of IgG occurs more slowly in the fetus than in the mother, so that transplacental maternal antibody is conserved during the neonatal period. A fetus exposed to an infectious process *in utero* or an infant exposed shortly after birth may produce small amounts of IgM detectable by sensitive techniques, but unexpected red cell alloantibodies of either IgG or IgM class are rarely formed during the neonatal period.¹⁴

The cellular immune system of neonates is also immature. Graft versus host disease (GVHD) has been reported in newborns, most often in infants who had confirmed or suspected congenital immunodeficiency. It has, however, occurred in infants who received intrauterine transfusion followed by postnatal exchange transfusion.¹⁵

A proposed explanation is that lymphocytes given during intrauterine transfusion could induce host tolerance, impairing rejection of lymphocytes given in the subsequent exchange transfusions. GVHD is not considered a significant clinical problem in exchange transfusions in immunologically normal newborns, and irradiation of blood to prevent GVHD is probably unnecessary. However, some neonatal nursery units provide irradiated blood for low-birth weight, low-gestational age, or septic preterm neonates, based on the belief, not yet universally accepted, that such infants are immunologically more vulnerable to GVHD.¹⁵ Irradiation should be performed on blood for intrauterine transfusion and on all subsequent transfusions that this infant receives; directed-donor units should be irradiated.¹⁶

Metabolic Problems

Acidosis or hypocalcemia may occur after large volume transfusion because the immature liver of the newborn metabolizes citrate inefficiently. Immature kidneys have reduced glomerular filtration rate and concentrating ability, and newborns may have difficulty excreting excess potassium, acid, and/ or calcium.

Potassium

Although potassium levels increase rapidly in the plasma of stored red cells, small volume, simple transfusions have little effect on serum potassium concentration in newborns. It has been calculated that transfusion of 10 ml/kg of red cells (hematocrit 80%) obtained from a unit of blood stored for 42 days in extended storage medium, would deliver 0.1 mEq of potassium if transfused slowly to a 1 kg neonate.¹⁷

This is much less than the daily potassium requirement of 2 to 3 mEq/kg. Serum potassium may, however, rise rapidly after infusion of large volumes of red cells in such circumstances as surgery, exchange transfusion, or extracorporeal circulation, depending upon the plasma potassium levels in the blood and manipulation of the blood component.

In stored, irradiated blood, the problem of potassium leak is potentiated; it may be desirable, for selected patients, to wash irradiated cells if they have subsequently been stored.¹⁸ It is preferable to perform irradiation as close to the time of administration as possible.

2, 3-Diphosphoglycerate

Neonates with respiratory distress syndrome or septic shock have decreased levels of 2, 3-diphosphoglycerate

(2, 3-DPG). Alkalosis and hypothermia may further increase the oxygen affinity of hemoglobin, shifting the dissociation curve to the left and making oxygen even less available to the tissues. Arterial oxygenation may be further compromised by respiratory distress syndrome or other pulmonary disease. Mechanisms that compensate for hypoxia in adults, such as increased heart rate, are limited in newborns. If a large proportion of an infant's blood volume has come from transfusion, transfusion of 2, 3-DPG-depleted blood may cause problems that would not affect older children or adults. Since 2, 3-DPG levels decrease in stored blood, exchange transfusion in newborns should use the freshest blood conveniently available. For small-volume transfusions, the medical necessity for fresh blood has never been demonstrated and arguments have been raised to suggest it is unnecessary.

Why use Component Therapy and not Whole Blood?

- Whole blood consists of six important components, each with a specialized function
- Some components can only be given effectively as components
- Safe approach
- Reduces volume of transfusion
- Allows optimal usage of each donor unit of whole blood.

Problems Associated with Neonatal Transfusions

- Frequent multiple, small volume transfusions needed
- Concept of 'fresh blood'
- Widespread and unnecessary use of whole blood
- Blood component therapy not yet practiced
- Blood wastage
- Multiple donor exposure

Compatibility Testing in Neonates and Young Infants

Neonates and young infants are immunologically immature; hence alloimmunization to RBC antigens is rare during this period.¹⁹ AABB standards²⁰ require only limited pre-transfusion serologic testing for infants below 4 months of age. This must include ABO and Rh typing of red cells and a screen for red cell antibodies. Wherever possible, samples from both mother and infant should be obtained for initial ABO and RhD group determination. If an unexpected red cell antibody is detected in the infant's specimen or if the mother's serum contains a clinically significant red cell antibody, the infant should be given either red cell units tested and found to lack the corresponding antigen(s) or units compatible by antiglobulin cross-match; this should continue for as long as maternal antibody persists in the infant's blood.

It is unnecessary to test the infant's serum for anti-A and/ or anti-B unless there will be transfusion of non-group-O cells.

A positive DAT on the neonate's red cells or an atypical red cell antibody in maternal or neonatal serum suggests possible hemolytic disease of the newborn (HDN). In such cases, special serological procedures will be necessary to allow selection of appropriate blood group.

Concerns with Cytomegalovirus in Neonates

Cytomegalovirus may be transfusion-transmitted; however current transfusion practice has made this uncommon.²¹ There is a high-risk of CMV in fetuses and infants <1.5 kg.

The "Guidelines of the UK Transfusion Service" state that blood transfused in the first year of life should be CMV negative.²² However, in an emergency, transfusion of leucodepleted components is acceptable as other authorities recommend use of blood components leucodepleted to $<5 \times 10^6$ /unit.^{22, 23} These have a significantly reduced risk of CMV transmission.²³

Irradiation

Irradiation of blood components (especially all red cell and platelet components) to prevent GVHD is essential prior to transfusion in the following cases:

- Intrauterine transfusion (IUT)
- Exchange transfusion of red cells after IUT.
- Top-up transfusion after IUT.

For more details refer to Chapter 80 on "Transfusion of Blood Components in Children".

RBC TRANSFUSIONS

The most commonly needed blood component support for neonates is packed RBC (PRBC) transfusions. Availability of small volume aliquots should be ensured in neonatal care units to maximize utilization of blood products.

RBC Transfusions are Needed

- To ensure adequate oxygenation during intensive care periods.
- After intensive care, to treat clinically significant symptomatic anemia.

Are there any Methods to Assess Tissue Oxygenation?

- Peripheral fractional oxygen extraction (FOE)—This method deserves further assessment.²⁴
- Capillary whole blood lactate.²⁵⁻²⁸
- There is no practical method available to everyday neonatal practice that accurately assesses tissue oxygenation.

What are the factors that influence Tissue oxygenation?^{29, 30}

- Concentration and type of hemoglobin.
- The concentration of 2,3-DPG within the RBCs.
- Cardiopulmonary function of the neonate.

None of these variables apart from Hb are easily measurable in day-to-day practice.

Indications for PRBC in the Newborn

- *Antenatal:* Blood loss due to feto-maternal or feto-placental hemorrhage
- *Intrapartum:* Ruptured cord, placenta previa and abruptio placentae.
- *Postnatal:* GI hemorrhage, slipping of the cord ligature, internally following traumatic delivery, iatrogenic blood loss following blood sampling.

There are 3 major factors contributing to small volume RBC transfusion requirements in VLBW infants.

- The rapid decline in Hb levels that occurs in the first weeks of life to a nadir at 2 months of life.^{29,31} It must be remembered that concomitant with the decrease in absolute hemoglobin levels, the switch from HbF to HbA production is also occurring, so that the change in oxygen-carrying capacity is not so marked as the change in the total Hb level might suggest.
- The associated respiratory illnesses often present in these neonates first as RDS and then as BPD. There is necessity of maintaining hemoglobin values at a predetermined level in these neonates.^{32,33}
- Phlebotomy losses. Because of the need for laboratory monitoring of ill neonates and the relatively large volumes of blood required in relation to these tiny infants' total blood volumes, phlebotomy losses contribute significantly to the need for RBC transfusions in VLBW infants.³⁴ In sick, neonates red cell replacement is usually considered when approximately 10% of the blood volume has been removed.

Trends in Clinical Practice, Restrictive Policy and Some Practical Considerations

Decreased use of RBC transfusions, even in the most preterm newborns is not associated with an increase in complications. There is less evidence from the reverse situation that is, does maintaining a high Hb improve outcome in preterm neonates?

Hb limited oxygen unloading capacity to the tissues is rare even in intensive care. However, Brooks et al,³⁵ who looked at maintaining a packed cell volume >40 percent in preterm neonates in an attempt to reduce retinopathy of prematurity, also reported no reduction in important neonatal complications (IVH, CLD, NEC) as secondary outcome measures. This study only assessed preterm neonates greater than 28 days of age—that is, outside the intensive care period. However, the fact that a low hemoglobin or packed cell volume by itself (as opposed to clinical concern about the adequacy of tissue oxygenation) is the sole trigger factor for transfusion in many intensive care situations^{9,26} suggests that hemoglobin limited

oxygen unloading capacity to the tissues is rare, even during intensive care.

Dedicating aliquots form a single donation of red cells (or apheresis platelets) to allow sequential transfusions from the same donor for neonates who are likely to be repeatedly transfused is considered good practice. When red cells are transfused they are usually given in small volumes. A transfusion of 10 mL/kg of RBCs at a hematocrit >80% should raise the Hb by ~3 g/dL.

However, other recent research in preterm neonates suggests that large volume (20 ml/kg) RBC transfusions lead to larger rises in Hb and fewer overall transfusions than small volume transfusions (10 ml/kg).³⁶ This volume of packed RBCs is well tolerated in the vast majority of preterm neonates.³⁶

There are three clinical settings in which newborns may require large volume RBC transfusion (exchange transfusion, surgery with cardiopulmonary bypass or during treatment with extracorporeal membrane oxygenation (ECMO)).³⁷

RBC units for transfusion to neonates are often chosen from a fresh (<5 days old) RBC unit at the time of his/her first small-volume RBC transfusion.

In settings of large volume RBC transfusion, replacement of plasma coagulation factors is often also required so that WB or reconstituted WB, i.e. an RBC unit mixed with a unit of fresh frozen plasma (FFP), can be used. For WB, or the RBC unit for reconstituted WB, the choice of ABO group is the same as that described above for small volume RBC transfusions. The ABO group of the FFP must also be compatible with the baby's RBCs. This may mean that the ABO groups of the RBC unit and the FFP unit are different, e.g. for a group A baby with maternal anti-A in his plasma, a unit of reconstituted WB would be prepared using a group O RBC unit and a group A FFP unit. To limit donor exposure, some experts use group O whole blood in this setting, although group O donors with high anti-A titers should be excluded.

WB units or RBC units for large volume transfusions should be relatively fresh, i.e. not >5 to 7 days old. The main reason for this precaution is the high potassium concentration in stored WB or RBC units.

Pretransfusion Testing³⁸

- Source of blood
- Donor
- For blood group compatibility

Donor sample: ABO and RhD groups, antibody screen

Neonatal sample: ABO and RhD groups, DAT, antibody screen if maternal sample not available

Maternal sample: ABO and RhD groups, antibody screen

Guidelines for Red Blood Cell (RBC) Transfusion Thresholds in Preterm Infants^{39,40}

Assisted Ventilation < 28 days

- $\text{FiO}_2 < 0.3$ —Hb < 12 g/dl or PCV < 0.40
- $\text{FiO}_2 > 0.3$ —Hb < 11 g/dl or PCV < 0.35
- ≥ 28 days—Hb < 10 g/dl or PCV < 0.30

CPAP

- < 28 days Hb < 10 g/dl or PCV < 0.30
- ≥ 28 days Hb < 8 g/dl or PCV < 0.25

Breathing Spontaneously

- $\text{FiO}_2 > 0.21$ —Hb < 8 g/dl or PCV < 0.25
- Well, in air—Hb < 7 g/dl or PCV < 0.20

RBC transfusion may be considered at higher thresholds for neonates with hypovolemia, septic shock, NEC, undergoing/ recovering from major surgery.

Role of Erythropoietin (EPO)

Recombinant human EPO may reduce red cell transfusion requirements in neonates. However, its effect appears to be relatively modest and does not reduce transfusion requirements within the first two weeks of life, when sick neonates are most transfusion dependent because of frequent blood sampling. The optimal dose, timing and nutritional support required during EPO therapy has yet to be defined and currently the routine use of EPO in this patient group is not recommended as similar reduction in blood use can probably be achieved by institution of appropriate transfusion protocols.⁴¹⁻⁴³

PLATELET TRANSFUSIONS

- Platelets have to be stored at 20 to 22°C on a constant agitator
- Should be transported quickly and infused over 20 to 30 minutes rapidly
- No glassware to be used
- One should use ABO/Rh identical/compatible donor

Newborns should receive platelet transfusions in similar clinical settings as for older children. However, since newborns frequently manifest thrombocytopenia and since preterm infants are at increased risk for PVH-IVH, it is possible that the platelet level at which prophylactic platelet transfusions should be administered to newborns is higher than that recommended for other patients. The platelet levels at which prophylactic platelet transfusions were given to neonates varied tremendously: from $< 20 \times 10^9/\text{L}$ to $> 50 \times 10^9/\text{L}$ in stable preterm infants and $< 20 \times 10^9/\text{L}$ to $> 80 \times 10^9/\text{L}$ in sick preterm infants. The non-bleeding premature infants with platelet counts $> 60 \times 10^9/\text{L}$ should not receive prophylactic platelet transfusions.⁴⁴

Neonates with thrombocytopenia due to maternal platelet alloantibodies require special consideration with

respect to the indications for platelet transfusion. These neonates require HPA-compatible platelets in addition to high dose IVIG. In these patients, a minimum platelet count of $30 \times 10^9/\text{L}$ is recommended.

What to do in an Emergency?

- Is there a role of Rh immunoglobulin prophylaxis?
- Platelet transfusion is common in neonatal intensive care units, occurring in 2 to 9.4 percent of all admissions.⁴⁵⁻⁴⁷
- Most platelet transfusions are given prophylactically to non-bleeding neonates.
- More than half of neonates given platelet transfusions receive more than one transfusion, with a significant proportion receiving more than four transfusions.⁴⁵⁻⁴⁷
- Thrombocytopenic neonates who receive platelets are up to 10 times more likely to die than neonates who do not receive platelet transfusion (Table 1).

TYPES OF PLATELETS³⁹

Random Donor Platelets

- Also called platelet pack and derived from a single unit of whole blood.
- Contains $5-6 \times 10^{10}$ platelets in 50 to 60 ml plasma per pack.
- In a newborn 5 to 10 ml/ kg will raise platelet counts to 75,000 to 1,00,000/mm³

Single Donor Platelets³⁹

- Also called platelet concentrate
- Obtained by apheresis

What is the Advantage of SDP?

- It contains $2-3 \times 10^{11}$ platelets in 50 to 70 cc of plasma.
- It has 6 to 7 times more platelets than RDP.
- In a newborn infant, small aliquots can be used from an RDP pack or one SDP pack can be used for 3 to 4 newborn babies.

Dose of Platelet Transfusion⁴⁹

- In small children (< 20 kg), 10 to 15 ml/ kg up to the adult dose of one platelet concentrate is used.
- The dose of platelets ($\times 10^9$) can be calculated in more detail, if required, from the desired platelet increment (PI), the patient's blood volume in liters and a correction factor (F) of 0.67.

Platelet Transfusion Efficacy⁵⁰

- Platelet recovery: The percentage platelet recovery (R) is calculated from the platelet increment ($10^9/\text{L}$) (PI), the blood volume (BV) in liters and the platelet dose transfused (10^9) (PD):
- $\text{R\%} = \text{PI} \times \text{BV} \times \text{PD}^{-1} \times 100$

Table 1: Guidelines for platelet transfusion thresholds for neonates⁴⁸

Platelet ($\times 10^9/l$)	Non-bleeding neonate	Bleeding neonate	Auto-ITP	NAITP (proven or suspected)
<30	Consider transfusion in all patients	Transfuse	Transfuse if bleeding present or IVIG unavailable	Transfuse (with HPA compatible platelets) if bleeding
30–49	Do not transfuse if clinically stable Consider transfusion if: <1000 g and <1 week of age Clinically unstable (e.g. fluctuating BP) Previous major bleeding tendency (e.g. grade 3–4 IVH) Current minor bleeding (e.g. petechiae, puncture site oozing) Concurrent coagulopathy Requires surgery or exchange transfusion	Transfuse	Do not transfuse if stable and not bleeding	Transfuse (with HPA compatible platelets) if bleeding
50–99	Do not transfuse	Transfuse	Do not transfuse	Transfuse (with HPA compatible platelets) if major bleeding
>99	Do not transfuse	Do not transfuse	Do not transfuse	Do not transfuse

- The corrected count increment ($10^9/l$) (CCI) is calculated from the corrected count increment (PI), the body surface area of the patient in square meters (BSA) and the dose of platelets transfused (10^{11}) (PD):
- $CCI = PI \times BSA \times PD^{-1}$

Giving Sets/Filters for Platelet Transfusion⁴⁹

- Platelet concentrates should be transfused through a standard blood or platelet administration set.
- Platelet concentrates should not be transfused through giving sets that have been used for blood.
- A screen filter is required for the giving of platelets via a syringe in the setting of neonatal or fetal transfusion.

Platelets for Neonatal Use

- Components should be free of clinically significant irregular blood group antibodies, including high titer anti-A and anti-B.
- Components should be negative for CMV.
- May be prepared by splitting an apheresis platelet pack (often into four), using a closed system.
- Components should contain $>40 \times 10^9/L$ platelets. Additional labeling is required: *Platelets for neonatal use*.

PLASMA AND ITS DERIVATIVES

Major plasma derivatives which are used are:

- Fresh frozen plasma (FFP)
- Cryoprecipitate
- Hepatitis B Ig

Fresh Frozen Plasma

Traditionally fresh frozen plasma (FFP) has been administered to neonates for a variety of reasons:

- Treatment of proven or suspected disseminated intravascular coagulation (DIC)
- Prevention of IVH
- Volume replacement
- During sepsis (addition of opsonising factors)
- During episodes of thrombocytopenia
- To “correct” prolonged indices of coagulation (unaccompanied by clinical signs of bleeding or other laboratory findings consistent with DIC—for example, thrombocytopenia or RBC fragmentation).

Except for treatment of DIC (which may also require the administration of cryoprecipitate or specific clotting factors), there is no evidence to support the use of FFP in the other clinical situations listed above.⁵¹

The only indications for FFP in neonates recommended in the recent BCSH guidelines and supported by evidence are:^{52–54}

- DIC
- Vitamin K dependent bleeding
- Inherited deficiencies of coagulation factors.

In VKDB life-threatening bleeding may require FFP treatment or in rare situations treatment with coagulation factor concentrates. Other possible scenarios where its use may be considered are:

- Reversal of pro-coagulant drug effect
- Invasive procedures in a baby with PT/PTTK 1.5 to 2 times normal
- To prepare reconstituted whole blood where this product is indicated

The use of FFP has been advocated for prevention of periventricular-intraventricular hemorrhage (PVH-IVH) in the preterm infant, but the current evidence does not support the routine use of prophylactic FFP in preterm infants at risk for PVH-IVH. Also, FFP should not be used as a fluid for hematocrit adjustment in erythrocyte transfusions nor as a replacement fluid in partial exchange transfusion for the treatment of neonatal hyperviscosity syndrome.

Dosage and Administration

When FFP is given for coagulation factor replacement, the dose is 10 to 20 ml/kg. This dose will usually raise the level of coagulation factors by 20% immediately after infusion. Post-transfusion monitoring of the patient's coagulation status (PT, APTT and/or specific coagulation factor assays) is important for optimal treatment.

Cryoprecipitate Transfusion

- The most inexpensive factor VIII concentrate is cryoprecipitate
- 250 ml of fresh plasma yields 1 bag of cryoprecipitate
- It contains 75 to 125 units of Factor VIII
- One bag/ 5 kg body weight raises the recipient's level by 50 percent
- Other indications: Afibrinogenemia/ hypofibrinogenemia/ VWD deficiency

PLASMA PRODUCT TRANSFUSION REACTIONS

- Acute hemolytic transfusion reactions (rare)
- Non-hemolytic transfusion reactions
- Ancillary effects of transfusion
- Graft versus host disease
- Infection

GRANULOCYTE TRANSFUSIONS

Newborns normally have a transient neutrophilia in the first week of life with mean normal absolute neutrophil counts ranging from $11.0 \times 10^9/L$ at birth to $5.5 \times 10^9/L$ this age.⁵⁵ Septic newborns frequently develop neutropenia, defined in the newborn as an absolute neutrophils count below $3.0 \times 10^9/L$. Between 1981 and 1992, 5 controlled trials of granulocytes transfusions for septic newborns with neutropenia were reported and have recently been reviewed.⁵⁶ The data suggest a beneficial role for granulocyte transfusion provided an adequate dose is administered. Nevertheless, the use of granulocyte transfusions for neonatal sepsis has not become widespread, possibly because of the difficulty of obtaining granulocytes as rapidly as would be required in this setting. More recently, investigators in the field have begun to study the role of G-CSF in the treatment of neonatal sepsis.⁵⁷

For neonates and small children, a daily infusion of 1×10^9 PMN's/kg should be given and for larger patients, $2-3 \times 10^{10}$ PMNs. As there is significant RBC contamination, units must be ABO compatible and if possible RhD negative for RhD-negative recipients and must undergo the usual compatibility testing. Because most patients receiving these products are severely immunosuppressed, apheresis granulocytes are usually irradiated to prevent TA-GVHD.

SPECIAL TOPICS

Transfusion in Necrotizing Enterocolitis

Infants with necrotizing enterocolitis (NEC) may occasionally be systemically infected with neuraminidase-producing organisms, such as *Clostridium* spp. Neuraminidase can strip sialic acid residues from red cell sialoglycoproteins exposing the T-crypto antigen; a state commonly known as 'T-activation'. T-activation can be detected simply and rapidly using a commercial lectin panel. Adult (but not neonatal plasma) almost invariably contains anti-T, a potentially hemolytic IgM antibody. There is currently no consensus either with respect to the frequency of T-activation or the clinical significance of this finding in infants with NEC.^{58,59} It is recommended that patients with NEC be transfused with red cells in SAG-M as this is relatively plasma-free. Platelets, FFP and/or cryoprecipitate should only be administered when clearly indicated. Any patient with NEC who develops hemolysis, should be investigated to determine the cause of this. This should include a lectin test to look for T-activation. If T-activation is the likely cause, then an ET may be necessary. There is support but no consensus for routine provision of 'low-titer anti-T' plasma and platelet product for patients with T-activation. Access to these rare products is limited.

Exchange Transfusion in Neonates

Exchange transfusion (ET) may be used to manage severe anemia at birth, particularly in the presence of heart failure, and to treat severe hyperbilirubinemia, usually caused by HDN. Controversial indications such as metabolic disease, septicemia and DIC have not been subjected to adequate clinical evaluation.

It is a specialist procedure associated with a potential for serious adverse events. While there is no consensus amongst neonatologists, plasma reduced red cells with a hematocrit (Hct) of 0.50 to 0.60 should be suitable for both hyperbilirubinemia and severe anemia.

Hemolysis may develop in fetuses and neonates who are ABO incompatible with their mother. Clinically significant hemolysis generally occurs only if the mother is group O and the infant group A (occasionally in group B babies). The hemolysis is due to the IgG anti-A or anti-B crossing the placenta and binding to the fetal red cells.

If an ET is required in ABO HDN, this should be with group O red cells with low titer plasma anti-A and anti-B, or with group O red cells suspended in AB plasma.

Exchanging the estimated volume of the baby's blood in a "single volume exchange" will remove 75 percent of red cells, while a "double volume exchange" (160 to 200 ml/kg, depending on gestation) removes 90 percent of the initial red cells. A double volume exchange can remove 50 percent of available intravascular bilirubin.

Red cells for ET should be:

- Group O or ABO compatible with maternal and neonatal plasma, RhD negative (or RhD identical with neonate)
- Negative for any red cell antigens to which the mother has antibodies
- IAT- cross match compatible with maternal plasma
- 5 days old or less
- Collected into CPD anticoagulant
- CMV seronegative
- Irradiated and transfused within 24 hrs of irradiation.

Calculations for neonatal exchange transfusion

- Two-volume red cell exchange transfusion for treatment of sickle cell crisis and neonatal hyperbilirubinemia
- Replace calculated blood volume with whole blood or red cells suspended in 5 percent human albumin
- Volume to be exchanged (ml):

$$[\text{Estimated blood volume} \times (\text{Patient's hematocrit (\%)} \times 2)] / \text{Hematocrit of transfused unit (\%)*}$$

* Hematocrit

Whole blood 35 to 45 percent

Red cell concentrates 55 to 75 percent

Red cell suspension 50 to 70 percent

Intrauterine Transfusion (IUT)⁶⁰

IUTs are usually administered only in specialized units. Red cell IUT is indicated to correct fetal anemia caused by red cell alloimmunization (most important antigen-RhD followed by RhC and K) or, less commonly, for fetal parvovirus infection. Platelet IUTs are indicated to correct fetal thrombocytopenia caused by platelet alloimmunization. The aims of IUT are (i) to prevent or treat fetal hydrops before the fetus can be delivered and (ii) to enable the pregnancy to advance to a gestational age that will ensure survival of the neonate (in practice, up to 36 to 37 weeks) with as few invasive procedures as possible (because of the risk of fetal loss). This is achieved by (i) starting the transfusion program as late as safely possible but before hydrops develops and (ii) maximizing the intervals between transfusions, by transfusing as large a volume of red cells as is considered safe.

COMPONENT AND PROCEDURE SPECIFICATION

Red Cells Preparations

Red cells preparations for IUT should:

- Be group O (low titre hemolysin) or ABO identical with the fetus (if known) and RhD negative. K-negative blood is recommended to reduce additional maternal alloimmunization risks. In exceptional cases, e.g. for hemolysis because of maternal anti-C, it may be necessary to give RhD positive, C-negative blood;
- Be IAT-cross-match compatible with maternal serum and negative for the relevant antigen(s) determined by maternal antibody status;
- Be <5 day old and in citrate phosphate dextrose (CPD) anticoagulant;
- Be CMV seronegative;
- Be irradiated;
- Have a hematocrit (packed cell volume, PCV) between 0.70 to 0.85;
- Not be transfused straight from 4°C storage. Any active warming must be carried out with great care and the blood product not exposed to temperatures higher than 30°C. Active warming may not be necessary if the infusion is conducted carefully and at an appropriate rate (see below);
- Be in a volume calculated from the formula of Rodeck and Deans (1999);
- $(\text{Desired PCV} - \text{Fetal PCV} / \text{Donor PCV} - \text{Desired PCV}) \times \text{Fetoplacental BV}$; where BV is blood volume;
- Be transfused at a rate of 5 to 10 ml/min.

Platelet Preparations

Platelet Preparations for IUT should

- Be group O RhD negative and test negatively for high-titre anti-A or anti-B (i.e. have a low titre hemolysin) or group specific/compatible with maternal antibody;
- Be human platelet-specific alloantigen (HPA) compatible with maternal antibody;
- Preferably be collected by apheresis. A platelet concentrate derived from whole blood donations is less preferred;
- Be irradiated;
- Be concentrated to a platelet count of at least $2000 \times 10^9/\text{L}$;
- Be warmed, if warmed at all, with extreme care. As the ambient temperature for storing platelet concentrates is 22°C, and as the recommended rate of infusion (see below) is slower than that for red cells, active warming may not be needed. If it is conducted, it should not be beyond 30°C;
- Be in a volume calculated from the formula:

$$(\text{Desired platelet increment} / \text{Platelet count of concentrate}) \times \text{Feto-placental BV}$$

- Be transfused at a rate of 1 to 5 ml/min (transfused more slowly than red cells because of the increased risk of fetal circulatory stasis and asystole).

Compatible platelets should be available at the time of diagnostic fetal sampling for alloimmune thrombocytopenia, even if the primary purpose is not that of transfusion, because in the presence of severe fetal thrombocytopenia, fetal hemorrhage can be prevented by platelet transfusion.

Guidelines at Sir Ganga Ram Hospital (SGRH)

RBC Transfusion Guidelines

- Transfuse infants at hematocrit <20 percent or hemoglobin <7 gm/dl even if asymptomatic.
- Transfuse infant at hematocrit <30 percent or hemoglobin <10 gm/dl
 - On minimal mechanical ventilation <35 percent O₂ under hood
 - If significant apnea with bradycardia (2 episodes in 24 hrs requiring bag and mask ventilation) while receiving therapeutic doses of methylxanthines)
 - If heart rate >180/min or respiratory rate >80/min persisting for 24 hours
 - If weight gain of <10 gm/day is observed over 4 days while receiving >100 kcal/kg/day
 - If undergoing surgery
- Transfuse packed red blood cells for hematocrit <35 percent and hemoglobin <12 gm/dl
 - If receiving more than 35 percent supplemental O₂ under hood
 - If on significant mechanical ventilation, MAP >6 cm water

Platelet Transfusion Guidelines

Prophylactic Platelet Transfusion

- Stable preterm neonate with platelet count <30,000
- Stable term neonate with platelet count <20,000
- Sick preterm neonate with platelet count <50,000
- Sick term neonate with platelet count <30,000
- Preparation for invasive procedure—lumbar puncture or minor surgery (central line insertion) with platelet count <50,000
- Major surgery with platelet count <1,00,000

Platelet Transfusion in Neonate with Clinically Significant Bleeding

- Neonate with platelet count <50,000
- Neonate with condition that increases bleeding, e.g. DIC and platelet count <1,00,000
- Neonate with documented platelet function disorder irrespective of circulating platelet count.

Definition of Sick Neonate for Following Guidelines

- Cardiovascular instability, HR >180/min or dopamine or inotropic infusion at >3 mcg/kg/min
- Respiratory instability, FiO₂ requirements >0.4 or significant mechanical ventilation MAP >7
- Central nervous system instability within 72 hours of seizure
- Bleeding neonate meeting the clinical or laboratory criteria for DIC, at discretion of treating physician
- Within 5 days of major surgery
- Preterm neonate with birth weight <1,500 g within first 7 days of life.

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Anemia in Newborn

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INTRODUCTION

Normal erythropoiesis is influenced by several factors, especially erythropoietin (EPO), which stimulates maturation of red blood cell (RBC) precursors. Neonatal Anemia is defined as hemoglobin or hematocrit concentration of >2 standard deviation below the mean for postnatal age. This may be due to three general causes: blood loss, increased RBC destruction or decreased RBC production. The major physiologic impact of anemia is decreased oxygen delivery to tissue, resulting in both compensatory responses and acute or chronic consequences including poor growth, decreased activity and limited cardiovascular reserve. Rapid changes in normal hematological parameters take place throughout the neonatal period. Therefore, the diagnosis of anemia in the newborn is made in relation to gestation and postnatal age. Anemia during 1st week of life is defined as hemoglobin level less than 14 gram/dl or Hct <45 percent in a term infant. Any significant fall in hemoglobin in a neonate, although, within normal range is suggestive of hemorrhage or hemolysis. For example, in a term newborn whose hemoglobin was 18.0 gram/dl at birth, hemoglobin of 14.0 gram/dl on D7 of life is abnormal. Similarly, failure of hemoglobin to rise during first few hours of life may be the first clue to a hemorrhage or hemolysis in a newborn. Severe anemia present at birth (i.e. Hemoglobin <8.0 gram/dl) is usually due to immune hemolysis or hemorrhage.

FETAL ERYTHROPOIESIS

Fetal erythropoiesis occurs in yolk sac, liver and bone marrow as gestation progresses. It originates initially between 10 to 14 days of gestation in yolk sac. By 6 to 8 weeks of gestation more definitive fetal erythropoiesis is taking place in the liver. The liver remains the primary site of erythroid

production throughout the early fetal period. By 6 months of gestation bone marrow becomes the principal site of erythroid development. At later part of gestation erythropoietin switches from less sensitive hepatic to the more sensitive renal site. The major difference between fetal and adult erythropoiesis is in the response to erythropoietin. Erythropoietin response is poor in newborns especially in premature neonates and it persists through the neonatal period, resulting in a reduced erythropoietic stimulus and lower hemoglobin levels. The erythroid blood cell indices change during gestation and continue to change throughout infancy. The red cell values on the first postnatal day during the last 16 weeks of gestation is shown in Table 1.

NORMAL HEMATOLOGICAL VALUES IN NEONATAL PERIOD

RBC values are more variable in neonatal period, than any other time of life and understanding of normal values of hemoglobin and other red cell indices is essential for diagnosing anemia in newborn (Tables 2 and 3).

Causes of Neonatal Anemia

Anemia in neonatal period is mainly due to three distinct causes:

- Blood loss/hemorrhage: Acute/chronic, prenatal/natal/ postnatal
- Hemolysis: Immune/non-immune
- Failure of red cell production

Blood Loss

It is the most common cause of neonatal anemia. It includes:

- Obstetrical causes
- Fetomaternal transfusion

Table 1: Red blood cell values on the first postnatal day

	<i>Gestational Age (Weeks)</i>							
	24–25 (7)	26–27 (11)	28–29 (7)	30–31 (35)	32–33 (23)	34–35 (23)	36–37 (20)	Term (19)
RBC count ($10^6/\text{mm}^3$)	4.65 ± 0.43	4.73 ± 0.45	4.62 ± 0.75	4.79 ± 0.74	5.0 ± 0.5	5.09 ± 0.5	5.27 ± 0.68	5.14 ± 0.7
Hb (g/dL)	19.4 ± 1.5	19.0 ± 2.5	19.3 ± 1.8	19.1 ± 2.2	18.5 ± 2.0	19.6 ± 2.1	19.2 ± 1.7	19.3 ± 2.2
Hct (%)	63 ± 4	62 ± 8	60 ± 7	60 ± 8	60 ± 8	61 ± 7	64 ± 7	61 ± 7.4
MCV (fL)	135 ± 0.2	132 ± 14.4	131 ± 13.5	127 ± 12.7	123 ± 15.7	122 ± 10.0	121 ± 12.5	119 ± 9.4
Reticulocytes (%)	6.0 ± 0.5	9.6 ± 3.2	7.5 ± 2.5	5.8 ± 2.0	5.0 ± 1.9	3.9 ± 1.6	4.2 ± 1.8	3.2 ± 1.4
Weight (g)	725 ± 185	993 ± 194	1174 ± 128	1450 ± 232	1816 ± 192	1957 ± 291	2245 ± 213	—

Hb: Hemoglobin; Hct: Hematocrit; MCV: Mean corpuscular volume; RBC: Red blood cell

Table 2: Normal hematological values during the neonatal period of the term infant (hemoglobin, hematocrit and RBC count)

	<i>Hb (gm%)</i>	<i>Hematocrit (%)</i>	<i>RBC (million/ mm³)</i>
Cord blood	16.2 ± 3.6	46.66 ± 5.1	4.9 ± 1.2
12 – 18 hours	18.79 ± 2.8	49 ± 4.8	5.3 ± 0.8
72 hours	17.38 ± 3.0	46.9 ± 5.3	5.2 ± 0.6
7 days	17.0 ± 2.4	45.0 ± 4.0	5.0 ± 1.1
15 days	16.36 ± 2.2	43.4 ± 4.1	5.01 ± 0.9
20 days	14.17 ± 2.4	42.1 ± 3.8	4.7 ± 1.0

Table 3: MCV, MCH, MCHC and normoblast count

	<i>MCV (fl)</i>	<i>MCH (Pg)</i>	<i>MCHC (%)</i>	<i>Normo- blasts (cells/ mm³)</i>
Cord blood	113.04 ± 5.3	34.33 ± 1.4	33.9 ± 0.8	600 ± 186
12–18 hours	108.96 ± 5	35.1 ± 1.9	34.4 ± 0.6	283 ± 122
72 hours	98.54 ± 2.9	35.82 ± 0.8	34.9 ± 0.5	36 ± 48
7 days	96.0 ± 3.4	34.0 ± 1.0	34.6 ± 0.8	
15 days	95.5 ± 4.0	33.2 ± 9.0	34.54 ± 0.5	
28 days	96.1 ± 3.2	31.6 ± 0.93	34.2 ± 0.7	

- Fetoplacental transfusion
- Twin-twin transfusion
- Internal hemorrhage
- Iatrogenic blood loss

Increased RBC Destruction

- Intrinsic causes: Hereditary RBC disorders (rare), including:
 - RBC Enzyme defects (e.g. G6PD deficiency)
 - RBC membrane defects (e.g. hereditary spherocytosis)
 - Hemoglobinopathies (e.g. α -thalassemia)
- Extrinsic causes:
 - Immune hemolysis
 - Rh incompatibility
 - a. ABO incompatibility
 - b. Minor blood group incompatibility (e.g. Kell, Duffy)
 - c. Hemangiomas (Kasabach-Merritt syndrome)
- Acquired hemolysis:
 - Infection
 - Vitamin E deficiency (of historical interest, now it is very rare)
 - Drugs

Decreased RBC Production

- Anemia of prematurity due to transient deficiency of erythropoietin
- Aplastic or hypoplastic anemia (e.g. Diamond-Blackfan)
- Bone marrow suppression (e.g. with Rubella or Parvovirus B₁₉ infection)
- Nutritional anemia (e.g. iron deficiency), usually after neonatal period.

Hemorrhage

About 5 to 10 percent of the cases of severe neonatal anemia are due to hemorrhage and this may occur during prenatal, intranatal or postnatal period. Blood loss may be the result of occult hemorrhage before birth, obstetric accidents, internal hemorrhage, or excessive blood sampling for diagnostic studies. In an anemic newborn not having jaundice and a negative Coombs test, hemorrhage is the most probable cause (Table 4).

Prenatal Blood Loss

Transplacental fetomaternal blood loss: Spontaneous leakage of small amount of fetal Hb into maternal circulation occurs in 50 percent of all pregnancies, but in about

Table 4: Types of hemorrhage in the Newborn Period

<i>Occult Hemorrhage before Birth</i>	<i>Obstetric Accidents and Malformations</i>	<i>Internal Hemorrhage</i>
<ul style="list-style-type: none"> Fetomaternal Traumatic amniocentesis Spontaneous After external cephalic version Twin to twin 	<ul style="list-style-type: none"> Nuchal cord with placental blood trapping Rupture of normal umbilical cord Precipitous delivery Entanglement Hematoma of the cord or placenta Rupture of abnormal umbilical cord- Varices, aneurysm Rupture of anomalous vessels Aberrant vessel Velamentous insertion Vessels in multilobed placenta Incision of placenta during cesarean section Placenta previa abruptio placentae 	<ul style="list-style-type: none"> Intracranial Giant cephalohematoma Subgaleal Retroperitoneal Laceration of the liver Ruptured spleen Pulmonary

1 percent it is of sufficient magnitude to produce anemia in the infant. In general, a loss of 20 percent of the blood volume acutely is sufficient to produce signs of shock and is reflected in a fall in hemoglobin concentration within 3 hours. The frequency and magnitude of fetomaternal hemorrhage is increased by invasive procedures like amniocentesis and external cephalic version. Fetomaternal bleed is diagnosed by demonstrating fetal red cells in the maternal circulation by Kleihauer–Betke technique (Acid elution method of staining for fetal hemoglobin). But in presence of thalassemia minor, sickle cell anemia, hereditary persistence of fetal hemoglobin Kleihauer Betke test is not useful. In such cases differential hemagglutination should be employed. Similarly in ABO blood group incompatibility, diagnosis may be missed as infant's A or B cells are rapidly cleared from maternal anti-A or anti-B. The amount of blood lost in fetomaternal hemorrhage can be calculated by following formula:

$$\text{ml. of fetal blood} = \frac{\text{Fetal RBC} \times 2400}{\text{Maternal RBC}}$$

Presence of 1 fetal RBC per 1000 maternal RBC's indicates 2 ml of fetomaternal hemorrhage.

Transplacental bleed may be acute or chronic. The characteristics of acute and chronic blood loss in a newborn are listed in Table 5.

Retroplacental Bleed

Abnormally implanted placenta and placental malformation can cause retroplacental bleed. This can be diagnosed by examination of placenta in an anemic newborn. Accidental incision of the placenta during cesarean section can also cause massive fetal hemorrhage.

Twin to Twin Transfusion

In 13 to 33 percent of mono-chorionic twins, significant twin to twin transfusion occurs. This condition should be suspected if there is difference of hemoglobin of over 5 gram/dl between the twins. There is maximal discrepancy of 3.3 g/dl in cord hemoglobin in dizygotic twins. Typically

Table 5: Characteristics of acute and chronic blood loss in the neonate

<i>Acute blood loss</i>	<i>Chronic blood loss</i>
Pallor	Pallor
Shallow tachypnea	Signs of cardiac failure
Poor peripheral perfusion	Cardiac enlargement
Hypotension	Tachypnea
No organomegaly	Hepatomegaly
Normochromic microcytic anemia	Ascites
	Hypochromic, microcytic anemia
	Reticulocytosis

the donor twin is smaller, pale and may show evidence of heart failure, hydrops and shock. The recipient twin is larger and polycythemic and may manifest signs and symptoms of hyperviscosity syndrome, disseminated intravascular coagulation and hyperbilirubinemia.

Postnatal Blood Loss

Anemia that appears in first 24 to 72 hours of life and is not associated with jaundice is commonly caused by hemorrhage at the time of birth or by a postnatal hemorrhage. One of the commonest causes of obvious bleeding in the newborn is slipped ligature of the cord. Traumatic delivery, especially forceps and breech delivery, results in subgaleal (scalp) intracranial or intra-abdominal hemorrhage. An infant with internal bleed may appear well for first 24 to 48 hours, but may then suddenly go into shock. Hemophilia, vit. K deficiency and disseminated intravascular coagulation are also important causes of postnatal bleed.

Iatrogenic Anemia

Frequent sampling for diagnostic and monitoring purposes in neonatal critical care unit is a common cause of anemia in newborn, especially in the preterm babies. Removal of more than 20 percent of a subject's blood

volume produces anemia. 1 ml of blood represents about 1 percent of total blood volume in preterm babies. In a 1500 gram baby this represents a blood loss of only 25 to 30 ml. Thus, excess sampling should be avoided.

HEMOLYTIC ANEMIA

Premature destruction of RBC leads to hemolytic anemia. Hemolysis as a cause of anemia should be suspected in presence of rapid fall of hemoglobin concentration with reticulocytosis, unconjugated hyperbilirubinemia and hemoglobinuria without any evidence of hemorrhage. Abnormal erythrocyte morphology also points towards hemolytic process. Hemolysis can be due to immune mediated or non-immune mediated mechanism. Non-immune hemolytic anemia involves defects in either red cell membranes or hemoglobin or enzyme defects.

Nonimmune Mediated Hemolytic Anemia

- *Red cell membrane defects* such as hereditary spherocytosis, elliptocytosis stomatocytosis can cause significant anemia in newborn. A family history of chronic anemia, cholelithiasis, unhealed leg ulcers, splenomegaly may be present in case of hereditary spherocytosis. Examination of peripheral blood smear and osmotic fragility test is diagnostic in hereditary spherocytosis.
- *Hemoglobinopathies*: Defect or deficiency of production of globin chains results in hemolytic anemia. In the newborn period, α -globin defect tends to be the most common and most severe, because γ chain defects are exceedingly rare and β chain production does not usually peak until about 3 months of age. Homozygous alpha thalassemia is due to absence of all four alpha globin chains and is associated with severe intrauterine hemolytic anemia, hydrops fetalis with massive hepatosplenomegaly. Most affected children are stillborn, although some may live for few hours after birth. The red blood cell in alpha thalassemia is hypochromic, fragmented and bizarre in shape and erythroblastosis is also seen.

Gamma thalassemia: Large deletion within the beta globin gene cluster sometimes removes both gamma globin chains as well as delta and beta globin chain. The resulting gamma-delta-beta thalassemia is lethal in the homozygous state. In heterozygous state, it produces a transient but moderate to severe anemia but this anemia improves spontaneously within first six months of life and afterwards the hematological picture is like thalassemia trait.

RBC enzyme abnormalities: Most commonly encountered enzymopathy in newborn is sex-linked G-6PD deficiency and others are pyruvate kinase deficiency, 5' nucleotidase deficiency and glucose phosphate isomerase deficiency. In India G-6PD deficiency is common in Parsi, Bhanushali, Sindhi

and Punjabi communities. It can cause significant neonatal hemolysis resulting in anemia and hyperbilirubinemia due to exposure to known hemolytic agent and cases have been seen without any exposure to oxidant or infection. Normal value of G-6PD level during acute hemolysis may not rule out G-6PD deficiency as younger RBC's contain high level of enzyme. Hence, G-6PD level should be repeated after 6 weeks of an episode of hemolysis.

Infection: Both prenatal and postnatal infections cause anemia and other hematological abnormalities in the neonatal period. Intrauterine infections of *Toxoplasma*, cytomegalovirus, syphilis, rubella, malaria and parvovirus (TORCH) can cause hemolysis. The hemolytic process is due to direct injury to the red cell membrane. Congenital infection is suspected due to clinical findings of chorioretinitis, pneumonitis, central nervous system abnormalities, hepatosplenomegaly, growth retardation and skin changes. If the spleen is enlarged, hypersplenism can increase the rate of red cell destruction. Laboratory features include thrombocytopenia, leukocytosis with immature form and reticulocytosis. Postnatal acquired infection produce marrow suppression and hemolysis of RBC thereby causing anemia in newborn. Vertical transmission of malaria is rare. Features of malaria in a newborn are fever, irritability, hepatosplenomegaly with severe anemia and reticulocytosis.

Immune Mediated Hemolytic Anemia

The immune causes are mainly due to blood group incompatibility between fetus and the mother. This incompatibility may be Rh (D), ABO or minor blood groups such as anti-C, Duffy, anti-C, anti-E, Kell, etc.

- *Rh isoimmunization*: Placental transfer of maternal antibodies directed against fetal RBC is the cause of hemolysis of neonatal RBC. Clinical features of Rh isoimmunization are anemia, which may be mild to severe, jaundice, hepatosplenomegaly. Laboratory investigations reveal blood group incompatibility, reticulocytosis and increased number of nucleated RBC's in peripheral blood smear and positive direct Coombs test.
- *ABO incompatibility*: In ABO incompatibility, maternal Anti-A or Anti-B antibodies enter fetal circulation and react with A or B antigen on the erythrocyte surface. ABO incompatibility frequently occurs during first pregnancy without prior sensitization. Hemolysis due to ABO incompatibility is clinically milder than Rh incompatibility but severe hemolysis occurs occasionally. In most cases pallor and jaundice are minimal and hepatosplenomegaly is uncommon. Direct Coombs test is frequently negative but indirect Coombs test is positive. On peripheral smear, spherocytes are found so it is sometimes confused with hereditary spherocytosis.

Failure of Red Cell Production

Congenital

Pure red cell aplasia (Diamond Blackfan anemia), congenital sideroblastic anemia, congenital dyserythropoietic anemia (CDA), Fanconi's anemia are some of the causes of congenital anemia in newborn. Diamond Blackfan syndrome is characterized by the absence of recognizable erythroid precursor cells in bone marrow. Physical abnormalities associated with Diamond Blackfan syndrome are triphalangeal or duplicated thumb, cleft palate, ocular defect, short or webbed neck, hypertelorism, ptosis. Diagnosis is confirmed by demonstrating virtual absence of erythroid precursors in bone marrow. Fanconi's anemia usually does not manifest in the newborn period. Most patients of CDA are diagnosed in late childhood or adolescence, however some present in neonatal period with variable splenomegaly, jaundice and normocytic normochromic anemia.

Anemia of Prematurity

All infants experience a decrease in hemoglobin concentrations after birth, as the infant transitions from a relatively hypoxic state *in utero* to a relatively hyperoxic state in room air. Increased tissue oxygenation leads to a decline in erythropoietin (EPO) concentration and, for the term infant, a physiologic and usually asymptomatic anemia at age 8 to 12 weeks. Anemia of prematurity (AOP) is an exaggerated and pathologic response of the preterm infant to this transition. AOP is a normocytic, normochromic, hyporegenerative anemia that is characterized by the existence of a low serum EPO level in an infant who has what may be a remarkably reduced hemoglobin concentration. AOP results from a combination of relatively diminished RBC production, shortened RBC life span, and blood loss. Frequent sampling, low level of hematopoietic growth factors such as insulin like growth factor-1 and 2, nutritional deficiencies of iron, vitamin E, vitamin B₁₂, and folate may exaggerate the degree of anemia. The frequency of anemia of prematurity (AOP) is inversely related to the gestational age and/ or birth weight of the population. As many as 50 percent of infants of less than 32 weeks gestational age develop symptoms as a result of AOP. AOP spontaneously resolves by the time most patients are aged 3-6 months. Although the physiology and pathophysiology for AOP are well studied, controversy surrounds the timing, method, and effectiveness of therapeutic interventions for AOP. In term infant the hemoglobin level reaches its nadir of 9 to 11 gm/dL at approximately 8 to 12 weeks of life. The more immature the infant, the more is the likely development of AOP. AOP is not typically a significant issue for infants born beyond 32 weeks' gestation. The nadir of the hemoglobin level is typically observed when the tiniest infants are aged 4 to 8 weeks, with concentrations of 8 to 10 g/dL if birth weight was 1200 to 1400 gm, or 6 to 9 g/dL if birth weight was less than 1200 gm. Clinically these infants may

have tachycardia, tachypnea, feeding problems, decreased activity and apneic attacks. The factors operating in physiological anemia of term baby is also present in preterm baby, but are exaggerated. The response to anemia or hypoxia to hepatic erythropoietin synthesis in preterm baby is poor as compared to that in term baby. Early administration of iron (2-4 mg/kg/d) does not modify the course of early physiological anemia of prematurity but would prevent the occurrence of late physiological anemia at around 6 months of age. Anemia of prematurity is treated with recombinant human erythropoietin. The dose of erythropoietin is 75 to 300 units/kg/week subcutaneously for 4 weeks starting at 3 to 4 weeks of age.

Diagnostic Approach to Anemia in a Newborn

Medical history and physical examination can give a lead to the cause of anemia in a newborn. Family history of anemia, cholelithiasis, unexplained jaundice and splenomegaly points toward some hereditary hemolytic anemia. Obstetric history of difficult labor, instrumentation, bleeding or placental abnormalities correlate with hemorrhagic anemia. The age at which anemia becomes manifest also is of diagnostic importance. Significant anemia at birth is due to blood loss or alloimmunization. After 24 hours, internal hemorrhage and other causes of hemolysis manifest. Anemia of prematurity, hypoplastic anemia and abnormalities of synthesis of hemoglobin chain generally appear several weeks after birth.

Coombs test, reticulocyte count, mean corpuscular volume (MCH) and blood smear are the key investigative tools for diagnosing the cause of anemia in newborn. Flow chart 1 shows a flow diagram of investigation of anemia in newborn.

Prevention and Treatment of Anemia in Newborn

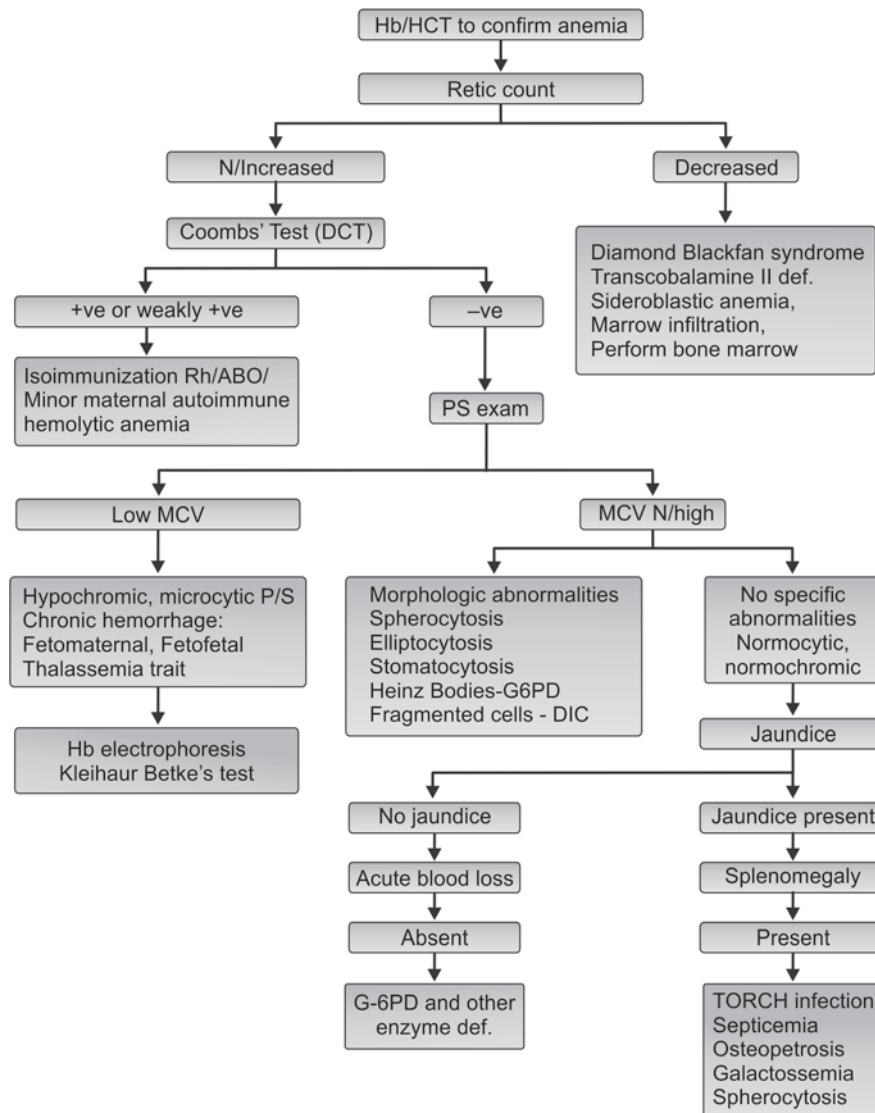
Prevention

In physiological anemia observed in infants born at term, the hemoglobin remains stable for several weeks and then increases progressively. Physiological anemia often presents without signs, and there is no need for RBC transfusions. In contrast, anemia of prematurity develops earlier (i.e. at four to 12 weeks of life) and may present with clinical signs such as tachycardia. In sick preterm infants, anemia of prematurity can be accentuated by non-physiological anemia. The most common cause of non-physiological anemia is blood loss, which may be acute or chronic. A common and potentially avoidable cause of postnatal blood loss is iatrogenic as a result of frequent blood sampling (phlebotomy) in sick preterm infants.

To prevent and reduce the severity of anemia, and to reduce donor exposure or the risks associated with RBC transfusions, strategies to consider may include:

- Delayed clamping of the umbilical cord;
- Restricting blood sampling;

Flow chart 1: Approach to neonatal anemia



- Using recombinant human erythropoietin to stimulate erythropoiesis;
 - Using iron supplementation or vitamins to minimize the severity of anemia;
 - Using appropriately collected and stored multipack RBC units;
 - Using appropriately screened and handled RBCs from regular or designated donors;
- Collecting and transfusing umbilical cord blood (autologous blood transfusion).

Iron Supplementation

Preterm infants exhibit a wide range of iron status at discharge, depending on their degree of prematurity, amount of transfusion, phlebotomy losses, number of RBC transfusions, bouts of infection, and timing of iron supplementation. Limiting phlebotomy losses and starting iron therapy at 2 weeks (as opposed to 2 months) of postnatal

age might be an effective preventive strategy against subsequent iron deficiency. The American Academy of Pediatrics recommends that preterm infants receive 2 to 4 mg elemental iron/kg per day; infants receiving EPO therapy should receive at least 6 mg/kg per day. After discharge, preterm infants continue to have increased iron needs because of rapid growth rate during the first postnatal year. There is a high rate of iron deficiency in preterm infants fed low-iron formula or breast milk. Recent data suggest that preterm infants with low serum ferritin concentrations might require additional iron supplementation. It might be prudent to supplement formula-fed preterm infants with iron at a dose of 1 mg/kg per day.

Prevention of Late Nutritional Anemia

Both term and preterm infants should be discharged from the hospital on supplemental iron, either as iron-fortified formulas or as an oral supplement of 2 to 3 mg/kg per day

elemental iron for breastfed infants. Enteral iron supplementation is feasible and probably safe in infants with birth weight <1301 g. Iron supplementation can reduce the incidence of iron deficiency and the number of late blood transfusions. Iron deficiency can occur in very low birth weight infants despite early supplementation with iron and should be considered in the case of progressive anemia. Because of their limited body supplies of water-soluble vitamins and their higher protein requirements, it is also prudent to supplement breastfed preterm infants at discharge with a multivitamin supplement containing vitamin B₁₂ and folate. It is important to monitor premature babies, especially after discharge, to diagnose late anemia in neonates.

Treatment of anemia in a neonate depends on the clinical condition. If the infant is in hypovolemic shock due to acute blood loss, 10-20 ml/kg of whole blood cross matched with mother should be transfused immediately through umbilical vein. In case of unavailability of cross-matched blood, O negative blood can be used. Asymptomatic anemic neonate with moderate hemorrhage or chronic blood loss does not require blood transfusion as such. The only therapy required for such a neonate is iron in the dose of 2 mg/kg three times a day for 3 months. Vit B12 and folate should also be supplemented in discharge to breastfed preterm infants. In severe anemia with congestive cardiac failure due to chronic blood loss partial exchange transfusion or packed cell transfusion is the treatment of choice. RBC transfusion is indicated for asymptomatic infant with venous hematocrit <20 percent and absolute reticulocyte count less than 3 percent. In hemolytic anemia main concern is hyperbilirubinemia, which may require phototherapy or exchange transfusion. Infants with ABO incompatibility not requiring an exchange transfusion for hyperbilirubinemia may have protracted hemolysis and may require RBC transfusion several weeks after birth.

In a hemodynamically unstable infant, hyaline membrane disease or severe bronchopulmonary dysplasia, hemoglobin level is maintained at the level of 12 to 14 gram/dl to improve oxygen delivery. Diamond Blackfan syndrome is managed with corticosteroids and blood transfusion. The criteria for transfusion of infants are given in Table 6.

Dose (Volume) of RBCs

In preterm neonates the small amount of research available suggests that large volume (20 ml/kg) RBC transfusions lead to larger rises in Hb and fewer overall transfusions than small volume transfusions (10 ml/kg). This volume of packed RBCs is well tolerated in the vast majority of preterm neonates.

Do not Transfuse

- To replace blood removal for laboratory tests alone or low hematocrit alone.

Table 6: Transfusions guidelines

Transfuse infants at hemoglobin less than 7

- No symptoms and an absolute reticulocyte count <1,00,000 cells/mL (RBC × % reticulocyte count)

Transfuse infants at hemoglobin <8 or less

No mechanical ventilation requirement and one or more of the following present:

- 24 or more hours of tachycardia (HR >180) or volumes if fluid sensitive) tachypnea (RR >80)
- An increased oxygen requirement from the previous 48 h
- An elevated lactate concentration (2.5 mEq/L or more)
- Weight gain <10 g/kg over previous 4 days while receiving 100 kcal/kg per day or more
- An increase in episodes of apnea and bradycardia (10 or more episodes in a 24-h period or 2 or more episodes in 24 h requiring bag-mask ventilation) while receiving therapeutic doses of methylxanthines
- Undergoing some surgery

Transfuse infants at Hemoglobin 10 or less

- Minimal mechanical ventilation requirement (any mechanical ventilation or CPAP > 6 cm H₂O and FiO₂ >0.4)

Transfuse infants at Hemoglobin 11 or less

- Moderate or significant mechanical ventilation requirement (MAP >8 cm H₂O and FiO₂ > 0.4)

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Approach to Bleeding in Neonate

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INTRODUCTION

Bleeding in the newborn is often a serious problem because of cardiovascular effects associated with a loss of blood and/ or the damaging effects of bleeding on neonatal tissues, especially the brain. Forty years ago, hemorrhagic disease of the newborn occurred in 1 to 2% of newborn babies.¹ With vitamin K administration routinely administered following birth, this problem is now rare in the normal newborn.² Babies in the neonatal intensive care unit (NICU) more commonly have abnormal bleeding or conditions that increase the risk of bleeding (e.g. thrombocytopenia with platelet count less than $100 \times 10^9/L$ occurs in 12 percent of babies in the NICU.³

CLINICAL ASSESSMENT

Bleeding in the newborn may be manifested by signs of shock, anemia, signs related to pressure from 'hidden' bleeding (e.g. intraventricular hemorrhage), or bleeding from the gastrointestinal tract, respiratory system or skin.⁴ With bleeding from the gastrointestinal tract, it is important to distinguish bleeding in the baby from swallowed maternal blood (an Apt test will distinguish fetal from adult hemoglobin).

First important task to do after identifying that the neonate is bleeding is to ensure the cardiorespiratory stability. A diagnosis to aid in more specific management may then be made.

HEMOSTATIC FUNCTIONS IN NEWBORN

Due to physiological immaturity there are both quantitative as well as qualitative differences in hemostatic functions in newborn as compared to older children.

Primary Phase of Hemostasis

- *Capillary fragility:* Though capillary fragility is normal in term infants, it is increased in preterms therefore vasoconstriction following injury is incomplete in them⁵ and hence intracranial hemorrhage is more common in premature babies.
- Platelet count in both term and preterm babies is similar to that in older child. However, platelet function such as adhesion, aggregation and release of factors like ADP and Thromboxane A2 are abnormal. Exact clinical significance of this defective qualitative function is not known.

Secondary Phase of Hemostasis

Coagulation factors are not transferred transplacentally from mother to the baby and hence the values estimated in newborn reflect the synthesis of the various factors in them.⁶

- At term, levels of factors V, VIII, are equivalent to older children and adults and hence if deficiency of these factors is present during newborn period then it suggests inherited factor deficiency in them.⁷
- Levels of factors II, VII, IX, X are decreased more so in preterm babies due to hepatic immaturity and poor availability of Vit. K. Hence hemorrhagic disease of newborn is more common in premature babies.⁷
- Clotting activities of all factors involved in initial activation of intrinsic pathway is decreased in varying degrees in the newborn, i.e. factor XII, XI, preKalliekrien, high molecular weight kininogen. More immature the infant, the lesser is factor XII activity. Reduced concentrations of factor XII, XI are partly responsible for prolongation of activated partial thromboplastin time so commonly observed in low birth weight infants.

- Factor XIII level in cord blood is 50 percent of that in adults, but as only small amount of factor XIII is required for its activation or clot stabilization, this low value in newborns have no clinical significance.⁷

Fibrinolytic Activity

In newborn it is transiently increased as compared to adults or older children. It declines to adult level by 6 hours in term child. Plasminogen levels are only half that of an adult. FDP is normally absent in healthy preterm and term infants. This low level of plasminogen along with physiological deficiency of circulating anticoagulants like antithrombin III, protein-C promotes thrombotic tendencies in neonates.

Neonates are thus susceptible for both hemorrhage and thrombotic tendencies. This paradox is due to a combined deficiency on one hand in coagulation factors and defective platelet function and decreased levels of natural inhibitors of coagulation and fibrinolysis on the other.

Role of Vitamin 'K' in Neonatal Hemostasis

Vitamin 'K' plays a crucial role in neonatal hemostasis. Vit. K is not required for synthesis of factors but is required for gamma carboxylation of glutamic acid residues of the protein precursors of the factors II, VII, IX and X which are synthesized in liver. These protein precursors are termed as PIVKA, i.e., proteins in absence of vitamin K activity. It is only after gamma carboxylation that these proteins acquire the ability to chelate calcium and to be subsequently activated during coagulation. This action of vitamin 'K' is limited in preterm, as precursor proteins themselves are deficient, often below 30 percent of adult value⁷ as immature liver is incapable of optimal synthesis of many of precursor proteins.

ETIOLOGY OF BLEEDING IN NEONATE

Bleeding in a neonate may be due to.^{5,8,9}

- Vascular abnormalities, e.g. in prematurity – intracranial hemorrhage.
- Platelets abnormalities: Quantitative platelet disorders include Immune thrombocytopenic purpura—child born to mother with SLE or ITP. Isoimmune thrombocytopenia—PIA +ve childborn to PIA –ve mother. Qualitative platelet disorders include drugs like aspirin given to mother and inherited disorders of platelet function like Glanzmann's thrombasthenia, Bernard Soulier syndrome.
- Exaggeration of transient deficiency of coagulation factors
 - Hemorrhagic disease of newborn.
- Transitory disturbances of coagulation mechanism as a result of associated systemic disease process, e.g. sepsis, liver disease, DIC, etc.

- Inherited permanent abnormality of coagulation factors, e.g. Hemophilia A & B, Von-Willebrand disease etc.
- Trauma alone or often associated with other factor deficiencies—slipped ligature, cephalhematoma, etc.

AN APPROACH TO THE BLEEDING NEWBORN

One must assess the total clinical setting because the history and clinical examination are as important as the laboratory findings. One must ask about the familial bleeding tendencies, maternal illnesses especially infections, medications both maternal and neonatal and documentation that vitamin K was given at birth.⁸ The general observation whether the child was 'sick' or 'well' at the onset of bleeding is very important. Certain hemorrhagic tendencies occur almost exclusively in 'sick' neonates. (babies with sepsis, shock, hypoxia, acidosis, hypoglycemia). On the other hand, bleeding manifestations in otherwise 'well' infants (normal birth weight, alert, vigorous, no evidence of any systemic disease) are usually due to classic hemorrhagic disease of newborn or immune-mediated thrombocytopenia or isolated clotting factor deficiencies. The physical examination further defines the nature of bleeding disorder. Petechiae or purpura in the skin are more characteristic of thrombocytopenia, while bleeding from injury sites (e.g. circumcision, heel lance) or the gastrointestinal system suggests other coagulation defects.

LABORATORY ASSESSMENT

Laboratory investigation should include an activated partial thromboplastin time (APTT), prothrombin time (PT) (or more commonly international normalized ratio [INR] to standardize for different reagents) and complete blood count with platelet count. Additionally, all sick newborns should have fibrinogen and fibrin degradation products (FDP) measured.⁴ Blood should preferably be taken from a venous site. Capillary samples are more prone to errors, with clotting in samples including platelet clumping. Although blood from an arterial line may be used if measures are taken to minimize heparin contamination and protamine is used to neutralize any heparin that may be present,¹⁰ this should be reserved for situations when other blood samples cannot be obtained.

Coagulation tests should be ordered whenever the cause of bleeding is not clear. Reference values for coagulation tests at varying ages are available. In general, the following are considered abnormal:

- PT 17 s or more
- INR 1.5 or greater
- APTT 60 s or greater (preterm 80 s or greater in first day of life)
- Fibrinogen less than 1.5 g/L
- FDP present
- Platelet count less than $1,00,000 \times 10^9/L$

While an INR 1.4 or less (or normal PT) rules out vitamin K deficiency, abnormalities in APTT without other evidence of DIC may require more detailed investigation. Measuring factor VIII may help distinguish DIC (low) from liver dysfunction (normal or high), although factor VIII may also be congenitally deficient. In many of these situations, consultation with a hematologist with pediatric experience is advisable to guide investigation and management.

Diagnosis and management of maternal thrombocytopenia may include intravenous immunoglobulin (IVIG), steroids and rarely fetal transfusion in an endeavor to minimize potential adverse effects on the fetus, especially intracranial hemorrhage.⁴ While thrombocytopenia in the newborn is relatively common, it is not always associated with bleeding. Thrombocytopenia has varied etiology (Table 1).^{11,12} Diagnosis may be helped by the microscopic examination of platelet size. Large platelets are more indicative of platelet consumption with new large platelets entering the circulation, while only small platelets may indicate disordered bone marrow function.¹¹ Flow cytometry may be used to look for reticulocytes and immunoglobulins on the surface of platelets. If thrombocytopenia

in the baby is otherwise unexplained, a maternal platelet count is useful.¹¹ Alloimmune thrombocytopenia may be suspected on the basis of a low platelet count in the absence of other etiologies or the absence of response to a platelet transfusion. More specific platelet typing and investigation for antiplatelet antibodies may be required. Investigation for uncommon qualitative defects in platelet function requires specialized tests usually in consultation with a hematologist. Table 2 shows the approach to a newborn with bleeding on the basis of physical examination, PT, APTT and platelet count.

VITAMIN K DEFICIENCY BLEEDING

Since the most common cause of a bleeding neonate is Vitamin K deficiency, it needs to be discussed in detail.

The term Hemorrhagic Disease of the Newborn (HDN) was coined by Charles Townsend in 1894 to describe bleeding in the early days of life which was not caused by traumatic delivery or hemophilia.¹³ The different causes of such bleeding were then unknown. HDN later came to mean bleeding due to Vitamin K (VK) deficiency but still implied a condition confined to neonates. The specific term Vitamin K Deficiency Bleeding (VKDB) was therefore adopted by the Perinatal Subcommittee of International Society on Thrombosis and Hemostasis (ISTH). VKDB is defined as bleeding due to inadequate activities of VK-dependent coagulation factors (II, VII, IX, X), correctable by VK replacement.¹³

Diagnostic criteria laid down by ISTH subcommittee are as follows—in a bleeding infant prolonged prothrombin time (PT) together with normal fibrinogen level and normal platelet count is highly suggestive of VKDB. Rapid correction of PT after VK administration is confirmatory.¹³ The subcommittee also added that acarboxy proteins—PIVKA (proteins induced in vitamin K absence)—are

Table 1: Common causes of thrombocytopenia

Increased destruction	Disseminated intravascular coagulation Localized (thrombosis, hemangiomas, necrotizing endocarditis)
Decreased production	Trisomy 13, 18 or 21 Fanconi anemia Syndromes (e.g., Wiskott-Aldrich, thrombocytopenia, absent radius (TAR))
Other or mixed	Rh disease Exchange transfusion Extracorporeal membrane oxygenation

Table 2: Approach to the differential diagnosis of bleeding neonate

<i>Laboratory investigations</i>				
<i>Health status</i>	<i>Platelets</i>	<i>INR (PT)</i>	<i>APIT</i>	<i>Possible diagnosis</i>
Sick	↓	↑	↑	Disseminated intravascular coagulation (usually low factor VIII)
	↓	N	N	Platelet consumption (infection, necrotizing enterocolitis, renal vein thrombosis)
	N	↑	↑	Liver disease, heparinization (usually normal factor VIII)
	N	N	N	Altered vascular integrity (e.g. extreme prematurity, severe hypoxia and acidosis)
Healthy	↓	N	N	Immune thrombocytopenia, occult infection or thrombosis, abnormal bone marrow function
	N	↑	↑	Hemorrhagic disease of the newborn (vitamin K deficiency)
	N	N	↑	Hemophilia
	N	N	N	Bleeding due to trauma or anatomic abnormalities, qualitative platelet abnormalities

↑ Increased; ↓ Decrease; APTT: Activated partial thromboplastin time; DIC: Disseminated intravascular coagulation; INR: International normalized ratio; N: Normal

present in these cases.¹³ In India and other developing countries such stringent diagnostic criteria may be difficult to follow. Fibrinogen and PIVKA estimation are usually not available. A deranged PT which gets corrected after VK administration should be enough to label the cases as VKDB. The inclusion age for VKDB was extended to 24 weeks.¹³

Early Vitamin K Deficiency Bleeding

E-VKDB has its onset in first 24 hours of life. It is classically described in babies born to mothers who are malnourished or are receiving drugs which interfere with VK activity. Due to transplacental transfer of these drugs, the VK dependent factor levels of the neonate may get reduced. These drugs include anticonvulsants (phenytoin, barbiturates and carbamazepine but not valproate), antitubercular drugs (isoniazid and rifampicin but not pyrazinamide) and VK antagonists (warfarins and phenprocoumons). The incidence of VKDB in babies born to mothers on these drugs have varied between 6 to 12 percent.¹³⁻¹⁵ E-VKDB often presents with serious life-threatening intracranial, intrathoracic, intra-abdominal or gastrointestinal bleeding particularly so if the delivery has been difficult.

Classical Vitamin K Deficiency Bleeding

Classical VKDB as described by Townsend¹³ begins in the first week excluding the first 24 h, usually between days 3 and 5 and in babies with delayed or inadequate feeding. Estimates of the frequency vary from 0.5 to 1.5 percent. Bleeding is usually from the umbilicus, the gastrointestinal tract and skin punctures and may cause significant blood loss. Surgical procedures such as circumcision unmask subclinical cases of VKD.¹³ Intracranial hemorrhage (ICH) is rare but can cause significant morbidity or death.

Late Vitamin K Deficiency Bleeding

Late VKDB begins on or after day 8, most often between weeks 2 and 8 but can occur up to 6 months. According to presence of associated factors, the disease is classified as primary-if no factor other than exclusive breast-feeding is identified and secondary-when other associated factors are present. The associated factors are cystic fibrosis, α -1-antitrypsin deficiency, biliary atresia, hepatitis, chronic warfarin exposure and celiac disease.¹⁶⁻¹⁸ Liver diseases have been associated in 73 to 90 percent cases and the cases are reported with bleeding being the first manifestation. Bleeding manifestations in these cases may be in the form of minor skin bleeds or mucosal, gastrointestinal, umbilical bleeding or bleeding from skin injection sites or on surgical intervention. Intracranial and other life-threatening bleeds are also very common.^{19,20} These serious bleeds at times are preceded by milder bleeds—the so called “warning bleeds” such as umbilical oozing, skin bleeds, etc.

Laboratory work up in VKDB, PT and APTT both are prolonged (diagnostic criteria include only prolongation of PT) and platelet count is normal. The activity of VK dependent factors II, VII, IX and X is decreased.¹³ Fibrinogen levels are normal. PIVKA are present and their presence is useful in diagnosis of cases who might have received VK because PIVKA remain detectable even after VK administration. Rapid correction of PT within 30 to 120 minutes of VK administration of VK is diagnostic of VKDB.

Treatment of VKDB

Replacement of VK is the treatment required. Intravenous or subcutaneous administration of 2 to 5 mg VK is recommended. Intramuscular administration should be avoided as it may result in hematoma formation.

VK-Prophylaxis: In most centers 1 mg of intramuscular VK is given at birth as VK prophylaxis for VKDB. Oral and intramuscular VK (one dose of 1 mg) protect equally well against classical VKDB but intramuscular VK is more effective in preventing late VKDB. It is due to the short half-life of VK because of which levels of VK decrease very rapidly. By 2 weeks VK levels in normal breastfed infants given 1 mg VK1 orally at birth are approximately 0.8 ng/ml, and subsequently fall to unsupplemented levels.¹³ So, repeated doses should be given orally. Oral VK prophylaxis is best provided by weekly oral doses of 1 mg VK or by daily oral doses of 25 to 50 μ g for 3 months.

MANAGEMENT OF A BLEEDING NEONATE

Firstly the cardiorespiratory stability should be checked in the baby with bleeding. In addition to ensuring adequate vitamin K, many coagulation factor abnormalities may be corrected with intravenous administration of 10 to 15 mL/kg fresh frozen plasma.¹ Use of cryoprecipitate may be indicated with factor VIII deficiency (congenital or acquired with DIC) and/ or hypofibrinogenemia. The potential hazards of transfusion of blood products should be kept in mind. The risks may be lessened by the use of heat-inactivated products and with appropriate blood banking procedures. The complications of continued bleeding are potentially more severe. Although no well controlled studies are available, suggestions have been given regarding indications for platelet transfusion.^{4,12} The following guidelines may be considered:

- For premature infants, platelet count of less than $50 \times 10^9/L$ in a stable infant as clinically assessed and platelet counts of less than $100 \times 10^9/L$ in a bleeding infant or if surgery is anticipated; and
- For term infants, platelet count less than $30 \times 10^9/L$ in a stable infant and platelet count less than $50 \times 10^9/L$ if there is bleeding or need for an invasive procedure.

More liberal criteria (e.g. platelets less than $100 \times 10^9/L$) may be used for platelet transfusions when bleeding is severe (e.g. DIC). Other therapy such as the use of IVIG for neonate alloimmune thrombocytopenia may also be helpful.¹²

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Hypothermia in Newborns

Avneet Kaur

Temperature control is essential to survival, and studies since 1950s have shown that neonates with hypothermia have poor outcomes. Despite all that is known about heat loss in infants, hypothermia continues to be a significant problem especially in VLBW infants. A newborn baby is physiologically homeothermic and his ability to stay warm may easily be overwhelmed by extremes of environmental temperatures. Neonatal hypothermia often due to lack of attention by health care providers continues to be a very important cause of neonatal deaths.

THERMOREGULATION IN NEWBORN

Fetal temperature is approximately half a degree (centigrade) higher than maternal temperature *in utero*. This temperature relationship (fetus > mother) results from a combination of endogenous heat production by the fetus and the surrounding core temperature of the mother. To dispose of excess endogenous heat, the fetus temperature must be greater than maternal core temperature, creating the necessary temperature gradient to support heat transfer. At birth, heat is lost rapidly secondary to the cold external environment and significant evaporative heat losses. Studies from the 1970s demonstrate that core body temperatures drops 0.1°C per minute which is equivalent to a heat loss of 200 kcal/kg/minute. The body temperature of premature infants drops precipitously after birth because of their disproportionate body mass-to-surface ratio, exposed body posture, decreased amounts of subcutaneous fat, poor vasomotor control, and thin skin with increased permeability. Indeed, despite attempts to reduce heat loss in the delivery room, data collected by the Vermont Oxford Network demonstrate that 27.8 percent of VLBW infants have admission temperatures less than 36°C. Unless someone gives immediate attention to heat loss, the neonate's temperature can drop approximate

4.5°C (8.1°F) during the first minute after birth. Because the infant is dependent on environmental temperature, providing thermal support is a primary nursing objective.

RESPONSE TO COLD

Muscular Activity

During exposure to cold, baby feels uncomfortable, cries and makes some movements of limbs but the effort is not sustained. Shivering does occur but is minimal especially in LBW babies and appears only when the environmental temperature falls below 25°C. Thus muscular activity is not a significant source of heat production.

Metabolic Thermogenesis

Nonshivering thermogenesis, as a result of metabolism of the brown fat, is the most important source of heat production in the newborn. The fetal brown fat is laid down mostly during the third trimester of pregnancy and is located at the nape of the neck, interscapular region, axillae, groin and around kidneys and adrenals. Brown fat is characterized by a rounded nucleus, granular cytoplasm with a large number of mitochondria (with yellow mitochondrial cytochromes) and fat vacuoles. This fat is metabolically very active in view of a large number of mitochondria and increased vascularity.

When the skin of the baby becomes cold, afferents convey the message to the heat regulating center located in the preoptic anterior hypothalamic area near the walls of the third ventricle. Neurogenic efferents, on reaching the brown fat, trigger the local release of noradrenaline so that triglycerides are oxidized to glycerol and fatty acids. The blood level of glycerol rises but fatty acids are locally consumed for the generation of heat. About 30 percent of nonesterified fatty acid are oxidized to generate heat, 60

percent are re-esterified and 10 percent are released in the circulation. The areas of brown fat become warm and heat is distributed to various parts of the body through blood stream. It is obvious that the baby would need extra oxygen and glucose for this metabolic effort in order to keep itself warm. Effective metabolic thermogenesis demands integrity of central nervous system pathways, adequacy of brown fat and availability of glucose and oxygen.

Thermoneutral Environment

The narrow range of environmental temperature at which a given baby can maintain normal body temperature with minimal oxygen consumption (and possibly minimal fuel consumption) is called thermoneutral temperature or zone of thermal comfort. This is the ideal temperature at which the babies should be nursed to achieve optimal somatic and brain growth. The baby is most comfortable and sleeps better when nursed in this temperature. This is also called as the zone of thermal comfort. An isolated measurement of body temperature may fail to indicate whether a baby is being subjected to a thermal stress or not. Even when the environmental temperature deviates beyond the thermoneutral range, the infant tries to maintain his body temperature by increasing oxygen consumption and heat production. A fall in the environmental temperature merely by 2°C below the neutral range, triggers infant's metabolic machinery to generate 25 percent additional heat. The environmental temperature at which the metabolic response becomes necessary is called the critical temperature. In a clinical setting, thermoneutral temperature can also be defined as that as a narrow range of environmental temperature in which a baby can maintain core temperature between 36.7°C and 37.3°C and his mean core and skin temperature does not change more than 0.2°C and 0.3°C per hour respectively when recorded continuously by an electronic thermometer.

Heat Loss (Fig. 1)

Newborn loses heat by:

- Evaporation particularly soon after birth (amniotic fluid from skin surface)
- Conduction (contact with cold objects cloth, tray, etc.)
- Convection (by air currents—cold air replaces warm air around baby—open windows, fans)
- Radiation (to colder solid objects in vicinity-walls).

Hypothermia (Fig. 2)

Hypothermia in a newborn is defined as a core temperature of <36°C. When core temperature is between 36 and 36.5°C it is known as cold stress. The difference in core and peripheral temperature is more than 1.5°C and extremities are cold and pale. Babies in cold stress have poor growth velocity as glucose is wasted for metabolic thermogenesis. Moderate hypothermia is diagnosed as core temperature

ranges between 32 and 35.9°C while a core temperature of <32°C is designated as severe hypothermia.

Risk Factors for Hypothermia

Situations contributing to excessive heat loss: Cold environment, wet or naked baby, cold linen, procedures like surgery. Increased airflow currents coupled with low humidity causes greater convective and evaporative losses.

Poor ability to conserve heat: Preterm and small for date infants have poor thermoregulation due to:

- High surface area and decreased subcutaneous tissue
- Decreased brown fat
- Decreased glycogen stores
- Inability to reduce effective surface area by assuming flexed posture and poor muscle tone.

Poor Metabolic Heat Production

- Central nervous system damage due to anoxia, intracranial hemorrhage and malformations interfere with the integrity of neurogenic pathways for stimulation of brown fat
- Hypoxia
- Hypoglycemia
- Deficiency of brown fat, e.g. preterm and small for dates babies.

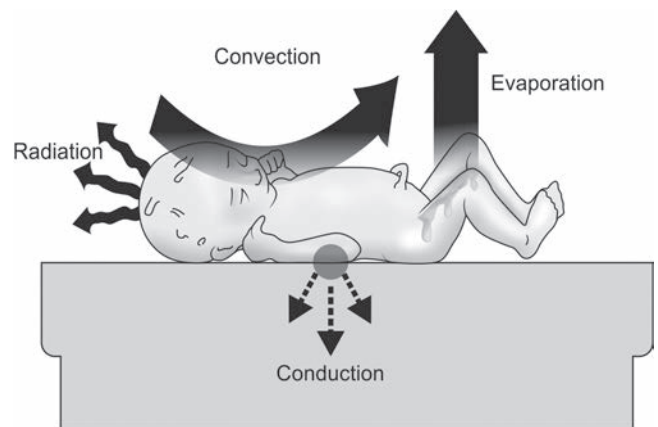


Fig. 1: Various mechanisms of heat loss

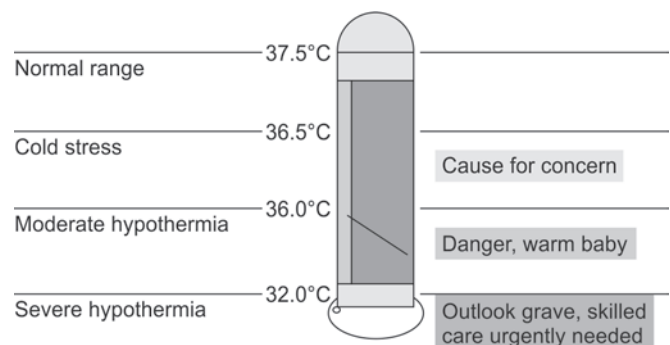


Fig. 2: Definition of neonatal body temperature variations

Clinical Manifestation and Consequences of Hypothermia (Flow Chart 1)

Numbers of manifestations are seen if thermal environment is below the neutral range of environmental temperature. The baby is uncomfortable, restless, and cries to generate muscular activity. Next the baby may become inactive and sluggish. Skin feels cold to touch and is mottled. Weak cry, poor feeding, bradycardia, shallow respiration, apnea, fall in blood pressure are other manifestations. Weight gain is unsatisfactory due to loss of energy in heat production rather than tissue growth.

The immunological system is depressed with enhanced susceptibility to develop sepsis, sclerema, DIC. Biochemical derangements include hypoglycemia due to increase glucose consumption during thermogenesis. Metabolic acidosis occurs due to anaerobic metabolism. There is rise in serum potassium and BUN levels following tissue catabolism.

Management of Hypothermic Newborn

Hypothermic babies should be rewarmed measures for warming infant includes:

- Ensuring infant is dry. Remove all wet towels.
- Radiant warmer or incubator can be used for rewarming. Set the desired temperature on the radiant warmer or incubator. Set the desired skin temperature on the radiant warmer or incubator and allow the baby to rewarm (set skin temperature at 36.5°C in skin

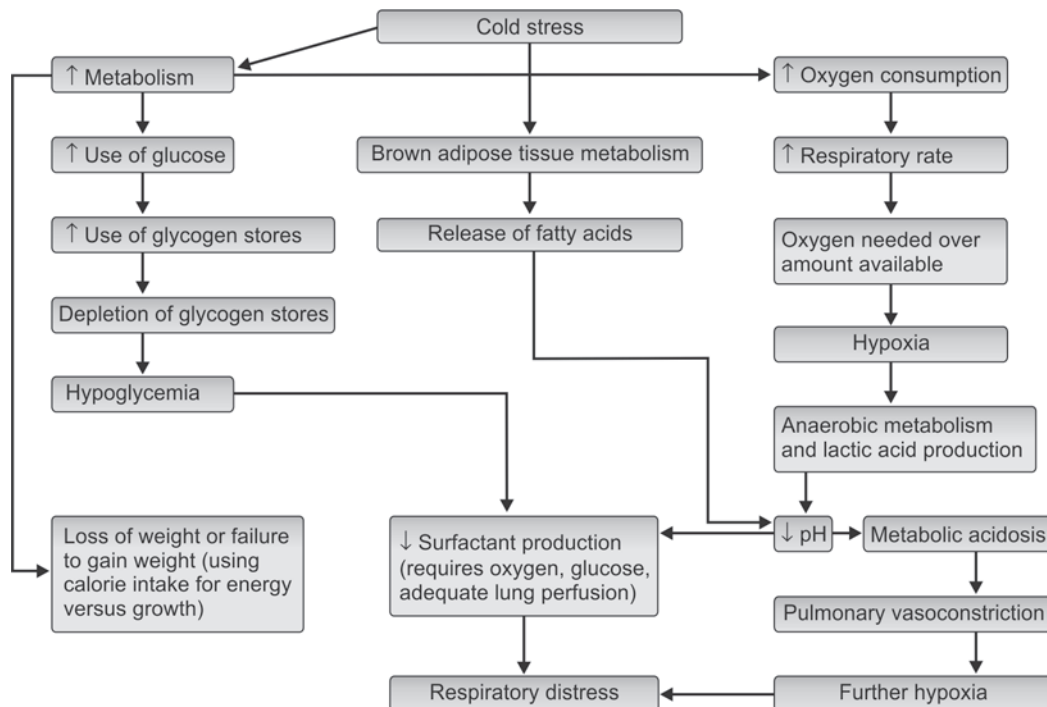
servo mode/or set air temperature at 35 to 36°C in air servo mode).

- Monitor temperature, oxygen saturation with pulse oximeter, CFT and blood sugar.
- In absence of a radiant warmer or incubator, a heating lamp kept at least 50 cm away from infant can be used. Warm blankets, cotton wool, hot water bags may be used under supervision.
- Providing supervised KMC, skin—skin contact is best method to rewarm a baby with hypothermia especially during transport.

Supportive Care

- Prompt detection and management of hypoxia, hypoperfusion and hypoglycemia.
- Dextrose infusion at 6 to 8 mg/kg/min and injection K should be given if not given at time of birth.
- If perfusion is poor give 20 ml/kg of ringer lactate or normal saline over 15 to 20 min. Provide oxygen in case of moderate to severe hypothermia
- Watch for apnea, hypoxia and hypoglycemia during rewarming. Very rapid rewarming can cause apnea. If an infant becomes apneic during rewarming, rate of rewarming should be slowed. Once the temperature reaches 34°C, the rewarming process should be slowed down to avoid overheating. On occasion it may be necessary to halt the warming process completely for a period to allow the infant to adjust to the new conditions, even though infant may still be hypothermic.

Flow chart 1: Physiological consequences of cold stress



Prevention of Hypothermia

Delivery Room

One basic mechanism to prevent heat loss is manipulation of the environmental temperature. Environmental temperature refers to the aggregate influence of the environment on body temperature. Delivery rooms are sometimes kept at a temperature comfortable for the mother and staff with little consideration of the newborn. This results in greater temperature gradients between the infant and the air (increased convective losses) and cool walls (increased radiant losses). Interventions that increase air temperature in delivery area reduce convective and radiant heat loss. Prewarming of surfaces and items coming in contact with the infant will result in reductions in conductive heat losses. Table 1 provides recommended delivery room temperatures on the basis of gestational age.

Heat Loss in Postnatal Ward and During Transport

Ensure that baby is kept warm with appropriate clothing and skin-to-skin contact with mother. Change wet clothing promptly and keep baby dry. Keep windows closed and cover baby adequately. Continue breastfeeding day and night. If a baby needs to be transferred inform NICU at least half an hour before the transfer so that radiant warmer is switched on to maintain thermoneutral environment. The simplest way to transport is by doing kangaroo mother care. If baby is unstable a transport incubator is preferred. If transport incubator is not available, thermocol box or plastic box with holes may be used. If baby is on oxygen ensure that it is adequately warm and humidified. If baby is not on IV fluids, feeding should be continued during transport. If mother is accompanying baby breastfeeding every 1 to 2 hours can be offered and if mother is not accompanying, careful spoon feeding or gavage feeding could be offered.

Kangaroo Mother Care

Kangaroo mother care is a nonconventional method of caring of low birth weight and preterm newborns. The major components of KMC are:

- Skin-to-skin contact. Babies are kept, day and night, between the mother's breasts firmly attached to the chest in an upright position

- Frequent and exclusive or nearly exclusive breastfeeding
- Early discharge from hospital regardless of weight or gestational age. Respiratory, thermal and feeding stabilization are crucial for the success of this intervention. Prolonged skin-to-skin contact between the mother and her preterm/LBW infant, as in KMC, provides effective thermal control and may be associated with a reduced risk of hypothermia.

Temperature Regulation in NICU

Healthy infant over 34 weeks can be adequately nursed fully clothed, in a cot, in a warm centrally heated room. Ambient room temperature should be 28 to 30°C for all babies. Smaller babies and mature, but ill infants, require a more controlled thermal environment. It is important to further reduce heat loss by controlling all 4 methods of heat exchange. To reduce conductive heat loss, it is recommended that any surface in direct contact with the infant be prewarmed. This includes radiant warmers, incubators, in-bed scales, blankets, wraps, clothing, thermal mattresses, and X-ray plates. Reduction in convective heat loss requires a warm environmental temperature without drafts and the need for warm gases for respiratory support. Evaporative heat loss can be controlled by drying the infant using a prewarmed wrap and hat, providing a humidified environment, and using humidified oxygen. Heat shielding mechanisms like polyethylene wraps, plastic heat shields can be tried. Epidermal barrier protections like aquaphor or emollients have also been used. When placing umbilical catheters utilize a clear plastic sterile drape during the procedure to prevent radiant heat transfer. Although radiant heat loss cannot be totally eliminated, radiant warmers along with measures to prevent other types of heat loss may improve outcomes in VLBW infants.

Radiant Warmer

Radiant warmers provide intense source of radiant heat energy. They also reduce the conductive heat losses by providing a warm microenvironment surrounding the baby. The overhead quartz heating element produces heat which is reflected by the parabolic reflector on to the baby on the bassinet. The quantity of heat produced is displayed in the heater output display panel. This system in which the heater output is determined automatically based on skin temperature information is called *servo system* or manually using *manual mode* of operation.

Convection Warmed Incubators

A modern incubator consists of an optically transparent, plastic hood (3 mm thick) covering the infant, with sidewall and hand-access ports. The infant lays on a bed platform, underneath which a tungsten element electronically heats the air. Air is forced over this element by a fan,

Table 1: Recommended stabilization room temperatures (based on PMA and birth weight)

Estimated postmenstrual age, week	Estimated birth weight, g	Delivery/stabilization room temperature
≤ 26	≤ 750	78-80°F
27-28	751-1000	
29-32	1001-1500	≥ 72°F (goals 75°F)

circulating heated air within the hood. Temperature may be controlled thermostatically to regulate either the air or infant skin temperature. Incubators are widely used for the care of low-birth-weight (LBW) and sick newborns. These devices have numerous advantages, in particular they provide a clean, warm environment in which the temperature and humidity may be controlled, and oxygen may be supplied when necessary. Furthermore, incubators allow easy observation of the naked neonate, and his/her isolation. However, infant incubators have also a number of disadvantages that should be carefully considered. In fact, these devices are expensive, have high running costs, and are potentially hazardous to the baby. Additionally, incubators create a barrier between mother and neonate, which delays bonding and makes breast feeding difficult and also makes difficult access for procedures.

Radiant Warmer Over Incubator

Advantages

- Easy accessibility
- Easy to connect the tubes of ventilated baby and do procedures
- Better monitoring especially if the baby has respiratory distress
- Less risk of infection as compared to closed incubator
- Can be used as resuscitation trolley in the labor room.

Disadvantages

- More insensible water losses
- Not uniform heating as compared to closed system
- More risks of episodes of hypothermia.

In a Cochrane review comparing cot nursing versus incubator for preterms, four studies (179 neonates) were included. The researchers followed the infants' body temperature, weight gain and whether or not they were breastfed. In one study, the cot nursed infants had a higher mean body temperature in the first week of life. Another study showed less weight gain for infants in cots when in a heated room for the first week of life. Higher numbers of infants cared for in cots were breastfed when leaving the health care facilities in a study from Ethiopia. Due to the small numbers of trials included and infants studied, and the resulting imprecision in the measures of effect for all

outcomes, the review does not give a clear indication for the role of cot-nursing for preterm infants.

Humidity

In addition to the air temperature, it is important to control humidity. The evaporative heat loss is very high with dry, draughty air and can lower the infant's core temperature below that of the surrounding air. It is easier to prevent hypothermia by reducing transepidermal water losses (TEWL) than by increasing heat production (Fig. 3). The epidermal barrier matures rapidly over the first 2 weeks of life. Nothing is known to accelerate this maturation process. However, we can alter TEWL by altering relative humidity (RH). At 100 percent RH, TEWL is zero because there is no water vapor pressure gradient driving water loss. An RH of 90 percent will result in a fall of the total body water loss of 45 percent for VLBW infants. At 80 percent to 90 percent RH, the decrease of evaporative skin cooling impedes the fall of body temperature with increase in weight, and decreased fatality in VLBW infants. When RH is raised TEWL will be low regardless of the effectiveness of the infant's epidermal barrier. Earlier there were reports of increased risk of infections with high humidity however no proven data is available. Humidity should be commenced in all infants born at <31 weeks gestation. If <27 wk then start humidity with 85 percent. Set humidity 75 to 85 percent for at least the first 14 days then gradually reduce humidity (5% daily) (Table 2).

Double Percent Walled Versus Single to Walled Incubator

The structural characteristics of incubators may also play a role in maintaining an optimal thermal environment for the newborn. Double-walled incubators, which direct warm air between the inner and outer incubator walls, have been shown to reduce radiant heat loss through the reduction of temperature gradients between the infant and its environment. A recent Cochrane review provided evidence that double-wall incubators compared to single wall incubators decrease both heat loss and oxygen consumption in VLBW infants, but was unable to support the proposition that double-wall incubators have a beneficial effect on long-term outcomes including mortality or the duration of hospitalization.

Table 2: Humidity based on gestation age and day of life

Days	1	2	3	4	5	6	7	8	9	10-15
<28 wk	80%	80%	80%	80%	80%	75%	75%	70%	60%	55-40%
	1	2	3	4	5	6	7	8	9	10
28-30 wk	75%	75%	75%	70%	65%	60%	55%	50%	40%	30%

(Humidity should be reduced with respect to gestation and temperature stability)

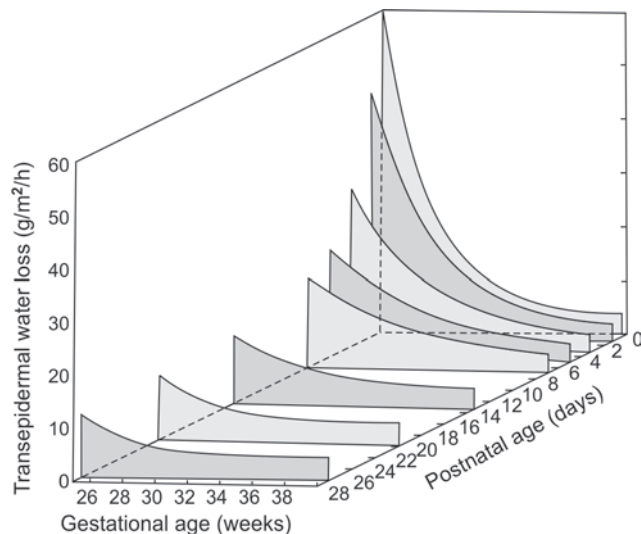


Fig. 3: Transepidermal water evaporation from the skin of premature neonates of gestations ranging from 25 to 40 weeks, followed longitudinally from birth over the first month of life. Dehydration is most dangerous in the most immature babies less than 28 weeks of gestation in the first week of life before skin keratinization occurs. (From Sedin G, Hammarlund K, Nilsson GE, et al. Measurements of transepidermal water loss in newborn infants. *Clin Perinatol* 1985; 12: 79-99, with permission.)

Weaning from Incubator to Cot

Weaning from isolette to open crib can be accomplished by manually lowering the incubator's ambient temperature. The infant should weigh at least 1500 grams, have five days of consistent weight gain, should be tolerating enteral feedings as well as an ambient temperature of less than or equal to 31°C and be free of medical complications. The infant's abdominal skin temperature should be 36 to 37°C (96.8-98.6°F) in order to wean to open crib.

Polyethylene Wrap in the Delivery Room

Studies have shown that using a plastic wrap made of polyethylene in babies immediately before or after drying can further minimize evaporative and convective heat losses. Radiant heaters are often used as the sole source of thermal care in the delivery room although they cannot achieve a positive energy balance to warm the premature infant immediately after birth. Occlusive wrap has been clearly established through 4 randomized controlled trials, involving 300 infants, and a Cochrane review, as effective in preventing hypothermia ($<36.5^{\circ}\text{C}$) in premature infants younger than 29-week gestation in the delivery room and significantly improving admission temperatures. A 2005 systematic review found that occlusive wrap significantly improved admission temperature and significantly reduced hypothermia. Occlusive wrap permits heat gain by the infant through radiation and reduces the amount of evaporative heat loss. Studies show decreased mortality in

infants who were cared for using plastic wrap and hat. Polyethylene wrap has shown to reduce insensible water loss by 70 percent and improve temperature control. Despite the use of polyethylene wraps, VLBW infants continue to have problems with hypothermia in the first few days of life and polyethylene wraps must be used in combination with other thermoregulatory measures. Polyethylene wrap placed on VLBW infants before drying in the delivery room may produce a microhumidified environment and improve TEWL and temperature control. The poorly developed epidermal barrier in VLBW infants leads to high TEWL, percutaneous absorption, and trauma. High TEWL leads to poor temperature control and difficulty in fluid balance. It can and should be reduced by manipulation of the ambient humidity and by covering the skin. The wrap serves as a shield for the infant and forms a barrier keeping higher ambient air humidity under the wrap. Once an infant is wrapped in the delivery room, it is essential to maintain that wrap. Reports have shown that infants in NICUs may be manipulated by health care providers up to 30 percent of the total day. The thermal microenvironment may be significantly altered by frequent wrap removal. For example, Lyon et al reported that a reduction in skin temperature of more than 1°C can result in thermal stress, which may lead to hypovolemia. Heat loss has been shown to be minimized by the humidified microenvironment for reasons discussed earlier. Relative humidity that builds up in the microenvironment underneath the wrap will drop quickly when the infant is unwrapped, TEWL will increase at the same time, and the infant's body temperature will fall. It may take a while once closed for humidity to increase again. The clear plastic wrap allows the provider to observe and assess the infant. It is essential for health care providers to learn techniques to effectively wrap the infant so that unwrapping is unnecessary even for procedures such as umbilical catheters. Despite advances in technology, 31 to 78 percent of VLBW infants exhibit cold body temperatures after delivery room stabilization, and improvement in care remains a significant challenge to the health care team. In 2005, the American Academy of Pediatrics and the American Heart Association recommended that polyethylene bags in the delivery room be considered for prevention of heat loss in VLBW infants. Optimizing delivery room temperatures combined with the use of occlusive skin wrap may be the best method for decreasing hypothermia in VLBW infants.

Transwarmer Mattresses

There has only been 1 small study evaluating the use of the transwarmer mattress in VLBW infants in the delivery room. Although this trial demonstrated improved admission temperatures in the mattress treated group, the study is too small to make recommendations.

Further studies are needed looking at the addition of transwarmer mattresses with wrap to ensure iatrogenic hyperthermia and burning are avoided. There may be a use for this type of warmer during transport in a cohort of infants who, despite maximal thermoregulatory control, still arrive cold in the NICU.

Hats

Heat exchange between the uncovered head and the environment is very high. Use of stockinet caps has not been shown to improve core body temperatures in VLBW infants and currently there are 2 studies evaluating woolen hats and showing an improvement in temperature in the first 30 minutes of life. A Cochrane review looking at measures to reduce hypothermia concluded that hats had only a minimal effect in reducing heat loss from the head. There have been no studies looking at the effect of hats in VLBW infants. One issue is that currently available hats prevent heat from escaping but do not prevent evaporative heat loss. In infants wrapped in plastic bags, the large surface area of the infant's head remains available for evaporative heat loss. About 50 percent of the total heat loss is through the head. One small study evaluated the use of a polyurethane-lined hat and was able to show a reduction in cranial heat loss between 63 percent and 72 percent. It is clear that the use of stockinet or cotton hats does not provide adequate thermoregulatory support for VLBW infants. The addition of the plastic wrap under the hat may make a significant difference in heat loss and improve thermoregulation in VLBW infants. Development of strategic wrapping techniques by delivery room staff to place the wrap under the hat may decrease thermal losses.

Warm Chain Ten Commandments

Warm chain should be maintained for maintenance of newborn's temperature. The warm chain is set of ten interlinked procedure carried out at birth and during the following hours and days which will minimize the likelihood of hypothermia in all newborns:

- *Warm delivery room:* Maintain delivery room temperature 25°C (28 ± 2)
- *Warm resuscitation:* Use warm equipment and sheets for resuscitation
- *Immediate drying:* Dry baby thoroughly immediately after birth, take care not to ignore head, axilla and groin. Discard the wet sheet used for drying baby and wrap baby in another dry and warm sheet.
- *Skin-to-skin contact between mother and baby:* Keep baby in between mother's breast in skin to skin contact this helps to keep baby warm.
- *Breastfeeding:* Initiate breastfeeding early, preferably within half an hour of birth.
- Bathing and weighing postponed
- Appropriate clothing and bedding

- Mother and baby together (rooming in)
- Warm transportation
- Training and awareness of health care providers.

Hypothermia as Neuroprotection

Neuroprotection with brain-specific therapies has been well studied in the preclinical arena over the past 20 years, with the aim of blocking or dampening the cascade of events triggered by hypoxia and ischemia. Brain hypothermia is a promising therapy for neuroprotection against encephalopathy presumably due to hypoxic-ischemia.

Mechanism of Action of Hypothermia

- Reduces cerebral metabolism, prevents edema
- Decreases energy utilization
- Reduces/suppresses cytotoxic amino acid accumulation and nitric oxide
- Inhibits platelet-activating factor, inflammatory cascade
- Suppresses free radical activity
- Attenuates secondary energy failure
- Inhibits apoptosis (cell death)
- Reduces extent of brain injury.

Various randomized, controlled trials and one large pilot study have been published evaluating hypothermia as neuroprotection for term and near-term infants who have HIE. The multicenter Cool Cap Study involved 243 infants who had moderate or severe encephalopathy and abnormal aEEG amplitudes and were either cooled to a temperature of 34.0 to 35.0°C for 72 hours or treated with temperature maintenance in the normothermia range with conventional care. The primary outcome of the study was death or disability at 18 months. Cooling was provided by selective head cooling and mild systemic cooling. Death or severe disability occurred in 66 percent of infants randomized to conventional care and 55 percent randomized to the cooled group (odds ratio [OR] 0.61, 95 percent confidence interval [CI] 0.34 to 1.09, $P < 0.10$). The effect of head cooling for infants who had the most severe aEEG changes was not protective, but the effect of head cooling for infants who had less severe aEEG changes ($n = 172$) was protective (OR 0.42, 95% CI 0.22 to 0.80, $P < 0.009$). The large randomized, controlled pilot study performed at seven centers of 65 infants involved moderate systemic whole body hypothermia to 33.0°C for 48 hours compared with normothermia maintained at 37.0°C. The safety report of this pilot study documented that infants in the hypothermia group had more significant bradycardia, longer dependence on pressor medications, higher prothrombin times, more seizures, and need for more plasma and platelet transfusions. At 12 months of age, death or severe motor scores were documented in 52 percent of the hypothermia group compared with 84 percent of the normothermia group ($P < 0.02$). In a subgroup analysis, out

born infants were more likely to die than inborn infants (OR 10.7, 95% CI 1.3 to 90.0). The National Institute of Child Health and Human Development (NICHD) Neonatal Research Network trial of whole-body hypothermia for infants who had moderate and severe encephalopathy randomized 102 infants to hypothermia to 33.5°C for 72 hours and 106 control infants to conventional care. The primary outcome was death or moderate/severe disability at 18 months of age. The infants in the hypothermia group had significantly lower heart rates than the infants in the control group throughout the 72-hour intervention period.

There was no significant difference in systolic or diastolic blood pressure between groups. The frequency of adverse events during study intervention was low: one infant in each group had arrhythmia, two infants in the hypothermia group had acidosis, three infants in the hypothermia group and two control group infants had bleeding, and four cooled infants had altered skin integrity. The primary outcome was noted in 44 percent of infants in the hypothermia group compared with 62 percent of infants in the control group, with a risk ratio of 0.72 (0.54 to 0.95). There was a trend for cooling to benefit infants in both moderate and severe encephalopathy groups. The Cool Cap and the NICHD Whole Body Hypothermia Trial used different entry criteria, distinguished primarily by the use of the aEEG in the Cool Cap trial. The mode of cooling used in each trial was different and it is not known if one cooling regimen is superior to the other. The primary outcomes were not defined in a similar manner in the two trials. Although not powered to evaluate moderate or severe encephalopathy separately, decreases in death and moderate/severe disability were seen in the whole body cooling trial in both the moderate and severe encephalopathy groups. The primary outcome of each trial was the combined end point of death or disability; hypothermia therapy did not salvage infants who had severe disabilities and would have died in the absence of the intervention. The rate of disabling cerebral palsy was reduced from 31 percent in the control group to 18 percent in the Cool Cap Study and from 30 percent in the control to 19 percent in the whole-body cooling trial of the NICHD Network.

Meta-analyses of Trials

Three independent systematic reviews have concluded that therapeutic hypothermia significantly reduces both death and disability after perinatal encephalopathy and is safe and that outcomes are homogeneous both within and between trials (Tables 3 and 4).

Gaps in Knowledge

All of the current published trials have evaluated hypothermia as a neuroprotective strategy with the primary

Table 3: Meta-analysis of hypothermia for term infants who have encephalopathy

<i>Outcome</i>	<i>Relative risk (95% confidence interval)</i>
Death or moderate/severe disability	
Shah 2007	0.76 (0.65 to 0.88)
Schulzke 2007	0.78 (0.66 to 0.92)
Jacobs 2007	0.76 (0.65 to 0.89)
Mortality	
Schulzke 2007	0.75 (0.59 to 0.96)
Jacobs 2007	0.74 (0.58 to 0.94)
Moderate/severe disability	
Schulzke 2007	0.72 (0.53 to 0.98)
Jacobs 2007	0.68 (0.51 to 0.92)

Table 4: Stage of HIE and response to therapeutic hypothermia

	<i>Death or disability: cooled</i>	<i>Death or disability: control</i>
Moderate HIE		
Whole body cooled		
NICHD trial	32%	48%
Cool Cap trial	45%	57%
Severe HIE		
Whole body cooled		
NICHD trial	72%	85%
Cool Cap trial	70%	91%

outcome of death or disability at 18 months of age. To assess efficacy in childhood, assessments of school-age outcome are being evaluated in the Cool Cap and NICHD Network Trial. The role of cranial imaging in predicting outcome among infants undergoing hypothermia is being evaluated from magnetic resonance imaging studies obtained in the NICHD trial. The role of initiating hypothermia beyond 6 hours of age in term infants is being examined because evidence suggests that effects of brain injury following hypoxia-ischemia in the preclinical model continues beyond the 6-hour therapeutic window. Hypothermia as neuroprotection for the 34 to 36 weeks' gestation neonate who has encephalopathy also is being investigated. The impact of hypothermia initiated during transport at less than 6 hours of age has not been demonstrated. The optimum depth and duration of cooling for demonstrating greater neuroprotection is unknown. Head cooling versus whole body cooling which is better is not known. Hypothermia in resource poor setting is still being evaluated. The role of pharmacologic agents used in conjunction with hypothermia as neuroprotection for hypoxic-ischemic brain injury is being investigated in preclinical studies. Of note, disability is high with severe HIE in spite of therapeutic hypothermia.

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Neonatal Abstinence Syndrome

Arun Soni, Saurabh Singh

INTRODUCTION

A newborn infant born to a mother addicted to opioids is at risk for drug withdrawal. At delivery, the discontinuation of opioids from the maternal circulation can lead to a constellation of withdrawal symptoms known as the neonatal abstinence syndrome (NAS).

The term opioid refers to natural and synthetic substances with morphine-like activity. Opiate refers to a subclass of opioids consisting of alkaloid compounds extracted from opium, including morphine, codeine, heroin, and methadone.

EPIDEMIOLOGY

Data from India is not available. In one study from California, the reported prevalence of maternal opioid drug use at the time of delivery was one percent.¹

Among infants with prenatal exposure to opioids, withdrawal will occur in 42 to 94 percent of infants.²⁻⁷ There appears to be a dose-response relationship because several studies have shown an increased risk of neonatal withdrawal and severity of symptoms as the cumulative maternal doses of opioids increase during the last trimester of pregnancy.^{3,8-11} However, in contrast, one large retrospective report of 330 women treated with methadone found no correlation between maternal methadone dose and rate of NAS.¹²

A recent retrospective study of 232 infants born to opioid dependent mothers identified perinatal risk factors for neonatal withdrawal. The data suggest that timing of delivery, mode of delivery, and last maternal methadone dose are significant risk factors for the development of NAS requiring treatment.¹³

In the United States, heroin and methadone are the most common opioids that infants are exposed to

prenatally. In the general population, heroin is the most commonly abused opioid. Because withdrawal of opioids from the mother is associated with significant fetal distress and demise, medical detoxification is rarely attempted and pregnant women need to be maintained on an opioid. For addicted pregnant women, methadone is the drug of choice because it is easier to administer and manage than other opioids.

CLINICAL MANIFESTATIONS

Newborn infants who withdraw from opioids present with a well-recognized constellation of symptoms known as the neonatal abstinence syndrome.¹⁴ These findings include:

- *Central nervous system:* Tremors, irritability, increased wakefulness, high-pitched cry,¹⁵ hypertonicity and hyperactive reflexes, seizures, yawning, sneezing, and skin excoriation due to excessive rubbing. In addition, they are more likely to have benign neonatal sleep myoclonus compared to infants without NAS.¹⁶ In the absence of other neurological findings, this condition requires no further evaluation or treatment.
- *Gastrointestinal:* Poor feeding, uncoordinated and constant sucking, vomiting or regurgitation, loose or watery stools, dehydration.
- *Autonomic/metabolic signs:* Increased sweating, nasal stuffiness, fever, temperature instability, tachypnea, and mottling of the skin.

Withdrawal from heroin is usually apparent within 48 hours after birth and with methadone 48 to 72 hours after birth. However, withdrawal may be delayed as late as four weeks with both drugs.¹⁴

In addition, infants born to mothers who are substance abusers are at risk for preterm birth and intrauterine growth restriction.¹⁷

Evaluation of *in utero* opioid exposure to premature infants <35 weeks gestation is more complicated because these infants appear to have decreased severity of withdrawal symptoms compared to term infants.³ Possible explanations of the decrease in symptomatology in preterm compared to term infants may be due to developmental immaturity of the preterm central nervous system (e.g. dendritic ramifications, specific opiate receptors, or neurotransmitter function), or reduced total drug exposure during the intrauterine period.

DIAGNOSIS

The diagnosis of prenatal opioid exposure is based upon a history of positive opioid identification in either a maternal or neonatal specimen. If there is a negative or no maternal screening, neonatal screening of meconium or urine samples is indicated in infants with maternal or infant characteristics known to be associated with drug use in pregnancy.¹⁴

Infants who have clinical findings that are suggestive of NAS should be screened.¹⁸

Meconium drug testing is more sensitive than neonatal urine testing in identifying fetal exposure to opioid drug use.² Urine screening of the newborn has a low sensitivity (high false-negative rate) because only infants with recent exposure will have a positive test. The ability to detect *in utero* drug exposure was reported to be similar in umbilical cord tissue compared to meconium samples.¹⁹

DIFFERENTIAL DIAGNOSIS

Other common neonatal problems may have similar features to the neonatal abstinence syndrome (NAS). This includes infantile colic, infections (such as sepsis), and metabolic abnormalities (such as hypocalcemia, hypoglycemia, and hypothermia). Clinical signs should not be attributed solely to withdrawal without appropriate assessment and diagnostic tests (such as screening of opioid exposure, complete blood count, blood cultures, and electrolytes) to differentiate these diseases from NAS.

MANAGEMENT

The goal in an infant who is not irritable, has no vomiting or diarrhea, can feed well and sleep between feedings, and yet is not heavily sedated. Neither give naloxone to these infants nor to one whose mother was on methadone it may precipitate immediate withdrawal or seizures.

Scoring Systems

Several abstinence scoring methods (e.g. Lipsitz tool, neonatal abstinence scoring system, and the neonatal withdrawal inventory) have been developed based upon the clinical manifestations of NAS.²⁰⁻²² These tools measure the severity of neonatal withdrawal and can be used to guide

management. In each clinical setting that cares for infants with NAS, an abstinence scoring system should be adopted as it provides a semiobjective and standardized assessment of the patient's withdrawal symptoms. Scoring systems are used to initiate, adjust, and wean pharmacologic therapy.

The neonatal abstinence Finnegan scoring system is the most widely used of these methods and assesses 31 specific clinical items.²¹ Pharmacologic therapy is generally started with three or more scores above eight. Each institution decides upon the number of consecutive scores below a threshold value for initiation of weaning. It is also mandatory to observe the infant for 2 to 3 days before discharge.

Supportive care: The initial treatment of NAS should be supportive, because pharmacologic therapy may not always be needed and will prolong hospitalization. Supportive care includes:¹⁴

- Decreased sensory stimulation (e.g. quiet room with low lighting and swaddling of the infant)
- Administer small frequent feedings
- Administer calorically dense formula (24 cal/oz) or fortified breast milk (for mothers on methadone) to supply additional calories. Estimated caloric intake for adequate growth ranges from 150 to 250 cal/kg per day because of the infant's increased metabolic needs.¹⁴

Breastfeeding: Breastfeeding by mothers who continue to abuse heroin is not recommended because heroin is excreted into breast milk resulting in adverse effects on the infants.²³ Breastfeeding by mothers who continue to use methadone appears to be safe.²³ Monitor weight and readjust dietary intake to ensure appropriate growth. Poor weight gain in the face of adequate caloric intake may reflect the need to introduce pharmacologic intervention as well as increase the pharmacologic doses being utilized.

- Monitor temperature stability, sleeping patterns, and gastrointestinal symptoms (e.g. diarrhea and vomiting). The presence and persistence of these findings may indicate the need for pharmacologic therapy.

Skin care: The best approach to prevent skin excoriation due to excessive rubbing is to swaddle the infant, thereby reducing trauma to the skin.

In those patients with skin excoriation, routine skin care includes keeping the area clean, dry, and open to the air. Topical barrier creams used to treat diaper dermatitis may also be applied to affected areas to protect the skin and prevent further damage.

Pharmacologic therapy: Pharmacologic intervention is aimed at the short-term improvement of clinical symptomatology. Long-term benefits from treatment, in the symptomatic infant, still remain unproven.

Indications for pharmacologic therapy: Infants with confirmed prenatal drug exposure who are asymptomatic or respond to supportive care do not require pharmacologic treatment.

Indications for drug therapy include:¹⁴

- Seizures
- Poor feeding with failure to gain weight, especially when adequate calories are being ingested
- Inability to sleep
- Fever unrelated to another source
- Significant diarrhea and/or vomiting resulting in weight loss or hypovolemia.

If an abstinence scoring method is utilized, pharmacologic treatment is initiated when the assessment of the infant's symptoms exceeds a predetermined score.

Opioid therapy: If pharmacologic treatment is necessary, opioid therapy is recommended. In a meta-analysis of randomized or quasi-randomized controlled studies, opioid therapy (morphine, paregoric, or methadone) was compared to supportive care alone or sedative treatment (Phenobarbital or diazepam).²⁴ Results of the same were as follows:

- In one study, opioid therapy compared to supportive care alone reduced the time to regain birth weight and duration of supportive care. Opioid therapy increased the duration of hospital stay. Infants included in this study had three consecutive scores on the Neonatal Abstinence Scoring System that exceeded the predetermined score indicated for treatment.
- In an analysis of four studies, there was no difference in treatment failure rate in infants treated with opioid compared to those who received Phenobarbital.²⁶⁻²⁸ In three of the four studies, inclusion criteria were based upon the infant exceeding a predetermined score on a NAS scoring system indicating requirement for treatment.^{25,26,29} In a subset analysis of one of the studies, opioid compared to phenobarbital therapy reduced treatment failure in infants with only prenatal opioid exposure.²⁹ In one of these studies, opioid therapy resulted in a shorter duration of therapy (8 versus 12 days).²⁶ There was no difference in the duration of treatment or hospital stay in two of the other studies.^{25,29}
- One study reported a small reduction in the incidence of seizures with opioid therapy compared to phenobarbital.²⁷
- One study reported a significant reduction in treatment days and nursery admissions in infants who received morphine.²⁵
- In an analysis of two studies, there was a reduction in treatment failure in patients who received opioid therapy compared to diazepam (RR 0.36, 95% CI 0.18 to 0.69).

A second meta-analysis compared sedative therapy (phenobarbital, chlorpromazine, and diazepam) to one another or to supportive therapy alone.^{30,31} Results are as follows:

- Phenobarbital compared to supportive care alone does not reduce treatment failure or the time required

to regain birth weight but reduced the duration of supportive care.

- In two studies, phenobarbital compared to diazepam reduced treatment failure.
- There were insufficient data on the use of chlorpromazine or clonidine to be able to recommend either drug in the treatment of infants with NAS.

These results suggest that opioid therapy is better at reducing the symptoms of withdrawal compared to phenobarbital therapy or supportive care alone in infants with significant withdrawal symptoms. However, caution should be exercised, as these studies were limited because many of the infants were exposed to more than one drug of abuse and the long-term effects of opioid therapy are unknown. Despite these concerns, opioid therapy should be used in infants who, despite supportive care, continue to have significant withdrawal symptoms. If a sedative agent is required then Phenobarbital is the preferred medication. Chlorpromazine or clonidine should only be used in the context of a clinical trial because there are insufficient data demonstrating that they are effective in the treatment of NAS.³¹

There are several different forms of opioid therapy, which include the following:¹⁴

- Neonatal morphine solution (NMS): Morphine sulphate is diluted in a concentration of 0.4 mg/ml in distilled water. Dosing scheme is as under

Score	Neonatal morphine solution
8-10	0.8 ml/kg/d divided q 4 hrly
11-13	1.2 ml/kg/d divided q 4 hrly
14-16	1.6 ml/kg/d divided q 4 hrly
17 or greater	2.0 ml/kg/d divided q 4 hrly; increase by 0.4 ml increments until controlled

Once an adequate dose has been found, and infant scores have been <8 for 72 hours, wean by 10 percent of total dose daily. If weaning results in scores >8, restart the last effective dose. Discontinue NMS when the daily dose is <0.3 ml/kg/d. If the scores are low, make sure that the infant is not over sedated.

- Tincture of opium is also referred to as deodorized opium tincture and DTO. The preparation that is used to treat NAS is a 25-fold dilution and contains the same concentration of morphine equivalent as paregoric.
- Paregoric contains anhydrous morphine (0.4 mg/ml) and is also referred to as camphorated tincture of opium. The use of this therapy has decreased because of its additional ingredients. These include antispasmodics (noscapine and paverine), ethanol (high concentration of 45 percent), and the additive benzoic acid (which may compete with bilirubin binding sites).

- Morphine, both parental and oral preparations are available for use in infants with NAS.
- Methadone.

A survey of academic neonatology centers in the United States reported a wide variation in the treatment of infants with NAS pharmacologic treatment.³² The majority of these sites initially used an opioid, most commonly tincture of opium, or morphine sulfate solution or methadone.³² Paregoric and methadone are the opioids most commonly used to treat NAS.³³

If the infant has been exposed to multiple drugs in utero including opioids, opioid therapy should be used if the infant has symptoms of withdrawal.¹⁴

Adjunct therapy: The use of adjunct therapy has been suggested in infants with severe NAS or in those who have been exposed to multiple drugs.

- *Phenobarbital:* Phenobarbital has been added to opioid therapy in infants with severe NAS and in infants exposed to multiple drugs. In one study, the combined use of opioid and phenobarbital therapy compared to opioid therapy alone reduced the length of hospital stay and duration of symptoms.³⁴
- *Clonidine:* Clonidine is used in older children and adults for opioid withdrawal. In a clinical trial of 80 neonates with intrauterine exposure to methadone or heroin, the addition of oral clonidine (1 µg/kg every four hours) versus placebo to standard opioid therapy decreased the duration of pharmacologic therapy (11 versus 15 days).³⁴ Higher doses of opioid therapy were needed in the placebo group. There were no significant short-term complications (e.g. hypertension, hypotension, bradycardia, or oxygen desaturations) in either group. There were three deaths in the clonidine group (myocarditis, sudden infant death syndrome, and homicide). Although, the authors state the deaths were not attributable to combined therapy with clonidine, further trials are needed to demonstrate the efficacy and safety of this therapeutic regimen.

Naloxone: Naloxone may precipitate rapid withdrawal symptoms,³¹ and therefore should be used with caution in the infant exposed prenatally to opioids. In the delivery room, the use of a small dose of naloxone has been suggested for apneic infants who have been exposed to opioids in utero.⁷

However, in most infants whose mothers received opioids during labor, naloxone is not required. This was illustrated in a prospective study that determined the frequency of naloxone administration after the introduction of resuscitation guidelines for neonatal naloxone administration in the delivery room.³⁵ Of the 1000 total births, 434 mothers (43%) received an opioid during labor but only 1 infant received naloxone after delivery. Thirty-six

infants of mothers who received opioids developed respiratory symptoms. In one case, respiratory symptoms may have been due to maternal opioid administration. This infant did not receive naloxone. In the remaining 35 cases, opioid exposure was ruled out as a cause of neonatal respiratory distress.

If naloxone is used, the clinician needs to be aware of the potential risk of rapid withdrawal and be prepared to treat the infant if they become symptomatic.¹⁴

New 2010 NRP guidelines does not recommend routine administration of Naloxone:

Opioid therapy is begun in patients with symptoms that exceed a predetermined level on an abstinence scoring system despite supportive care. The choice of opioid therapy is physician dependent. The dose of opioid therapy is determined by the response of the patient. If the patient remains symptomatic, an increase in drug dose is indicated. Once the patient responds to therapy and a decrease in withdrawal symptoms and weight gain is established, medication can be weaned. Understanding that there are increased metabolic demands of the patient who is withdrawing becomes an important parameter to follow while making decisions in weaning the opioid. The rate of wean is dependent on the patient's clinical status. Use of abstinence syndrome scoring method facilitates this process.

Long-term outcome: It has been difficult to ascertain the long-term effects of prenatal opioid exposure on the developmental outcome of affected children because of confounding variables. These include prenatal factors, such as other drug exposures, prematurity, and low birth weight, and postnatal factors, such as care provider's socioeconomic and educational level.

There have been reports of developmental and behavioral problems in both prenatal methadone and heroin exposed children. However, these studies have had small numbers of patients and confounding risk factors making it difficult to determine the primary contribution of prenatal drug exposure to abnormal outcome.^{36,37}

In contrast, other studies have reported normal outcome as evaluated by the Bayley scales of infant development at six months and one year of age.^{38,39} Another report of in utero opioid exposed infants compared to patients without *in utero* exposure, which controlled for socioeconomic status and birth weight, reported that the amount of prenatal care and the postnatal home factors were more predictive of the infant's developmental performance at two years of age than prenatal drug exposure.⁴⁰

Further large studies controlled for confounding medical and socioeconomic factors are required to determine whether *in utero* opioid exposure has an independent adverse effect on development.

Table 1: Neonatal abstinence score

[illegible]

SUMMARY

1. A newborn infant born to a mother addicted to opioids is at risk for drug withdrawal. These infants present with a constellation of withdrawal symptoms known as the neonatal abstinence syndrome (NAS).
2. Heroin and methadone are the most common opioids that infants are exposed to *in utero*. Withdrawal from heroin is usually apparent within 48 hours after birth and with methadone from 48 to 72 hours after birth. However, withdrawal may be delayed as late as four weeks with either drug.
3. The diagnosis of *in utero* opioid exposure is based upon a positive identification of an opioid in either a maternal or neonatal specimen. Neonatal screening of meconium or urine samples is indicated if maternal or infant characteristics known to be associated with drug use in pregnancy are present and/or if the infant exhibits symptoms suggestive of NAS.
4. Other common neonatal problems including colic, sepsis, and hypoglycemia, have similar features to the neonatal abstinence syndrome (NAS). Careful clinical assessment and diagnostic tests (e.g. neonatal screen for NAS, complete blood count and blood cultures for sepsis, or serum blood glucose level for hypoglycemia) help differentiate NAS from these disorders.
5. It is unclear whether there are any long-term adverse effects on neurodevelopmental outcome in children who were exposed to prenatal opioids.

Treatment—Management of infants with NAS includes:

1. Evaluation of the severity of NAS and response to treatment. We suggest the use of an abstinence scoring method to measure the severity of neonatal withdrawal and guide management.
2. *Supportive care:* Initial treatment of NAS is supportive, because pharmacologic therapy may not be needed and will prolong hospitalization. Supportive care includes decreasing sensory stimulation, providing adequate nutrition for the infant's increased metabolic needs, and assessing the need for pharmacologic therapy (e.g. monitoring temperature stability, sleeping patterns, and gastrointestinal function).
3. *Pharmacologic therapy:* Pharmacologic therapy is indicated for infants who have seizures, weight loss or failure to gain adequate weight, inability to sleep, or fever. If an abstinence scoring method is utilized (Table 1), pharmacologic therapy is initiated when the infant exceeds a predetermined symptomatic score.
4. If pharmacologic treatment is necessary, the initial drug of choice should be an opioid. There are no controlled studies comparing the different forms of opioid therapy including tincture of opium, paregoric, morphine, and methadone. The choice of opioid agent is physician dependent.

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Evaluation of the Hypotonic Neonate

Nirupama Laroia

INTRODUCTION

Hypotonia, which manifests as a “floppy infant” is a difficult neurologic problem in the newborn. It is nonspecific and the differential diagnosis includes sepsis, other acute illnesses, systemic disorder such as congestive cardiac failure, central or peripheral neurologic disease, myopathy, metabolic disorders and many genetic disorders. A physician must not only determine tone and strength, but also whether there is motor or psychomotor delay. The process must then be localized to the nervous system. It is useful to divide localization to 2 large groups; the supraspinal conditions that include the brain, brainstem, and the cervical spinal junction that constitute the central nervous system. The other large group of disorders is those affecting the motor unit including the anterior horn cell, peripheral nerve, neuromuscular junction and muscle. A systematic approach to a newborn with hypotonia is discussed in this chapter.

CLINICAL ASPECTS

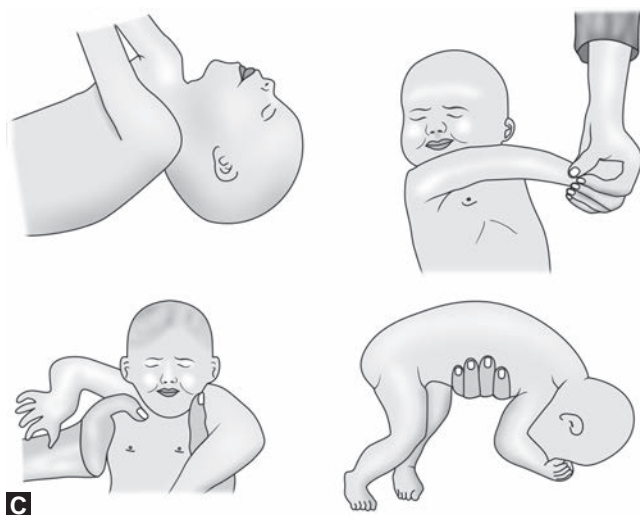
The first step in evaluation of a hypotonic infant is to obtain a family and past medical history (prenatal, perinatal and neonatal assessment). The prenatal history should include information on fetal movement *in utero*, fetal presentation, and the amount of amniotic fluid present. The obstetric history occasionally may identify both a cause and timing of onset. Maternal exposure to toxins or infection suggests a central cause. It is important to establish an approximate timing of onset of hypotonia. Was it present from birth, did it develop over days? Were fetal movements present throughout pregnancy or did they diminish. Presence of joint contractures at birth (arthrogryposis) especially those affecting ankles and wrists, suggest chronic *in utero* hypotonia. Congenital dislocation of the hip may be seen. Bell-shaped chest and pulmonary

hypoplasia is typically seen when reduced in-utero respiratory effort occurs. Low apgar scores may suggest floppiness from birth and a hypotonic infant should be considered septic until proven otherwise. A full term infant who develops floppiness 12 to 24 hours or so after birth may have a metabolic disorder.

EXAMINATION OF THE HYPOTONIC INFANT

Physical examination will assist in identifying specific constellation of features of recognizable chromosomal or genetic abnormalities such as trisomy 21, Prader-Willi, Smith-Lemli-Opitz, Angelman, and many deletion syndromes. The list of possibilities is extensive and will often require consultation with a geneticist for accurate diagnosis. A discussion of genetic disorders is beyond the scope of this chapter.

Clinical evaluation includes a detailed neurologic assessment including tone, strength, and reflexes. Neurologic examination should include head shape, size, and the size and fullness of the anterior fontanelle. Fundoscopy has limited value. There is paucity of movement while awake and the infant assumes a ‘frog leg’ posture while supine. Truncal tone should be assessed by ventral and horizontal suspension. In ventral suspension, the baby is held upright under the arms; hypotonic infants tend to slide through the examiners hands. In horizontal suspension, the infant is held prone with the examiners hands supporting the infant’s chest and upper abdomen. Infants with hypotonia drape themselves over the examiners hand forming an inverted U, whereas those with normal tone can hold their back straight, their head and legs even with their body. Head control can also be evaluated by pulling the supine newborn up by the arms. The normal term infant should be able to hold the head even with the trunk as they are pulled up. The ‘scarf sign’ is another useful indicator of tone. One arm is pulled across the chest



C

Figs 1A to D: Demonstration of hypotonia; (A) Pull to sit; (B) Scarf sign; (C) Shoulder suspension; (D) Ventral suspension

to the opposite shoulder and the position of the shoulder is observed. The elbow does not cross the midline in normal infants (Figs. 1A to D).

It is important to distinguish weakness from hypotonia. Hypotonia is the impaired ability to sustain postural control and movement against gravity. Thus careful observation of posture in a neonate at various stages of arousal is a sensitive way to assess for hypotonia. In the neonate assessment of gestational age is very important in evaluation of tone. The premature infant demonstrates a

normally lower tone than a full term infant. Weakness is the reduction in maximal power that can be generated. This requires the patient's cooperation and is therefore not possible to test in the newborn. Weak infants always have hypotonia, but hypotonia can exist without weakness.

LOCALIZATION OF HYPOTONIA

Because dysfunction at any level of the nervous system can cause hypotonia, the differential diagnosis is extensive. Central causes are more common than those affecting peripheral nervous system. Hypotonia must first be categorized to central or peripheral origin (Table 1). An alert hypotonic infant that responds appropriately to surroundings, and shows normal sleep wake cycling is more likely to have peripheral nervous system disorder or spinal cord disease. Central causes (Table 2) of hypotonia are often associated with depressed level of consciousness, predominantly axial weakness, and normal strength with hypotonia. A newborn with cortical brain dysfunction is also likely to have early seizures, abnormal eye movements, apnea, or irregular breathing patterns. Peripheral causes (Table 3) are associated with profound weakness in addition to hypotonia and hyporeflexia. Affected infants show an alert, inquisitive face but profound distal weakness. Conversely, an infant who does not track visually, appear lethargic are more likely to have cerebral disorders. Presence of dysmorphic features of face, scalp and malformations of other organs are also suggestive of cerebral involvement.

Table 1: Differentiation of central and peripheral hypotonia

	<i>Central</i>	<i>Peripheral</i>
Mental state	Depressed	Normal
Oculocephalic reflex	Normal or abnormal	Normal or abnormal
Dysmorphic features	May be present	Absent
External anomalies	May be present	Absent
Deep tendon reflexes	Decreased acutely, increased late	Depressed or absent
Cry	High pitched	Weak

Table 2: Causes of central hypotonia in the newborn

Hypotonia present at birth

- Brain and spinal cord injury or trauma: Hypoxic-ischemic encephalopathy, intracranial hemorrhage
- Genetic and chromosomal disorders: Down syndrome, Prader-Willi syndrome
- Cerebral dysgenesis, and other structural abnormalities
- Peroxisomal disorders: Zellweger syndrome, neonatal adrenoleukodystrophy
- Other rare metabolic, genetic disorders
- Benign congenital hypotonia

Hypotonia developing after birth

- Sepsis, including meningitis and encephalitis
- Metabolic derangements or disorders
- Endocrine: Hypothyroidism
- Drug intoxication

Table 3: Peripheral causes of hypotonia*Anterior horn cell (lower motor neuron)*

- Spinal muscular atrophy type I (Werdnig-Hoffman disease)
- Glycogen storage disease type II (Pompe's disease)
- Neonatal poliomyelitis

Level of peripheral nerve

- Demyelinating neuropathies: Hereditary or chronic inflammatory
- Lysosomal (Krabbe's disease)
- Mitochondrial

Level of neuromuscular junction

- *Myasthenia*: Neonatal transient or congenital myasthenia syndrome
- *Toxic-metabolic*: Hypermagnesemia, aminoglycosides
- Infant botulism

Level of muscle

- *Muscular dystrophy*: Congenital myotonic, congenital muscular dystrophy
- *Metabolic myopathies*: Mitochondrial, glycogen disorder, lipid disorders
- *Congenital myopathies*: Nemaline rod, myotubular, others

CENTRAL HYPOTONIA**Systemic Disease**

The most frequent examples of hypotonia from central causes include systemic disorders like congenital cardiac failure, or sepsis. These infants spend all their energy breathing and do not move much. Septic infants also have hypotonia that can be quite severe. These infants have other systemic signs that help the clinician separate systemic disease from neurologic disease.

Infants with hypoxic ischemic encephalopathy may present with altered consciousness initially, and then become hypotonic before becoming hypertonic, as they get older. Infants with metabolic disease may present with hypotonia that may be indistinguishable from sepsis, and the diagnosis may not be clear until the results of the metabolic screen are available.

Nonsyndromic Central Hypotonia

These infants do not have recognizable dysmorphic features, but have abnormalities of the central nervous system and can be categorized based on neuroimaging (MRI) findings.

Cerebral Dysgenesis

Infants may have minor anomalies of the brain, most of which are not in the category of namable cerebral malformations but represent subtle anomalies of brain formation. These infants have a grossly normal brain on neuroimaging. Over time, these children may not be normal but tone may improve with maturation. Subsequent imaging may show delayed or normal myelination.

Benign Congenital Hypotonia

The term 'benign congenital hypotonia' has been used to describe infants who are hypotonic at birth but without a specific underlying diagnosis at birth, and whose tone normalizes during early childhood. The term likely encompasses many different pathologies and affected infants may have other features of cerebral dysfunction (e.g. learning difficulties). Ongoing effort should be directed to establishment of a specific diagnosis.

PERIPHERAL HYPOTONIA

While disorders of the central nervous system may be the most common cause of hypotonia in the newborn, disorders of the peripheral nervous system or the motor unit make up an important group of diagnosis. Early identification is necessary for genetic diagnosis and counseling.

The diagnostic workup is based on an understanding of the anatomy of the motor unit (Fig. 2). A motor unit consists of an alpha motor neuron in the anterior horn of the spinal cord, its single axon, which runs distally in the peripheral nerve, its many neuromuscular junctions, and all the peripheral fibers with which that neuron makes connections. Therefore, the number of motor units in an individual equals the number of motor neurons. The size of a single motor unit is equal to the number of muscle fibers innervated by that single neuron. The number and size of motor units can be determined by both an EMG and muscle biopsy, often essential in arriving at a diagnosis.

Many disorders of the peripheral nervous system can be localized to the various components of the motor unit. The process of evaluating a hypotonic infant is therefore a logical attempt to localize the lesion to the motor unit and consider a differential diagnosis. The common disorders

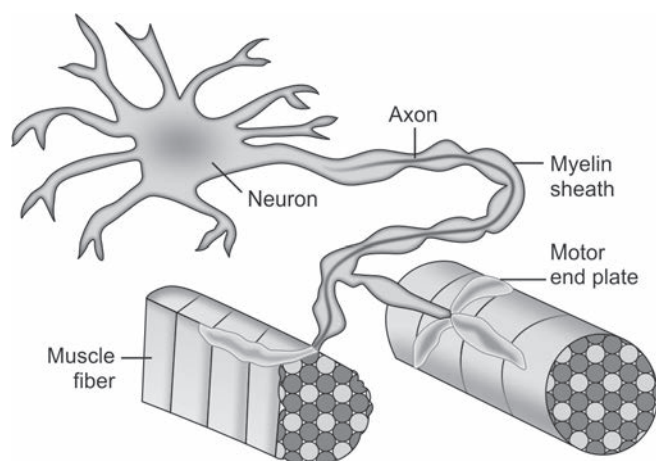


Fig. 2: Motor unit sketch

that present at birth include spinal muscular atrophy (SMA), congenital myotonic dystrophy (MD) and transient myasthenia gravis (MG).

Spinal Muscular Atrophy

Spinal muscular atrophy (SMA) is a recessive genetic disorder of the motor neuron that may present at any age, although the majority of patients develop symptoms within the first 6 months of age. The most typical symptoms of the most severe form, SMA type I (Werdnig Hoffman's disease) are hypotonia and weakness presenting as poor head control. Feeding difficulties are less common initially as bulbar weakness is rare in this disorder. Mothers may have a history of decreased fetal movement.

Clinical observation will show that the infant has minimal spontaneous activity, and minimal antigravity activity except in the distal muscles (fingers and toes). The infant is typically very alert, and is able to fix and follow with normal eye movements. Atrophy of face muscles may not be obvious initially in the newborn because of subcutaneous fat. The deep tendon reflexes (DTR) are depressed or absent, while sensation is normal. Tongue fasciculation is a classic feature of motor neuron disease but may not always be obvious in the newborn period.

Diagnosis during lifetime depends on blood chemistry, EMG, and muscle biopsy. Muscle enzymes may be normal or slightly elevated (1.5 to 2 times normal). The EMG is helpful if abnormal. Nerve conduction velocity must be normal for the diagnosis of SMA to be made. Muscle biopsy will show a pattern of innervation denervation. A pattern of marked atrophy of muscle fibers associated with hypertrophic type I fibers is pathognomic of SMA.

The prognosis for SMA patients is variable. With infantile onset (onset <6 months), there is 50 percent mortality by 2 years of age. There is no treatment for the progressive weakness. Supportive respiratory care and

physical therapy is important. Death is usually a complication of respiratory failure. It is important to present as much information to the family as possible, so that they can make an informed decision regarding long-term care for their child. The child has normal intelligence.

Spinal muscular atrophy (SMA) is an autosomal recessive disorder; the gene has been localized to chromosome 5q 11 to 13. In families with more than one affected child, linkage analysis may be possible for prenatal diagnosis. Each child of the same parents has 1 in 4 chance of having the disease. Severity of disease is not necessarily consistent.

Disorders of the Neuromuscular Junction

Affected infants have hypotonia, cranial nerve dysfunction (ptosis, bulbar dysfunction, weak cry), areflexia, and normal sensory function.

Transient neonatal myasthenia gravis occurs in about 12 percent of mothers with myasthenia gravis. It is not related to severity, or duration of maternal illness or to maternal antibody levels. Affected infants present with hypotonia, ptosis, feeding difficulties that resolve over weeks or months. The diagnosis is confirmed by an intramuscular or subcutaneous test dose of edrophonium or neostigmine. Neostigmine is preferred to edrophonium as with the former a response is expected within 15 to 30 minutes and lasts for 1 to 3 hours. Ongoing treatment is supportive care and pyridostigmine.

Impaired presynaptic release of acetylcholine by toxins (hypermagnesemia following maternal treatment of pre-eclampsia with magnesium sulfate, or treatment of neonate with aminoglycosides) may result in a hypotonic neonate, but slowly improves over time (hypermagnesemia). Since this hypotonia may be confused with sepsis, further antibiotics may exacerbate it.

Infant botulism results from presynaptic neuromuscular blockade by the toxin released by *Clostridium botulinum*, which may be present in the gastrointestinal tract of the neonate. The disorder has been described in exclusively breast fed infants. The organism originates from the soil, agricultural products, and honey. In addition to hypotonia, there may be feeding difficulties, abnormal pupillary responses and respiratory failure. The diagnosis is confirmed by positive stool culture, or isolation of toxin from stool. Supportive management may be necessary for months until recovery. There is no proven benefit from antibiotics or antitoxin.

Congenital Myotonic Dystrophy

Congenital myotonic dystrophy (MD) occurs in infants born to mothers with MD. Affected infants are extremely hypotonic, with severe facial diplegia and feeding difficulties evident at birth. Respiratory failure and aspiration are frequent complications, often leading to early death.

Infants are often hypotonic at birth, and may present with joint contractures and dislocated hips, suggesting long standing hypokinesia. Examination of the mother often reveals previously unsuspected MD. While normal mental development is possible, intellectual disabilities are common. Individualized support for the infant and family is desirable.

The diagnosis is dependent on physician's ability to diagnose MD in the mother. There may be other affected relatives with early cataracts, diabetes or mild mental retardation. Adults with MD often consider themselves asymptomatic.

The course of MD in the neonate appears to be biphasic. The ventilator dependent infant may begin to have sufficient spontaneous respiration by week 1 to 3. The risk of aspiration decreases after the neonatal period. Although milestones are initially delayed, the child may begin to meet them after 2 to 3 years of age. Joint deformities and club foot are common. The characteristic facial appearance and clinical myotonia become apparent by school age.

The genetic abnormality is a triplet (CTG) repeat in the noncoding region of the DMPK gene. This autosomal dominant gene not only has variable penetrance, but also penetrates to a greater extent with each generation. CTG repeat a length exceeding 34 repeats is abnormal. Molecular genetic testing detects mutations in nearly 100 percent affected individuals and is clinically available. The disease affects both sexes but the mother is usually the affected parent.

Muscular Dystrophy

Genetically determined myopathies are characterized by progressive weakness. The investigation of these disorders is rapidly evolving with the discovery of specific gene mutations. Muscle biopsy may be nonspecific.

Congenital Myopathies with Distinct Histology

Many myopathies are classified according to their histopathology appearance on muscle biopsy. Most present with hypotonia and mild weakness, with the exception of nemaline myopathy and X-linked myotubular myopathy which have severe neonatal presentation with respiratory failure. All congenital myopathies are genetic disorders and inheritance pattern and gene diagnosis are available for many of them.

Metabolic Myopathies

Mitochondrial cytopathies (cytochrome oxidase deficiency, carnitine deficiency, glycogen and lipid disorders) may present in the neonatal period. Diagnosis depends on enzyme assays and muscle biopsy results.

LABORATORY EVALUATION OF THE HYPOTONIC NEWBORN

The laboratory evaluation should help rule out systemic disorders. Routine studies include serum electrolytes, glucose, calcium, magnesium, creatinine and complete blood count. Urine drug screen for maternal drug use, and blood culture and spinal tap should be considered to rule out infection. Serum ammonia and liver function tests may reveal a urea cycle defect. Imaging of the brain is indicated in infants suspected of having central hypotonia. Magnetic resonance imaging (MRI) is superior to computed tomography (CT) scan or ultrasound for revealing anatomic detail of the brain and can delineate structural abnormalities, neuronal migration defects, basal ganglia (mitochondrial disorders) or brain stem defects. Some infants may not be stable enough for an MRI, when CT or ultrasound may be considered.

Karyotype may be indicated when dysmorphic features are present. Hepatosplenomegaly and calcifications in the brain may suggest TORCH infections and urine or saliva culture for CMV may be indicated. If the infant is acidotic, an arterial lactate should be obtained with urine organic and amino acids. Very long chain fatty acids would evaluate a defect in peroxisomal metabolism, such as Zellweger's disease.

With peripheral hypotonia a battery of laboratory investigations (e.g. serum creatine kinase CK, cerebrospinal fluid CSF analysis, nerve conduction studies and electromyography, neostigmine or edrophonium test, and muscle or sural nerve biopsy) may be performed to determine the precise level of the pathological process affecting the motor unit. Great advances in recent years have been made in molecular genetic testing, which in many instances have obviated more invasive investigations. Specific DNA testing must be performed when available.

Specific aspects of these investigations relevant to newborns require clarification to avoid pitfalls in the interpretation of results. Thus, elevated levels of serum concentrations of CK generally imply skeletal or cardiac muscle necrosis, as may occur in rapidly progressive muscular dystrophies and metabolic myopathies. The blood for CK measurement should be obtained before performing the electromyography or muscle biopsy, as these procedures may cause false elevation of CK levels. The CK and isoenzyme levels may be increased 10-fold for up to 1 week following normal vaginal delivery (presumably due to muscle trauma). The CK may be even higher in the context of acidosis (e.g. severely asphyxiated newborns). Other biochemical investigations (e.g. serum lactate and carnitine levels) may be required in specific circumstances. Because of the uncertainty of the normal range for CK values in the newborn, a normal value does not rule out muscular dystrophy before 6 weeks of age.

A chest radiograph may demonstrate a bell shaped chest and enlarged cardiac silhouette signifying cardiomyopathy or thin ribs, presumably related to diminished fetal respiratory movements. The latter observation is a useful clue to antenatal onset of neuromuscular disease. Markedly increased protein concentration in CSF may indicate peripheral neuropathy or specific degenerative conditions (e.g. Krabbe's disease). Nerve conduction studies are consistent and reliable after 32 weeks of gestation. Nerve conduction velocities, which are slower in normal newborns than in older individuals, may be very slow or unrecordable in the context of congenital peripheral neuropathies. The technical performance and interpretation of the electromyogram (EMG) may be problematic in the newborn. For example, myotonic discharges, which occur in older individuals with myotonic dystrophy, are rarely elicited in the newborn. Muscle biopsy (either by open surgical technique or needle biopsy) is technically feasible in the newborn. Early biopsy may be required if there is severe respiratory muscle involvement to provide definitive diagnosis and prognosis to assist management decisions. Otherwise, muscle biopsy is often postponed for several months, as it may be difficult to interpret in the newborn period. In some instances (e.g. congenital muscular dystrophy), repeated muscle biopsies may be useful for establishing an accurate diagnosis.

SUMMARY

The approach to a newborn with hypotonia should not differ substantially from that to an older child. The

examination may be more difficult, however, history, laboratory studies (serum enzymes, EMG, muscle biopsy), and genetic studies (when indicated) may be helpful in arriving at a diagnosis, even in premature infants.

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Long-term Follow-up of High-risk Babies

Praveen Suman

INTRODUCTION

The birth of a baby is an event of joy and happiness for everyone—parents, grandparents, siblings and friends. However, taking a premature baby or a baby who has special needs home from the hospital is both an exciting and overwhelming adjustment for most parents. As you prepare to take your baby home, you may be thinking of his or her future medical and developmental needs. High-risk follow-up programs are specifically designed to monitor the development of children who are at increased risk for emerging delays and it can provide special attention and answers to questions about child's health, growth, nutrition and development. Unlike traditional child-development clinics, which address problems in children who have already been identified as having a delay or disorder, follow-up clinics focus on identifying problems as they emerge. In general, the focus of these clinics is on identification of emerging problems related to neonatal risk factors.

Follow-up Criteria

Children who are considered to be at “high-risk” for developmental problems and those already identified as having developmental concerns require more extensive screening than children at lower risk. Close monitoring of development, together with coordination of treatment for any emerging problems, is often referred to as “developmental follow-up.” Children who are at increased risk for developmental problems include those born very prematurely or at very low birth weight, as well as those with known neurological abnormality at birth and those who are very ill during the newborn period.

Which Children Need Long-term Follow-up?

Babies who need follow-up include:

- Babies with <1800 g birth weight and/ or gestation <35 weeks
- Small for date (<3rd centile) and large for date (>97th centile)
- Perinatal asphyxia: Apgar score 3 or less at 5 min and/ or hypoxic ischemic encephalopathy
- Mechanical ventilation for more than 24 hours
- Metabolic problems: Symptomatic hypoglycemia and hypocalcemia
- Seizures
- Infections: Meningitis and/or culture positive sepsis
- Shock requiring inotropic/vasopressor support
- Major morbidities such as chronic lung disease, intraventricular hemorrhage, and periventricular leukomalacia
- Infants born to HIV-positive mothers
- Twin with intrauterine death of cotwin
- Twin-to-twin transfusion
- Hyperbilirubinemia >20 mg/dl or requirement of exchange transfusion
- Rh hemolytic disease of newborn
- Major malformations
- Inborn errors of metabolism/other genetic disorders
- Abnormal neurological examination at discharge.

DISCHARGE FROM NICU

Discharge planning in the NICU is a multidisciplinary effort that begins with the infant's birth and admission to the unit. Important aspects include the parents' involvement in their infant's care, plans for special needs such as oxygen and apnea monitoring, and teaching the parents special skills.

Social criteria for discharge include the following:

- Confirmation that the parents can provide the basic physical needs of the infant
- Assurance that the parents are knowledgeable about their infant's needs and know how to identify problems that may arise following discharge

- A specified plan for continuing health care and parenting support. The stress parents experience while their infant is hospitalized may interfere with their ability to learn; therefore, parents' education often needs to be reinforced after the infant's discharge. Also, parents should have sufficient help at home to support them in the care of their infant.

Most NICU's have no minimum weight requirement for discharge. Medical guidelines for discharge are as follows:

- Body temperature is maintained while the infant is in an open crib, usually at 34 weeks of gestational age or at 2,000 g (4 lb, 6 oz) of weight
- The infant feeds by mouth well enough to have a weight gain of 20 to 30 g per day
- The infant is not receiving medications that require hospital management
- No recent major changes in medications or oxygen administration have occurred.

Before discharge, premature babies also need an eye examination and hearing test to check for problems related to prematurity. Parents need information about follow-up visits with the pediatrician for baby care and immunizations. Many hospitals have special follow-up healthcare programs for premature and low birth weight babies.

Who can Provide Follow-up Services?

Even though high-risk babies are otherwise ready for discharge, some babies continue to have special needs such as extra oxygen or tube feedings. With instruction and the right equipment, these babies are often able to be cared for at home by parents. A hospital social worker can often help coordinate discharge plans when special care is needed. At a minimum, developmental follow-up for high-risk infants should involve periodic screening for sensory impairment, developmental delays, and any other condition for which an individual infant is considered to be at increased risk. Comprehensive follow-up involves close evaluation of medical, psychological, and social factors in addition to assessment of developmental progress. Children who are suspected of having had neurological injury will need close evaluation of neurodevelopmental functioning to investigate the possibility of long-term impact as their nervous systems mature. The follow-up team also must be able to integrate information from the various specialty physicians, care of each high-risk neonate after discharge must be carefully coordinated to provide ongoing multidisciplinary support of the family. The discharge planning team should include parents, the primary care physician, the neonatologist, social worker, developmental pediatrician, pediatric occupational, physical, speech, and respiratory therapists, nutritionists are included as needed.

Pediatricians may incorporate developmental follow-up into their routine well-child care. Administration of a brief screening instrument requires an additional 10 to 15 minutes of examination time. More time is required for children who do not pass an initial screening. Coordination of additional tests, specialty services, and therapies, is necessary when delays or impairments are identified. When problems are identified on initial screening, pediatricians may choose to refer the family for further evaluation and follow-up (child development clinic, or to a specialized follow-up program for high-risk).

When to Follow-up?

- Infants with <1800 g birth weight and/or gestation <35 weeks:
 - Follow-up after 3 to 7 days of discharge to check if the baby has been adjusted well in the home environment. Every 2 weeks until a weight of 3 kg (immunization schedule until 10 to 14 weeks to be covered in these visits)
 - Follow-up at 3, 6, 9, 12 and 18 months of *corrected* age and then every 6 months until age of 8 years.
- All other conditions:
 - Follow-up—2 weeks after discharge
 - At 6, 10, 14 weeks of postnatal age
 - At 3, 6, 9, 12 and 18 months of *corrected* age and then every 6 months until age of 8 years.

ASSESSMENT OF FEEDING AND DIETARY COUNSELING

Caloric intake, fluid intake, and vitamin and mineral supplementation should be monitored during weekly visits. Nutritional requirements in the NICU are usually 120 kcal per kg per day. This amount usually drops to 100 kcal per kg per day by the time of discharge.

Breast milk protects against infection, and breastfed infants have better developmental scores at 18 months of age than formula-fed infants. Mothers who plan to breast-feed should use a hospital-quality electric breast pump after the infant's birth to stimulate their breasts. The pumped milk may be fed to the infant. When the infant is able to suckle, the mother should start breastfeeding to further encourage milk production. By the time of discharge from the hospital, most premature infants require feedings at least every three hours. Human milk fortifier (a supplement that is added to pumped breast milk) should be used as advised by the NICU.

If there is a question about the mother's supply of breast milk, she should nurse every one and one-half to two hours during the day in the first 24 to 48 hours after the infant's discharge to ensure adequate milk production. After this initial period, the infant is normally nursed every two to three hours, or eight to 10 feedings per day.

Six to eight wet diapers per 24 hours indicate an adequate fluid intake. Fluid should not be withheld for longer than four hours.

Solid food should be introduced at four to six months past the infant's due date. The infant's swallowing mechanism will not accept or handle solid food until two and one-half to three and one-half months past the infant's due date. Sick infants, such as those with bronchopulmonary dysplasia, often require special dietary intervention. In this instance, coordination between the dietary staff and other care providers is necessary.

VITAMINS AND MINERALS

Vitamins D, E and K, and folic acid are especially important for low birth weight infants. Except for vitamin D deficiency, vitamin deficiencies are unlikely to occur after discharge from a neonatal intensive care center. The signs and symptoms of vitamin D deficiency are enlarged costochondral junctions (rachitic rosary), bowlegs and knock knees (which usually develop after the child has started walking), failure to thrive, hypocalcemia, and hypophosphatemia.

Although vitamin deficiencies are rare, all breastfed infants should probably receive vitamin supplementation during the first year of life. Standard dose of infant vitamins that provides 400 IU of vitamin D per day is advised for both premature and term infants. If a special formula is used, its vitamin content should be checked to determine if supplementation is required.

Supplemental iron is advised, either as iron-fortified formula or as a liquid, given in a dosage of 2 to 4 mg per kg per day in breast-fed infants or infants receiving low-iron formulas. Iron supplementation should be started two weeks to two months after birth and continued for 12 to 15 months. The infant should receive 0.25 mg of fluoride supplementation daily if the water in the household is not fluoridated. Many dental problems, including enamel hypoplasia, dental caries and delayed dental development, are reported to be more common in preterm infants than in term infants.

Although rare, deficiencies of zinc and copper have been reported in premature infants at three to six months of age.

IMMUNIZATIONS

The timing of immunizations should be based on the infant's chronologic age, not the gestational age. The only exception is hepatitis B vaccination. The American Academy of Pediatrics Committee on Infectious Diseases has issued a statement indicating that it may be advisable to delay administration of hepatitis B vaccine until the infant weighs 2,000 g. The full dose of all immunizations should be given.

GROWTH MONITORING

During the first two years of life, growth is plotted using age corrected for prematurity. Growth charts for the "average" premature infant have been designed for this purpose. Special neonatal growth charts are also available for the sick or small-for-gestational-age infant. After the infant reaches two years of age, a standard growth chart for chronologic age may be used.

Many premature infants have catch-up growth. Catch-up growth is usually first noted in the infant's head circumference, followed by the infant's weight and length. This usually occurs during the first two to three years of life and is maximum at 36 to 40 weeks after conception. Little catch-up growth occurs after three years of age. Premature infants with intrauterine growth retardation and no catch-up growth have a higher risk of developmental delay and other medical problems than premature infants with a normal growth rate. Even in adolescence, children who were born prematurely may be smaller than children not born prematurely. Menarche also occurs later in girls who were born prematurely. One study showed that women who were born prematurely are more likely to deliver premature infants themselves. Another study found a trend for this to happen, but it was not statistically significant.

Catch-up Growth

However, for the child to become the same size as his or her full term peers, growth will have to be faster than usual. This is called "catch-up growth".

85% of premature infants have catch-up growth and land on the regular growth chart by two years of age.

Delays in catch-up growth—Some common reasons a child may not catch-up fully by two years of age are:

- Starting out very far below the growth chart with a long, long way to catch-up
- Ongoing problems, which increase the nutritional requirements
- Some babies (but not all) with BPD or chronic lung disease may have an increased metabolic rate and need more nutrition than other infants. This increased metabolic rate can also last for a long time after discharge. Another potential ongoing problem is illness and a reduction in feedings as a result. Some children with cerebral palsy also have higher metabolic rates. There are other ongoing problems, which might apply, as well
- Poor appetite

A few other studies have looked at long-term growth. *The bottom line is that catch-up growth can continue into adolescence, and the majority of tiny premature infants should be normal sized adults.*

Neurodevelopmental Follow-up of High-risk Neonates

In a time when health care is increasingly rationed, the cost of acute and long-term care for VLBW infants is a controversial subject. These infants frequently require months of care in an intensive care unit, and there is concern that their increased survival may be accompanied by a higher incidence of physical, neurologic, sensory, and developmental handicaps. As more infants survive, neonatal specialists are faced with evaluating the effectiveness of these changes in treatment.

Improvements in neonatal care have had a significant impact on infant mortality rates in the 20th century. Several changes in neonatal care have occurred in the second half of this century that have resulted in improved survival of LBW preterm infants. Refinements in the use of oxygen and incubators in the 1940's and 1950's; improvements in thermoregulation in the 1960's; development of neonatal intensive care units and ventilators in the 1970's; and the use of high-frequency ventilators, surfactant, and regionalized care in the 1980's and 1990's, have substantially improved the premature neonate's chances of survival. The increase in the survival rate of infants considered LBW (less than 1,500 g) and VLBW (less than 1,000 g) has led investigators to assess carefully the quality of life of these survivors.

Increased Vulnerability

The preterm infant's neurologic system is at increased risk because it is immature anatomically, chemically, and physiologically. The migration of neurons to the cerebral cortex is generally complete by around 20 weeks' gestation; however, the gray and white matter is poorly differentiated, and the neurons have not reached functional maturity. Synaptic-dendritic organization and myelination is just beginning in the third-trimester. Neurologic function and response occur at the cord and brainstem level, with little inhibition from the immature cerebral structures. The preterm infant is not capable of fully modulating extrauterine stressors. Sympathetic function is generally not seen until 32 weeks' gestation, and autonomic regulation is usually not achieved until 35 to 36 weeks' gestation.

The vascular germinal matrix surrounding the cerebral ventricles is just beginning to mature at 18 to 20 weeks' gestation, and full maturation is not reached until 35 to 36 weeks. The friability of this area and poor vascular regulation during the period of maturation, place the preterm infant at increased risk for the development of an intraventricular hemorrhage or periventricular leukomalacia.

The neurosensory system is also immature. Retinal vascular maturation does not occur until close to term, and rod and cone development is not complete until several months after the infant reaches term. This retinal immaturity places the preterm infant at risk for the development of retinopathy of prematurity (ROP) and possible visual impairment. Neurologic immaturity, coupled with

neurosensory stressors, can have significant long-term effects in the preterm infant.

Risk Factors for Neurodevelopmental Delay

In addition to birth weight and gestational age, numerous intrauterine and extrauterine factors may place a preterm infant at increased risk for neurodevelopmental impairment. Factors most commonly cited include: economic and social-environmental factors; physiologic factors, such as intraventricular hemorrhage, periventricular leukomalacia, chronic lung disease, ROP, and ototoxicity; and the neonatal intensive care environment.

Economic and Social-Environmental Risk Factors

Economic and social-environmental risk factors are the most frequently reported predictors of neurodevelopmental outcome. The possibility of poor neurodevelopmental outcome is heightened when these factors are combined with medical and neurologic risk factors.

Intraventricular Hemorrhage

The presence of intraventricular hemorrhage increases the risk of neurodevelopmental sequel. The severity of the intraventricular hemorrhage is usually graded from 1 to 4, with Grade 4 the most severe. The higher the grade of intraventricular hemorrhage, the more likely are neurodevelopmental problems such as cerebral palsy or mental retardation may occur.

Periventricular Leukomalacia

The area surrounding the ventricles of a LBW infant is particularly susceptible to injury. Ischemia in this area may lead to permanent damage, referred to as periventricular leukomalacia. The areas of the brain most commonly affected are the motor and visual tracts, although other areas may also be affected. Periventricular leukomalacia may also be graded according to severity: mild, moderate, or severe. The greater the severity the higher is the risk for sequel. A child with periventricular leukomalacia is at increased risk for cerebral palsy, mental retardation, and visual impairment.

Neonatal Intensive Care Environment

In recent years, stressors that face the infant in the environment of the neonatal intensive care unit (NICU) have been implicated in long-term developmental problems. The effects of tactile stimulation, noise, light, and absence of diurnal rhythms frequently encountered in an intensive care unit and their impact on the immature neurologic system have been evaluated by numerous researchers.

Retinopathy of Prematurity

Retinopathy of prematurity is an additional risk factor for neurosensory impairment. It is a disorder that disrupts

the normal maturation of the retina and can place the premature infant at increased risk for visual impairment. Maturation of the retina is generally not complete until 40 to 44 weeks gestation. Until then, retinal vessels are vulnerable to injury.

Ototoxic Factors

Numerous factors have been identified as potential causes of permanent hearing damage: environmental noise; low birth weight; hypoxia; use of such ototoxic medications as gentamicin, kanamycin, or furosemide; congenital infection; prolonged assisted ventilation; hyperbilirubinemia; and meningitis. These factors, alone or in combination, may play a role in the development of sensorineural hearing loss in the premature infant.

Importance of Neurodevelopmental Assessment in High-risk Babies

When neurodevelopmental impairment is diagnosed, a common misconception is that the child is always severely affected. It is for this reason that some researchers use the terms major and minor to refer to the severity of a child's disability. Types of neurodevelopmental impairment: major, referring to cerebral palsy, mental retardation, visual impairment, and hearing loss; and minor, referring to cognitive and learning deficits, neuromotor deficits, behavioral, and emotional abnormalities.

An encouraging finding in outcome studies of preterm infants is that the majority of LBW infants survive with little or no disability. In results of studies of neonates weighing less than 1,500 g, 62 to 80 percent have been reported as normal, 16 to 21 percent as having mild or moderate disability, and 5 to 12 percent as having severe disability. The lower the gestational age, however, the higher the incidence of major disability. Minor disability rates are reported at 15 to 25 percent for the VLBW infant. Children may exhibit more than one minor or major disability.

MAJOR NEURODEVELOPMENTAL IMPAIRMENTS

Cerebral Palsy

The incidence of cerebral palsy (CP) in the preterm population is generally reported as 6 to 10 percent. The most common form of CP found in the preterm population is spastic diplegia. Cerebral palsy is non-progressive; a child with a mild form will not progress to a more severe form. A child with CP is at higher risk for mental retardation or learning disabilities, particularly if CP is severe; but it is important to note that many children with CP have normal cognitive skills.

Mental Retardation

The incidence of mental retardation in the preterm population is generally reported at 4 to 8 percent. Mental

retardation varies in severity, with mild referring to both measurements of adaptive function and IQ scores between 50 to 70; moderate, 35 to 55; and severe or profound, less than 40. Most preterm infants diagnosed with mental retardation are in the mild to moderate range.

Visual Impairment

Visual impairment in the preterm population is generally a result of ROP. Retinopathy of prematurity is reported to occur in approximately 80 percent of infants with birth weights 750 to 1,000 g and in 90 percent of infants with birth weights less than 750 g. Retinopathy of prematurity, even if mild and fully regressed, places the preterm infant at higher risk for later visual sequel. The most common sequel of ROP includes myopia, strabismus, and amblyopia.

Hearing Loss

The incidence of neurosensory hearing loss in the preterm population is generally reported at 1 to 6 percent. Hearing loss is usually in the mild to moderate range (26 to 55 dB), with complete deafness atypical. A hearing loss of 30 dB or more in the speech-frequency range (500 to 4,000 Hz) will interfere with the normal development of speech.

Minor Neurodevelopmental Impairment

Minor neurodevelopmental problems include cognitive deficits, learning deficits, behavioral difficulties, and subtle neuromotor deficits. Although termed minor, impairments in this category can have a substantial impact on the life of a premature child.

Cognitive Deficits

Subtle cognitive deficits have been found in results of some studies comparing performance of school-age LBW preterm children with that of full-term children. Although mean IQ's were still in the average range (100 ± 15), the mean IQ of LBW children has been reported to be 8 to 10 points lower than the mean IQ of full-term children. Borderline intelligence, defined as having measurements of adaptive functioning and IQ scores between 70 and 84, has been reported in one-fifth of those with birth weights 750 to 1,500 g and in one-third of infants with birth weights less than 750 g. Because this problem can easily go undiagnosed, children in this category are at greatest risk of receiving educational services that do not meet their needs.

Learning Deficits

Although the incidence of learning disabilities in the LBW population is unclear, partially because of differences in defining terms, the widespread prevalence of these difficulties is clear in results of outcome studies in school-age children. In findings in a study of 8-year-old LBW children, 45 percent reported having difficulty with one or more subjects in school, compared with 11 percent of full-term children reporting such difficulties.

Deficits in reading, spelling, and math skills are more common in LBW children. Language deficits, which result in difficulty with receptive comprehension, expressive vocabulary and word retrieval as well as in articulation and fluency, are also more common in LBW children. In the classroom setting, these children may seem to follow directions poorly, may have difficulty comprehending reading and may avoid classroom participation. Visual-perceptual-motor problems are also more common. In addition to weaknesses in fine motor control, finger agnosia, and motor planning LBW children are more likely to have difficulties in sequencing, in organizing visual information, and in visual motor integration. These problems become evident when a child is asked to write by hand, arrange pictures, assemble objects, or copy designs. Deficits in cognitive functioning have also been reported and include difficulty in memorization, in logical and abstract thinking, and in spatial relations. In the classroom setting, children with these deficits demonstrate difficulties in using common sense, managing new information, remembering assignments, and making decisions.

Behavioral Difficulties

Low birth weight children are more likely to exhibit deficits in results of measurements of adaptive behavior than are full-term children. Impulsive behavior, distractibility, poor attention span and autistic spectrum disorder are reported with a higher frequency. Difficulties with self-control when making transitions between activities, over aggressiveness in play, noncompliance with requests, and difficulty in parental separation are also reported. In reported results of studies, attention deficit disorder and hyperactive behavior occurs more frequently in preterm children (7%) than they do in control subjects (1%). An increased frequency of depressed behavior and internalizing behavior (i.e. timidity, passivity, and anxiety) has also been reported

Subtle Neuromotor Deficits

LBW school-age children: One-third of children with birth weights less than 1,500 g demonstrate poor gross motor skills in standardized testing. Difficulties with balance, coordination, and postural control have been reported. In a survey of teachers, responses showed that LBW children were more likely to be identified as having less athletic competence than their full-term classmates. These gross motor difficulties can affect a LBW child's ability, as well as desire, to enter into playground activities or sports with peers.

What should Neurodevelopmental Follow-up Involve?

Information about the developmental needs of the high-risk infant should be provided to NICU parents through group classes, handouts, or videos. It is also important

to individualize the education plan to encompass specific cultural needs in each family. Parental involvement is considered vital to the implementation of developmental care. Parents must be able to interpret their child's behavioral cues and learn how to respond appropriately. Screening tests designed for initial screening in the general population should not be relied upon for the identification of delays in children known to be at high-risk for developmental problems. When used with groups of high-risk children, such tests do not have a satisfactory rate of accuracy in identifying developmental problems. It is also not appropriate to use screening tests to "rule out" problems about which parents have voiced a concern. That is, passing a screening test should not be used as an indication that there is no problem when there is cause for concern due to the child's early history and/or parent report of unusual behavior. When children are known to be at high-risk for developmental problems or when parents have noted something worrisome about their child, more in-depth evaluation is needed.

Development Assessment

The infant's development during the first two years should be plotted from the infant's estimated due date rather than the infant's birth date. The Denver Prescreening Developmental Questionnaire, the Denver Developmental Screening Test and the Gesell Screening Inventory are all accepted tests. Using a standardized developmental test is more important than the choice of test.

Developmental screening does not replace the neurologic examination. Because of this, detailed standardized examinations, such as the Neonatal Neurodevelopmental Examination, have been developed. The latter has been used primarily by developmental pediatricians and pediatric neurologists. It assesses postural reflexes and muscle tone, cranial nerve and motor function, sensory responses and behavior. If an abnormal finding is noted, such as neck extensor hypertonia, consultation with a developmental specialist should be considered.

In an attempt to prevent disabilities, a number of intervention programs have been developed and evaluated. These include interventions in the neonatal nursery, at home and at special centers. A review of various intervention programs for low-birth-weight infants, all evaluated since 1971, found that intervention programs provide support and improve parent child interaction. Most NICU's have developmental follow-up programs, and the physician should encourage the parents to participate in these programs. The most severe diagnoses are usually evident by ages 2 to 4 (CP, major retardation, blindness, deafness). The less severe diagnoses (low or mildly retarded IQ, learning and behavior problems, mild visual and hearing problems and problems with hearing and visual processing) are not always known till age 8 to 11 or even later. There are even some problems that may not

show up till late adolescence or adulthood—e.g. seizures, or late loss of vision from ROP.

Vision and Hearing Assessment

Strabismus is more common in premature infants than in term infants. Because strabismus can be a sign of intraocular pathology, ophthalmologic consultation is generally indicated in infants with strabismus. In many very-low-birth-weight infants, strabismus at six weeks of age resolves by the time the infant reaches nine months of age. Strabismus that is present at nine months of age is likely to persist.

Retinopathy of prematurity occurs in some infants born at 32 weeks of gestation or less, and evaluation for this condition will already have taken place in the NICU. The American Academy of Pediatrics, the American Association for Pediatric Ophthalmology and Strabismus, and the American Academy of Ophthalmology recommend obtaining an initial screening examination at four to six weeks' chronologic age, with follow-up examinations performed as required on the basis of the initial findings.

Most NICU's obtain brainstem auditory evoked potential testing before the infant's discharge. Hyponatremia, metabolic alkalosis and prolonged mechanical ventilation with high oxygen concentrations are risk factors for hearing loss. The use of an aminoglycoside or furosemide is an additional risk factor. The World Health Organization defines hearing loss as an average loss of greater than 25 dB at frequencies of 500, 1,000 and 2,000 Hz, classified according to the less impaired side. Using this definition, about 5 percent of premature infants born before 32 weeks of gestational age have hearing loss by five years of age. Parents should be asked if they notice signs of hearing impairment in their infant. The infant's response to loud noise can be checked in the physician's office, and receptive and expressive language can be assessed with a developmental screening tool. Audiologic consultation should be obtained if the parents notice signs of hearing loss or if findings on the screening procedure are abnormal.

SUMMARY

Changes in neonatal care have resulted in an increase in the survival rate of LBW infants, with most preterm infants surviving without neurodevelopmental impairment. However, although it is nearly impossible to predict directly the type and severity of an individual child's neurodevelopmental problems, the lower the birth weight, the higher the risk for impairment. In addition, an increase in the severity of disability can be seen with decreasing birth weight. Fortunately, most problems in the preterm population are mild to moderate, and although LBW infants are faced with a higher rate of morbidity than that of their full-term counterparts, results of a recent study of

adolescent VLBW infants showed that most viewed their health-related quality of life as quite satisfactory. Because more LBW infants are surviving, the specialist team is challenged with determining and providing care that minimizes the neurodevelopmental problems seen in preterm infants.

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CHAPTER 30

Approach to a Newborn with Suspected Cardiac Disease

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INTRODUCTION

A newborn with cardiac disease can have variable presenting features. Also most of these presentations can mimic the common neonatal disorders such as septicemia, shock, respiratory disorders, persistent pulmonary hypertension of newborn (PPHN), inborn errors of metabolism and so on. But with a meticulous approach, working cardiac diagnosis can be made and appropriate management started.¹ This chapter emphasizes the approach to common neonatal cardiac disorders and management of various clinical scenarios which a neonatologist comes across in his day to day practice.

HISTORY

Detailed medical history about antenatal and perinatal events is very important to determine the possibility of cardiac disease. In today's world where antenatal diagnosis is getting more and more precise and fetal echo is providing great insights into the disease, neonatologist must inquire about these reports.² Similarly, antenatal history about drugs and diseases may point to a specific diagnosis and should be sought. Perinatal events leading to respiratory distress and cyanosis at birth may point to the diagnosis of non-cardiac cause of cyanosis and uneventful delivery with sudden onset of cyanosis or shock after 24 to 48 hours of birth should give a suspicion of duct dependent circulation. A history of preterm baby with hyaline membrane disease getting better after surfactant therapy and then again worsening with need for ventilator is a good pointer to look for patent ductus arteriosus (PDA). One more common feature in preterm babies is apnea followed by cyanosis which is perceived as gastroesophageal reflux related episode, may also be due to a hemodynamically significant PDA. Any neonate who presents within first two weeks of life with sudden onset of unexplained

collapse or cyanosis must be suspected for a duct dependent cardiac disease.

EXAMINATION

Neonatal cardiac examination alone may not give complete information but with an insight of cardiology, this examination can be fruitful enough to have a working differential and with the help of chest X-ray and ECG, can point to a specific cardiac etiology. Dymorphology may point towards a syndrome and help in diagnosing a heart lesion. Down's syndrome is a well known example where cardiac defects are known to occur with high frequency in particular atrio-ventricular canal defects (AVCDs). Examination of upper and lower limb pulses and BP is a critical step in diagnosing coarctation of aorta where there are normal heart sounds and no murmur. Absent lower limb pulses, radiofemoral delay or upper limb hypertension will diagnose a coarctation. Systolic BP of upper limbs more than 10 mm Hg than the lower limbs suggests coarctation of aorta. Again if PDA is large in such cases, this feature of coarctation will be absent as large PDA will supply the descending aorta. In such scenario lower limb desaturation will help to diagnose. Low volume pulses in all extremities will suggest left-sided obstructive lesion like aortic stenosis. Similarly, bounding pulses will be felt in PDA, aortic regurgitation, truncus arteriosus and systemic arteriovenous fistula.

Pulse oximetry can be a valuable tool and important assistant to clinical examination. Naked eyes can not diagnose cyanosis in patients where saturation is less than 85 percent and so will miss cyanotic heart disease in many cases unless pulse oximetry is used. This may be a valuable exercise to diagnose cyanotic heart diseases in newborn and may be a routine in our neonatal units soon.³ The best time would be after 24 hours of life as many normal neonates will have lower saturation in first 24 hours of life.



Fig. 1: Chest X-ray of a neonate with situs solitus, dextrocardia where high possibility of a complex cardiac lesion should be kept

The cardiac examination should be performed in a systematic manner. Situs solitus with dextrocardia should point towards a complex cardiac lesion (Fig. 1). Left-sided precordial bulge will suggest cardiac enlargement and a left parasternal heave indicates right ventricular hypertension. Also look for a palpable precordial thrill. Any of these additional findings in the term infant with a heart murmur suggest pathologic murmur. Abnormalities of the second heart sound are often seen in congenital heart disease, making it perhaps the most important element of auscultation in the pediatric patient. Third and fourth heart sounds can be normal. The Grades IV, V, and VI murmurs are associated with a palpable precordial thrill, and are always pathologic. The innocent murmurs are soft (Grades I or II) and ejection in quality. Although diastolic murmurs are much less common in the child, the auscultation of a diastolic murmur indicates that structural heart disease is present.

Last, a simple, noninvasive indicator of cardiac output is the capillary refill time. This is obtained by blanching the nail bed or digit, and observing the time to reperfusion, normally less than 3 seconds.

HEMODYNAMIC CONSIDERATIONS IN NEONATE⁴

Neonates are born with pulmonary arterial hypertension and this makes the assessment of left to right shunts difficult by clinical examination or echocardiography. Appearance of murmur in left to right shunts is delayed for 2 to 3 weeks till the pulmonary vascular resistance drops. This change in hemodynamic is also important for many critical cardiac evaluations. Some examples are important to consider here. A small or moderate ventricular septal

defect (VSD) will not have a PSM at birth (characteristic of a restrictive VSD shunt) due to high PVR and ECHO may not show volume overload of Left atrium and left ventricle and pulmonary pressures will always be high enough to cause confusion in the estimation of true hemodynamics of VSD shunt till 2 to 3 weeks of age. In such cases it is mandatory to repeat echo after 2 to 3 weeks to assess such patients. Similarly, right-sided obstructive lesions may be under diagnosed in neonatal period with presence of PAH (like pulmonary stenosis and TOF physiology) where gradient across pulmonary valve will be underestimated in presence of pulmonary hypertension and such cases will need follow-up evaluation after 1 to 2 weeks to reassess the severity of true obstruction by Doppler.

CLINICAL PRESENTATIONS IN NEONATE⁵ (TABLE 1)

Neonates with cardiac disease can vary in their presentations and most of these manifestations can be seen in more common neonatal disorders including septicemia, PPHN and congenital respiratory disorders. With a meticulous examination and following a standard approach for the neonate, it can help in identifying the neonate with cardiac disease and also in management of the critical disease.⁵⁻⁷

TIMING OF PRESENTATION

Timing of presentation of neonates helps in identifying the cause and initiation of timely therapy. Normally, the duct closes after 24 to 48 hours of life and so a clinical clue can be drawn from the time of onset of symptoms. If a newborn presents immediately after birth with shock or cyanosis, this can be regarded as non-duct dependent lesion and other causes should be sought. We have come across many such situations where prostaglandin was started within first two hours of life for cyanosis and subsequent echo showed normal cardiac anatomy. Although this will also happen in many instances where prostaglandin is started empirically after 48 hr of life, it should always be remembered that starting prostaglandin is justified and there are no major adverse effects and it can always be discontinued once an echocardiogram has ruled out duct dependent lesion. Keep a low threshold to start prostaglandin in suspected duct dependent lesion even if the patient is stable because there rapid deterioration will be seen once the duct closes.⁸ There is increasing evidence that starting prostaglandin empirically has better outcome than not starting it.

Lesions which present in first 48 hours of life are critical left-sided obstructive lesions like hypoplastic left heart syndrome, interrupted aortic arch, critical aortic stenosis and obstructed TAPVC, bradyarrhythmias. Later in the first week, coarctation of aorta and duct dependent lesions may present.^{5,7} Also, obligatory shunts (which

Table 1: Clinical presentations in neonates with congenital heart disease**Shock***Duct dependent systemic circulation and left ventricular outflow tract obstructions*

- Critical aortic stenosis
- Interrupted aortic arch
- Severe coarctation of aorta
- Hypoplastic left heart syndrome (HLHS)

Rhythm disturbances

- Tachyarrhythmias
- Bradyarrhythmias (e.g. complete heart block)

Cyanosis*Duct dependent pulmonary circulation*

- Pulmonary atresia, intact ventricular septum
- Pulmonary atresia, VSD and PDA
- Single ventricle with pulmonary atresia
- Severe forms of Ebsteins anomaly

Critical right ventricular outflow tract obstruction with intracardiac shunt

- Critical pulmonary stenosis with interatrial communication
- Tetralogy of Fallot with critical pulmonary stenosis
- Double outlet right ventricle, VSD with pulmonary stenosis

Admixture lesions

- Transposition of great arteries, intact interventricular septum
- Total anomalous pulmonary venous connection
- Truncus arteriosus
- Double outlet right ventricle with VSD
- Single ventricle anomalies with or without pulmonary stenosis

Congestive heart failure*Cyanotic heart disease with high pulmonary flow*

- Truncus arteriosus
- Single ventricle physiology without pulmonary stenosis
- Transposition of great arteries with VSD
- Double outlet right ventricle with VSD
- Total anomalous pulmonary venous connection

Acyanotic heart disease

- Preterm with significant post-tricuspid shunt lesions (e.g. VSD, PDA, aortopulmonary window)
- Severe valvular regurgitant lesions (e.g. mitral regurgitation associated with AV canal defects or isolated mitral regurgitation, aortic regurgitation)
- Anomalous left coronary artery from pulmonary artery (ALCAPA)
- Cardiomyopathy

Rhythm disturbances

- Tachyarrhythmias
- Bradyarrhythmias (e.g. complete heart block, high degree second heart block)

Noncardiac causes

- High output states like anemia, thyrotoxicosis, systemic Arteriovenous malformations (i.e. vein of Galen)

Asymptomatic newborn with murmur

- Mild to moderate obstructive lesions (aortic stenosis, pulmonary stenosis)
- Mild to moderate regurgitant lesions
- Physiological murmurs (including peripheral pulmonary stenosis)
- Left to right shunt lesions

don't depend on pulmonary vascular resistance) such as left ventricular to right atrial shunt also present in the first week of life. Later in the first week or in second week, cyanotic heart lesions with high pulmonary blood flow may present with Congestive heart failure where as acyanotic left to right shunts (post-tricuspid lesions like VSD, PDA, and aortopulmonary window) usually present beyond 2 to 3 weeks of age. These shunts are nonobligatory (shunts which depend on pulmonary vascular resistance) and so present only when pulmonary vascular resistance falls. Although, it must be remembered that overlap exists in the timing of presentation of these cases and coexisting diseases in such cases may lead to earlier presentation.

Neonates Presenting with Cardiovascular Collapse

The most important diagnosis in such cases is obstructive lesions like critical Aortic stenosis (AS), critical coarctation with left ventricular dysfunction and also critical pulmonary stenosis (PS) with RV dysfunction. This also includes cases of hypoplastic left heart syndrome (HLHS) and obstructive TAPVC (total anomalous pulmonary venous connection) who present in shock.

Neonates presenting with sudden onset of shock after 48 hr of life may be all the above cases (critical AS, critical PS, coarctation, HLHS, obstructive TAPVC) and also duct dependent circulation which present after duct closure with collapse.

This neonate is usually a healthy newborn who presents after 48 to 72 hr of life with sudden onset of pallor, gray appearance and breathing difficulty. Parents complain that baby is not passing urine and not taking feeds over last 4 to 6 hr. There is usually an evidence of metabolic acidosis. These newborns should be started immediately with prostaglandin E1 suspecting duct dependent systemic circulation among other measures to stabilize including ventilation and inotropes (unless echo rules out cardiac lesion).

If duct is still open these newborns may be picked up during routine evaluation with a harsh systolic murmur of obstructive lesion (aortic stenosis or pulmonary stenosis). Coarctation of aorta will be picked up by careful palpation of all 4 limb pulses and blood pressure. Any evidence of radio femoral delay should prompt the diagnosis of coarctation of aorta. Differential cyanosis with lower limb showing desaturation compared to upper limb should prompt for the cause of PDA shunting right to left (e.g. interrupted aortic arch, severe coarctation of aorta or PPHN) (Fig. 2).

ECG must be done in all neonates presenting with shock to detect arrhythmias in the neonates. Supraventricular and ventricular tachycardia, or extreme bradycardia, can be associated with pallor, diaphoresis, dizziness, and syncopal or pallid spells, all related to the decreased

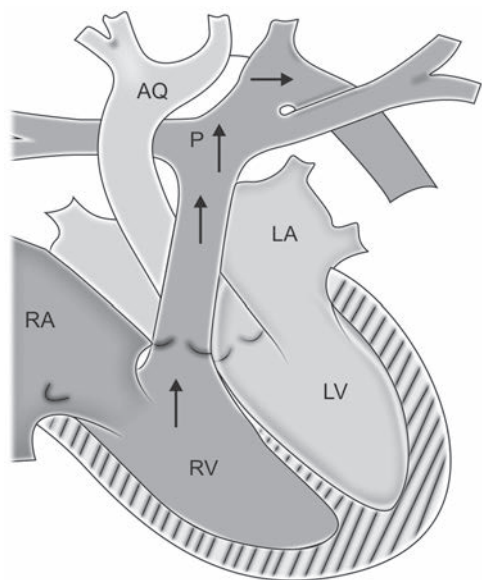


Table 2: Noncardiac causes of cyanosis in the neonate		
Pulmonary		
Primary lung disease	Airway obstruction	Extrinsic compression of the lungs
Respiratory distress syndrome, meconium aspiration, persistent pulmonary hypertension of the newborn, pneumonia, tracheo-esophageal fistula	Choanal atresia, laryngotracheomalacia laryngeal web, vocal cord para-lysis	Pneumothorax, chylothorax, hemothorax, diaphragmatic hernia, space occupying lesions in lungs
Neurologic		
CNS dysfunction	Respiratory neuromuscular dysfunction	
Drug-induced depression of respiratory drive, intracranial hemorrhage, post-asphyxial cerebral dysfunction, or central apnea	Spinal muscular atrophy, infant botulism, or neonatal myasthenia gravis	
Hematologic		
Methemoglobinemia or polycythemia		

Fig. 2: Schematic description of a interrupted aortic arch where there is no forward flow from arch into the aorta. PDA supplies blood from pulmonary artery to descending aorta which is a deoxygenated blood explaining the lower limb desaturation (arrows depict direction of blood flow). If PDA closes in this case, there will be no blood supply in the descending aorta and patient presents with shock

cardiac output. Occasional premature atrial or ventricular contractions are usually benign findings in the newborn.

Newborn Presenting with Cyanosis^{5,7,9}

Cyanosis in a newborn is a serious sign and can occur due to cardiac and noncardiac causes. Peripheral cyanosis must be differentiated from central cyanosis. Peripheral cyanosis (acrocyanosis) results from peripheral vasoconstriction or autonomic disturbances and may last for few days after birth. This may also happen after exposure to cold. Central cyanosis is characterized by bluish discoloration of tongue or mucous membranes. Pulse oximetry will help in the diagnosis of central cyanosis with a high degree of

accuracy. It must be remembered that murmurs may be absent or non-specific in many cases of cardiac cyanosis.

The causes of central cyanosis in the newborn are of cardiac, pulmonary, neurologic, or hematologic origin (Table 2). This is important to differentiate the cardiac causes from noncardiac ones. Clinical clues to diagnosis of respiratory central or cardiac causes of cyanosis in a newborn can be drawn from the respiratory pattern, pulse oximetry in right upper limb and lower limbs and response to oxygen on pulse oximeter (Table 3).

Differential Cyanosis

Pulse oximetry should be documented at preductal and postductal sites to assess for differential or reverse differential cyanosis. If the preductal saturation is higher than the

Table 3: Differential diagnosis in a cyanotic neonate				
Parameters	Respiratory pattern	Saturation difference between right upper limb (RUL) and lower limb (LL)	PCO ₂	Response to 100% oxygen
Cardiac disease	Increased respiratory rate with no or minimal distress	Usually no difference unless specific lesions	Normal or low	No significant change
Primary pulmonary disease	Increased respiratory rate with distress	No difference	High	Increased saturations
PPHN	Increased respiratory rate with distress	>10% RUL>LL	Normal or high	May or may not change
CNS disorder	Shallow respiration or apnea, hypotonia and lethargy	No difference	High or low	No significant change

PPHN: Persistent pulmonary hypertension of newborn

postductal saturation, differential cyanosis exists, which results when there are normally related great arteries and deoxygenated blood from the pulmonary circulation enters the descending aorta through a PDA. Differential cyanosis is seen in persistent pulmonary hypertension of the newborn (PPHN) and in lesions with left ventricular outflow tract obstruction such as interrupted aortic arch, critical coarctation of the aorta and critical aortic stenosis.

In rare cases of reverse differential cyanosis, the postductal saturation is higher than the preductal saturation. This occurs only in children with transposition of the great arteries (TGA) with left ventricular outflow obstruction (i.e. critical coarctation of the aorta, interrupted aortic arch, critical aortic stenosis) or TGA with PPHN. Oxygenated blood from the pulmonary circulation enters the descending aorta through PDA.

Cardiac Causes of Cyanosis

These are usually healthy neonates who present with sudden onset of cyanosis after being well for 2 to 3 days when PDA starts constricting or it may be picked up during evaluation when soft faint murmur of PDA (for example Pulmonary Atresia, VSD as shown in Figure 3) may be heard and saturation of baby reveals central cyanosis. Newborns with TGA will present with mild tachypnea without respiratory distress with saturation of around 90 percent (it should be remembered that naked eyes may not pick up cyanosis where saturation is above 85 percent, so always pulse oximeter should be used to determine cyanosis).

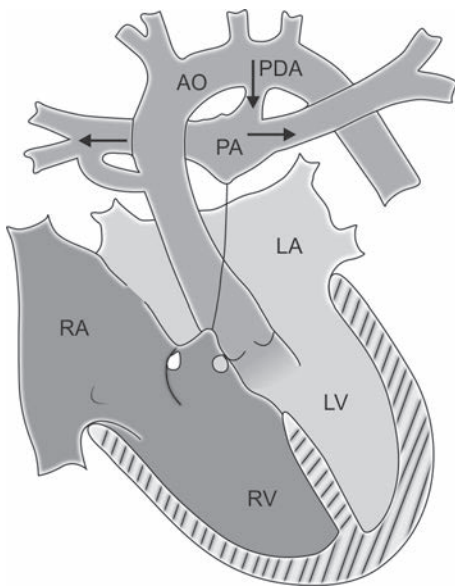


Fig. 3: Schematic diagram illustrating the aortic pulmonary valve with a VSD. There is no antegrade blood flow across pulmonary valve from right ventricle and PDA supplies blood to pulmonary circulation. Arrows depict the direction of blood flow from aorta to pulmonary artery through PDA

There is obviously no response to oxygen in such cases and hyperoxia test fails. Although, it should be remembered that its not necessary to conduct hyperoxia test before starting prostaglandin especially if child has sudden onset of desaturation after being well for first 48 hr of life.

Chest X-ray (Figs 4 to 7) should be obtained as soon as possible to rule out respiratory issues. It will help in assessing the pulmonary blood flow and presence of cardiomegaly. Increased pulmonary blood flow with cardiomegaly will suggest the possibility of TGA (egg on string appearance), truncus arteriosus (high pulmonary artery take off) or unobstructed TAPVC where as pulmonary edema without cardiomegaly will suggest obstructed TAPVC. Reduced pulmonary blood flow with no or minimal cardiomegaly will point to duct dependent pulmonary circulation or critical RVOT obstructions with intracardiac mixing. Massive cardiomegaly with reduced pulmonary blood flow will suggest a diagnosis of Ebstein anomaly. ECG will also be helpful in identifying the type of disease. Tricuspid atresia will have superior axis, Critical PS or PA/IVS will have axis in 0 to 90 quadrant whereas TOF will have axis 90 to 180.

Hyperoxia Test

A hyperoxia test should be used in a neonate to differentiate mainly cardiac from respiratory illness and is performed when resting saturations are less than 95 percent. It is performed with administration of 100 percent O₂ through head mask for 10 minutes. Direct arterial blood gas sample is taken from right upper limb (preductal) and

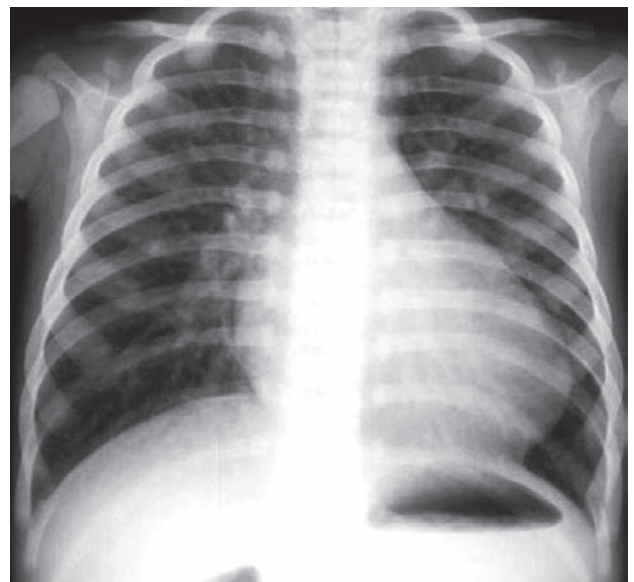


Fig. 4: Chest X-ray of transposition of great arteries. Note the narrow upper border of mediastinum (due to anteroposterior relationship of great arteries and absence of thymus) and classical egg on string appearance. There is clear evidence of high pulmonary blood flow

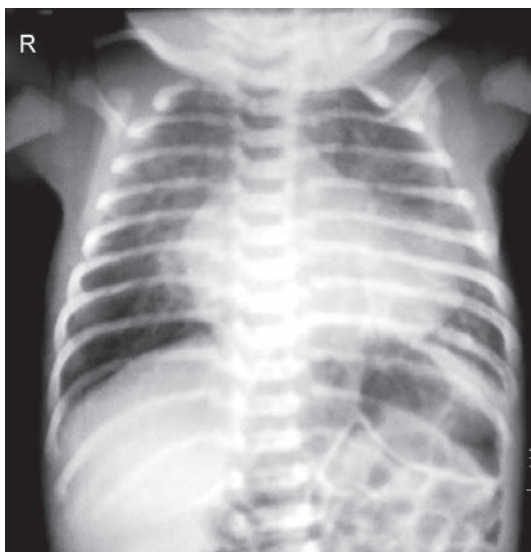


Fig. 5: Chest X-ray showing cardiomegaly with high pulmonary blood flow and narrow upper border of mediastinum. There is a high take off of pulmonary arteries suggesting possibility of truncus arteriosus

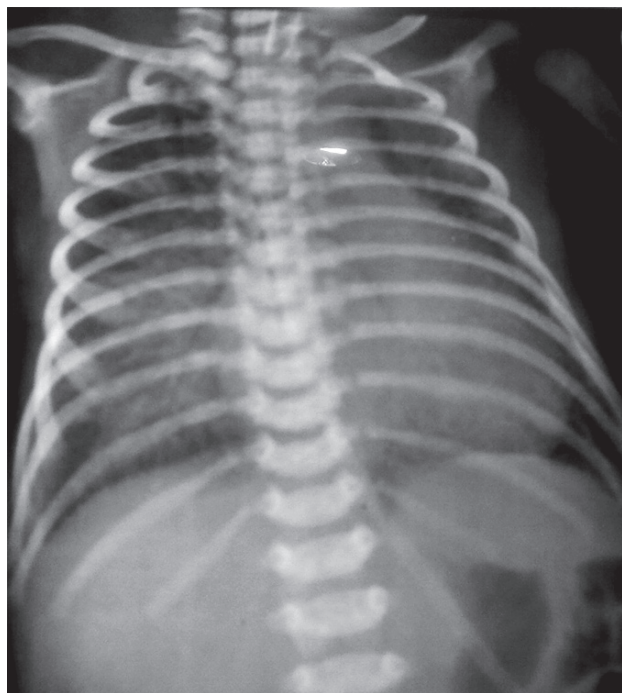


Fig. 6: Chest X-ray of a neonate with infracardiac obstructed TAPVC. Note the normal sized heart with diffuse reticular infiltrates due to pulmonary edema

any lower limb or left upper limb (postductal) measured at baseline ($\text{FiO}_2=0.21$) and after 100 percent oxygen delivery (Table 4 for interpretation). PaO_2 more than 250 mm Hg in an arterial sample from right arm after 100 percent oxygen for 10 minutes excludes cyanotic congenital



Fig. 7: Chest X-ray in a neonate with pulmonary atresia and VSD. Note the boot shaped right ventricular apex, no cardiomegaly and pulmonary oligemia

heart disease, and if PaO_2 is more than 150, cyanotic heart disease is unlikely.¹⁰

Limitations of Hyperoxia Test

- Total anomalous pulmonary venous drainage (TAPVD) and hypoplastic left heart syndrome may respond to oxygenation.
- Pulmonary disease with a massive intrapulmonary shunt may not respond to oxygenation.
- This test is not as reliable as an echocardiogram and is not as important as resuscitation and attendance to cardiorespiratory support, especially if acidosis or respiratory distress is present
- Failed hyperoxia test will not differentiate cardiac disease from PPHN

All cyanotic lesions in the newborn should be considered as an emergency and pediatric cardiologist opinion should be sought as soon as possible. But critically ill newborns those are duct dependent will not give time and will need emergency administration of prostaglandin E1 infusion hence the need for every neonatal ICU to keep the prostaglandin in the emergency trolley (Table 5).

NO RESPONSE TO PROSTAGLANDIN INFUSION

If there is no response to prostaglandin infusion consider the following:

1. Noncardiac diagnosis.
2. Obstructed TAPVC.
3. TGA with Intact interventricular septum and restrictive PFO which needs emergency balloon atrial septostomy (BAS)

Table 4: Interpretation of hyperoxia test

	At $\text{FiO}_2 = 0.21$ PaO_2 (saturation %)	At $\text{FiO}_2 = 1.00$ PaO_2 (saturation %)	PaCO_2
Normal	>70 (>95)	>300 (100)	Normal
Pulmonary disease	50 (85)	>150 (100)	High
Neurological disease	50 (85)	>150 (100)	High
Methemoglobinemia	>70 (<85)	>200 (<85)	Normal
Cardiac disease	40-60 (75-93)	<150 (100)	Normal
PPHN	Preductal 40-70 (75-95) Postductal <40 (75)	Variable Variable	Normal

PPHN: Persistent pulmonary hypertension of newborn

Table 5: How do we start prostaglandin?

Dosage and administration

Prostaglandin is started at a dose of 0.001-0.4 microgram/kg/min infusion. Higher doses in the range of 0.1 microgram/kg/min should be used to reopen the closed PDA (or if there is sudden onset of severe cyanosis or shock). If prostaglandin fails to open the duct, the dosage should be increased in the increments of 0.05 microgram/kg/min every 5-10 minutes till 0.4 microgram/kg/min. Once the duct has opened, dose can be reduced to a minimum to keep the duct patent.

Lower doses in the range of 0.01 microgram/kg/min should be used once duct has opened and continued till definitive surgical repair. With proper monitoring in ICU for saturations and under echocardiographic guidance (for PDA monitoring), dose can be reduced to 0.001 microgram/kg/min.

Preparation

Prostaglandin is available at strength of 500 microgram per vial, dilute it in 50 ml of 5% dextrose and start in infusion pump.

According to formula (this formula can be used for any inotropes)

$3 \times \text{wt} \times \text{microgram/kg/min}$ divided by concentration (mg) in 50 ml = flow rate in ml/hr

So for wt of 3 kg child and dose of 0.1 mic/kg/min

$3 \times 3 \times 0.1/0.5 = \text{ml/hr}$ (0.9/0.5) = 1.8 ml per hr infusion will give you 0.1 microgram/kg/min prostaglandin in 3 kg child if you add 0.5 mg prostaglandin in 50 ml syringe.

The effect of prostaglandin usually is seen in half hour and infusion should be continued till the definitive diagnosis rules out duct dependent lesion.

enterocolitis). Bounding pulses in such cases along with wide pulse pressure should give a suspicion for the presence of hemodynamically significant PDA. One more common scenario in preterm PDA is after surfactant therapy, they show improvement and ventilatory requirements go down. As hyaline membrane disease improves and PVR falls, PDA shunt becomes significant and ventilatory requirements become higher. Other post-tricuspid lesions can also be seen in preterm neonates (e.g. large VSD, AP window) where they can present with CHF in early neonatal period. These post-tricuspid shunts usually don't present in full term neonates as PVR falls after 4 to 6 weeks and then shunt lesions start manifesting as CHF.

Among other acyanotic lesions with CHF are valvular regurgitant lesions like aortic regurgitation or pulmonary regurgitation (which may be secondary to vegetations of these valves also). Congenital mitral valve lesions with severe MR can also present in neonates with CHF. Diastolic murmur in AR or PR and pansystolic murmur in MR will give a significant clue. Chest X-ray in such cases will show Cardiomegaly of the respective chambers (cardiothoracic ratio >0.6). This is important to remember that thymic shadows and extracardiac shadows can lead to over diagnosis of cardiomegaly on chest X-ray (Figs 8 and 9).

Among cyanotic heart diseases which present in neonatal life with CHF are those with significant high pulmonary blood flow like truncus arteriosus or single ventricular physiology without pulmonary stenosis.¹¹ Important point to remember in such cases is that these neonates will not be significantly cyanotic due to torrential pulmonary blood flow and saturation may vary in the range of 90's, so naked eyes will not pick up the cyanosis and pulse oximetry will help in the early detection of such congenital lesions.

Asymptomatic Newborn with Murmur

This is a group where lesions are usually mild forms of obstructive or regurgitant lesions. These lesions can be aortic stenosis or pulmonary stenosis. These obstructive lesions are characterized by presence of harsh murmur

Neonate Presenting with Congestive Heart Failure

The early features of congestive heart failure in neonates will be difficulty in feeding, subcostal indrawing, sweating with feeds, tachypnea, tachycardia, gallop rhythm and hepatomegaly. Most common group would be preterm neonate with post tricuspid shunt lesion, mainly patent ductus arteriosus. Preterm with PDA can also present with steal phenomenon like cerebral steal (manifesting as apnea) or steal from gut (manifesting as necrotizing

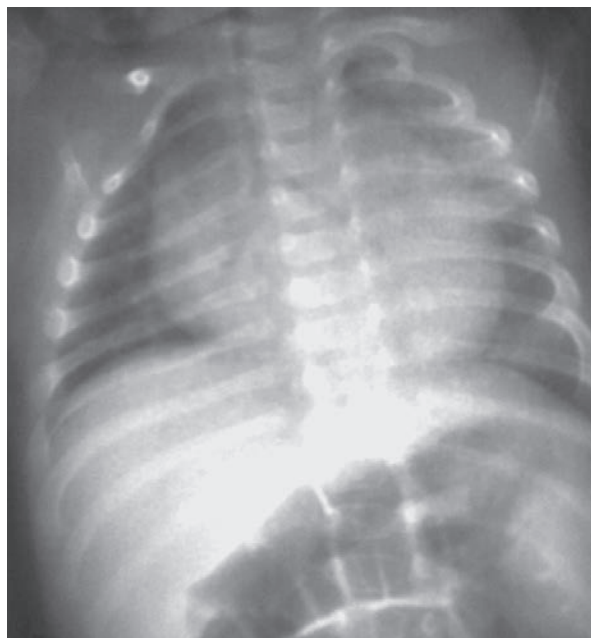


Fig. 8: Chest X-ray (rotated film) of a normal neonate with large thymus appearing as cardiomegaly

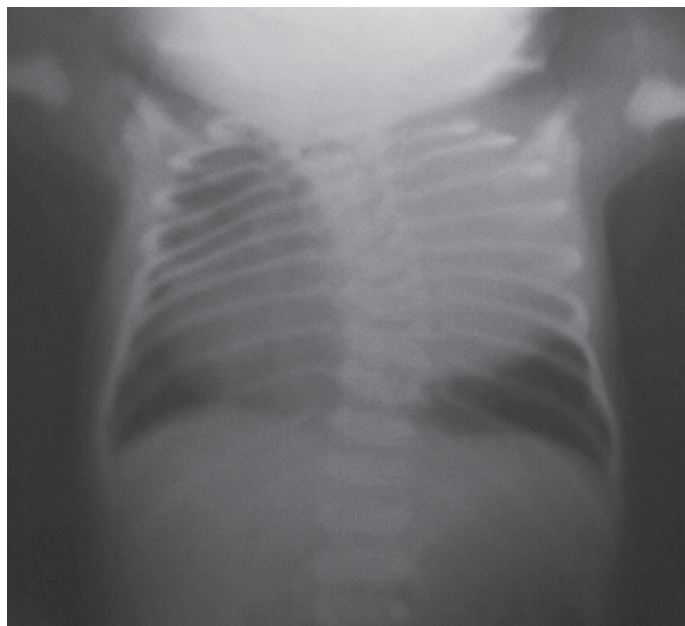


Fig. 9: Chest X-ray showing left-sided space occupying lesion with dextroposition of heart mimicking cardiomegaly. Patient had cyanosis and respiratory distress at birth due to space occupying lesion in thorax

and click if obstruction at the valvar level. TOF with absent pulmonary valve will present with to and fro murmur which is very classically heart in left 2nd intercostal space. Ebstein with TR will present with PSM at tricuspid area and multiple ejection clicks will confirm the diagnosis. Classical forms of Ebstein anomaly will have box shaped heart on CXR. Severe forms of Ebstein anomaly will present with cyanosis due to lack of forward flow across pulmonary valve and may need prostaglandin infusion for pulmonary circulation. Mitral regurgitation may be seen in isolation or with atrioventricular canal defects with cleft mitral valve. These defects may present as asymptomatic or may present with CHF at 10 to 14 days of life with CHF if MR is severe.

Another group of neonates presenting with murmur will be left to right shunt (post-tricuspid) lesions which are restrictive (small or moderate shunts) and usually present with a murmur when PVR falls (after the age of 2 to 4 weeks). Few cases of small defects may present with murmur in first week also. This group of neonates are usually asymptomatic in the neonatal period due to restrictive nature of shunts and start having symptoms beyond the neonatal period. This is important to mention in such cases that preterm neonates may have symptoms within neonatal period as in preterm PDA cases.

Physiological peripheral pulmonary stenosis is a frequent finding in neonates and there may be a significant systolic murmur in such cases. Pediatric cardiologist must

take care not to miss cases of syndromes associated with peripheral stenosis like Alagille, congenital rubella syndrome and William's syndrome. Physiological peripheral pulmonary stenosis is reduced in two-thirds of cases by 6 weeks of age and in most others by 6 months. The etiology of the murmur is secondary to both relative hypoplasia of the pulmonary artery branches and an associated angulation at their origin.

This is important to understand that many duct dependent lesions in the immediate neonatal period may be totally asymptomatic till the PDA is open and minimal cyanosis or a murmur of PDA may be the only finding in such cases. These are the cases which may go undetected, discharged and later comeback in critical situation.¹² In such cases repeated and careful clinical examination, pulse oximetry along with chest X-ray and ECG are helpful to assess the severity of lesion.

SUMMARY

Neonates with cardiac disease may present in one of the four groups-shocks, cyanosis, CHF and asymptomatic. Differentiating from noncardiac causes is feasible on bed side examination along with pulse oximetry, chest X-ray, ECG and other basic investigations such as hyperoxia test.¹ Also not all murmurs are due to heart disease and not all newborns without a murmur are free of CHD. Prostaglandin E1 may be started empirically in shocky neonates and also in failed hyperoxia test which can be life saving.⁸

Critical congenital heart lesions in neonates have a better outcome if referred early for a surgical repair in today's world even in developing countries.

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Diagnostic Cardiac Evaluation of a Neonate

Poonam Sachdev, Neeraj Agarwal, Manvinder Singh Sachdev

INTRODUCTION

Congenital heart diseases (CHDs) are considered important as they are a leading cause of morbidity and mortality in infancy.¹ According to studies the incidence of congenital heart defects is 7 to 8 per 1000 live-born infants and cause 3 percent of all infant deaths. The CHD are the commonest group of congenital anomalies which cause 46 percent of deaths attributable to congenital malformations. Many of the critical congenital heart diseases are recognized when the infant manifests life-threatening symptoms of cardiovascular collapse. A critical CHD can be defined as a congenital heart disease which requires surgery or catheter intervention in infancy. Early detection can prevent death or cardiovascular collapse with its attendant morbidity and improve the outcome of congenital heart defects.²

CLINICAL PRESENTATION

Congenital heart disease (CHD) may be diagnosed at any age from newborn period to adulthood. Many CHD's always present in the newborn period whereas others are rarely identified during infancy.³ Many studies indicate that of all the CHD 50 percent are detected by 1 month, 75 percent by 3 month of age and about 100 percent by 3 to 4 years of age.¹ The presentation of different CHD's varies with time owing to the variable rate of decrease or change in pulmonary vascular resistance (PVR) after birth and variation in the time interval for closure of ductus arteriosus.¹ The common presentations of neonates who need care of a pediatric cardiologist are:³

- Asymptomatic murmur
- Cyanosis (often without a murmur)
- Gradually progressing symptoms of heart failure or
- Catastrophic heart failure and shock.

These findings are not always evident before the newborn is discharged from the hospital at about 48 hours of life.¹ The latter two presentations mostly occur after

discharge from the hospital.³ Many newborns with critical congenital heart disease present with sudden significant deterioration of clinical status in the first few days or weeks of life and some may be so severely sick at presentation that they die before surgical intervention. Studies suggest that timely recognition of critical congenital heart disease could improve outcomes hence, it is important to have strategies that can help in timely diagnosis and treatment of these infants.^{1,3}

DIAGNOSIS

The evaluation and diagnosis of a newborn with congenital heart defect is challenging. The current objective of CHD diagnosis is presymptomatic identification of life-threatening congenital heart defects and other clinically significant congenital heart defects as timely recognition can improve outcomes. Strategies for timely identification of critical and clinically significant congenital heart defects include fetal echocardiography and physical examination within the first 24 hours of life and on subsequent nursery visits. Pulse oximetry, electrocardiograms, chest radiographs, echocardiograms are supplemental tests which are done in suspicious cases.⁴

Physical Examination

Cardiovascular system examination at the time of clinical newborn examination is considered to form part of newborn screening for congenital anomalies. The newborns are also examined at the subsequent nursery visit and again at 6 to 8 weeks of age. However, this strategy has not been effective in improving outcome for infants with congenital heart defects.²

Fetal Echocardiography

Prenatal ultrasound to detect fetal anomalies can advance the time of diagnosis of congenital anomalies from postnatal

to fetal life.⁵ The risk of death due to congenital heart disease before diagnosis has decreased with the increased application of fetal echocardiography and improved understanding of the presentation of critical congenital heart diseases (CCHDs). However, mortality due to CHD continues to remain significant.^{2, 4}

According to some studies short-term outcomes of CCHD has improved with prenatal diagnosis as compared to postnatal diagnosis.^{6,7} However, improved survival with prenatal diagnosis has not been observed in numerous other studies.^{8,9}

Fetal echocardiography for congenital heart anomalies is usually done at 18 to 20 weeks' gestation. A methodical scan can identify many cases of CHD if not all. If a CHD is identified or suspected during the scan the patient may be referred to a pediatric cardiologist for confirmatory imaging and counseling. With knowledge that the fetus has CCHD, arrangements for delivery of the newborn at a hospital with advanced medical facilities like a tertiary level neonatal intensive care unit where intensive care, prostaglandin infusion, mechanical ventilation, etc. are available can be made. After stabilization the newborn can be transferred to a center specializing in surgery and care of children with congenital heart disease.⁴

A methodical scan can identify many cases of CHD if not all when it is done by a health care professional with specific training in congenital heart disease. However according to many studies even when fetal ultrasound is regularly done during pregnancy, less than 50 percent of cases of CCHD are recognized as many scans may be done by professionals with inadequate training. Besides the concerns about the quality and low detection rate on anatomic ultrasounds limited access to prenatal ultrasound also remains a major problem.⁴ Even in developed countries like the United States, an anatomic ultrasound is not performed in all women.¹⁰ Therefore this methodology alone is not adequate to identify a high proportion of cases.⁴

PULSE OXIMETRY AND DETECTION OF CHD

Currently many investigators have suggested that pulse oximetry should be used along with newborn physical examination after delivery to enhance timely detection of CCHD.^{11,12} Pulse oximetry is an accepted modality of assessment of young children in neonatal intensive care units and in other emergencies.¹³

Hypoxemia is often present in many congenital heart diseases. It occurs due to mixing of systemic and venous circulations or parallel circulations as present in d-transposition of the great arteries. Hypoxemia may cause obvious central cyanosis but for this 4 to 5 g of deoxygenated hemoglobin should be present irrespective of total hemoglobin concentration. Hence, if a newborn has a hemoglobin concentration of 20 g/dL, cyanosis will

become evident when arterial oxygen saturation is <80 percent and in an infant with hemoglobin concentration of 10 g/dL, it will become obvious when the saturation is <60 percent. Cyanosis may not be obvious in children with mild hypoxemia that is if the arterial oxygen saturation about 80 to 95 percent. Besides this, identification of cyanosis can be difficult in dark skinned neonates and infants because of skin pigmentation. Majority of CCHD have some amount of hypoxemia in the newborn period.⁴

According to some experts pulse oximetry should be considered as a vital sign equivalent to pulse, respirations, and blood pressure during clinical examination.¹⁴ Centres where pulse oximetry is routinely used have noted that it has contributed to improved detection of congenital heart disease in neonates. Although some studies have observed improved detection rate with pulse oximetry the efficacy of oximetry in clinical practice for CCHD is not well established. There are some limitations of pulse oximetry in detection of CCHD. Pulse oximetry cannot identify all cases of CCHD, hence if the test result is negative possibility of a heart disease is not excluded. In addition oximetry screening is not very effective in identifying the CCHD lesions which are at greatest risk for acute cardiovascular compromise, namely, obstructive left heart lesions such as aortic stenosis, and coarctation of the aorta. Further studies are needed to establish the usefulness of pulse oximetry for detection of CHD and whether it should be considered as standard of care in the routine assessment of the neonate.⁴

Chest X-ray

Chest X-ray (CXR) may not be useful for detection of many of the CCHD lesions in the newborn period however it is still considered as an important modality of investigation for CHD. Several changes in the CXR due to congenital cardiovascular abnormalities have been described which are recognized to be clinically important. Whenever the CXR of a child is being reviewed consider the age of the patient, the posture (that is whether if the film was taken in the sitting or lying position) and evaluate the X-ray systematically.¹⁵

- *Check alignment and penetration:* The CXR is considered adequately penetrated if the disk spaces of the lower thoracic vertebrae are seen through the heart shadow. On the right hand side a minimum of 5 anterior rib ends should be visualized. To assess the alignment the medial ends of both clavicles is observed. They should be equally spaced about the spinous processes of the upper thoracic vertebrae.
- *Check bones, cartilage and soft tissues:* Observe the ribs, clavicles and vertebrae. Evaluate both the lung fields systematically and check for pleural effusions, pneumothorax, changes in vascular markings (increased or decreased that is plethoric or oligemic lung fields),

fluid in the fissures, consolidation or hemorrhage. Assess the cardiac size and the cardiothoracic ratio. In infants the normal heart can be up to 60 percent of the thoracic diameter, and later is about 50 percent of the thoracic diameter. However, a normal cardiac shadow does not exclude the possibility of cardiac disease. Interpreting Cardiac shadow in a neonate may be tricky because of thymus or expiratory film which may present as cardiomegaly in many cases (Fig. 1).

- *Check diaphragm:* Assess the cardiophrenic and costophrenic angles. Both should appear clear and well demarcated.
- Some of the well recognized appearances of heart disease on CXR are:¹⁶
- *'Egg-on-side':* Transposition of great arteries (Fig. 2)
- *Boot shaped heart:* Tetralogy of Fallot (lung fields appear oligemic) (Fig. 3)
- *'Snowman in a snowstorm':* Obstructed total anomalous pulmonary venous connection in a neonate (Fig. 4)
- *Globular heart:* Usually associated with pericardial effusions, dilated cardiomyopathy (Fig. 5)
- *Situs:* In the normal situation (situs solitus) the heart is on the left with the gastric bubble on the left and the liver on the right. In situs inversus these relations are reversed.
- *Oligemic lung fields:* Associated with cardiac conditions with reduced pulmonary blood flow such as TOF and pulmonary atresia (Fig. 3)
- *Plethoric lung:* Observed in cardiac conditions with increased pulmonary blood flow such as VSD and ASD (Fig. 6)



Fig. 1: Apparent cardiomegaly on CXR due to a prominent thymus



Fig. 2: Egg on end appearance of the heart in a patient with transposition of great arteries; this appearance on a CXR is due to the presence of cardiomegaly with a narrow pedicle; artifact caused by cable noted



Fig. 3: The classic boot shaped appearance in a patient with tetralogy of Fallot

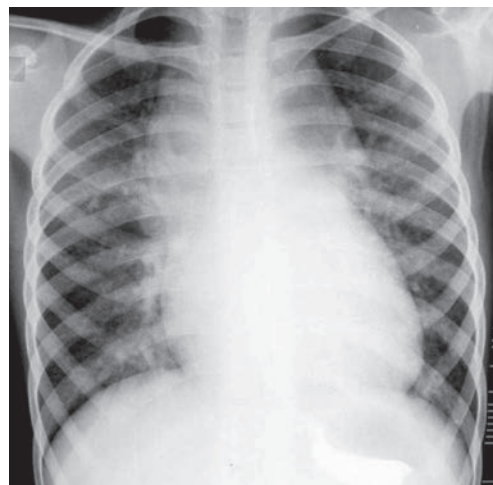


Fig. 4: Snowman in a snowstorm appearance in a patient with obstructed supracardiac TAPVC

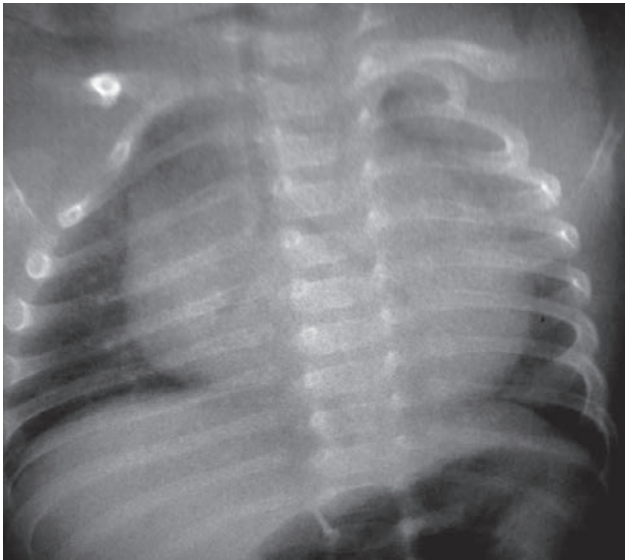


Fig. 5: Globular appearance of cardiac silhouette in this neonate with pericardial effusion



Fig. 6: Pulmonary plethora as evidenced by more than four end on vessels in the middle 1/3rd

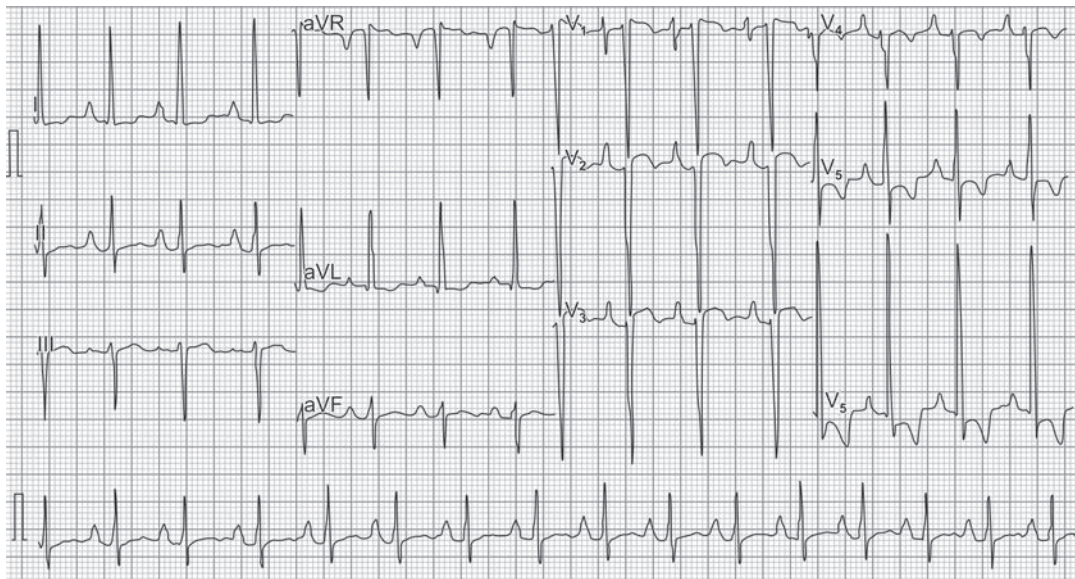


Fig. 7: ECG showing left axis deviation, LVH, No right ventricular forces in a 6-week-old with tricuspid atresia, restrictive VSD, pulmonary stenosis (on treatment with β -blocker)

Electrocardiogram (ECG)

The ECG may be useful to investigate rhythm and conduction abnormalities, as well as assessing chamber hypertrophy and strain. The use of ECG in neonates for a guide of diagnosis is considerably limited in view of Right ventricular preponderance in a neonate and most cyanotic neonates too have right ventricular dominance as their ECG findings. Nevertheless ECG may be helpful in certain conditions as below.

- Left axis deviation with left ventricular dominance in a neonate with tricuspid atresia (Fig. 7)
- Superior axis in patients with endocardial cushion defects
- Neonates with abnormality of rhythm (Bradyarrhythmia or tachyarrhythmia) (Fig. 8)

ECG alone may not be useful but when used in conjunction with chest X-ray findings it may help to narrow down the differentials in patients presenting with heart failure (Table 1).

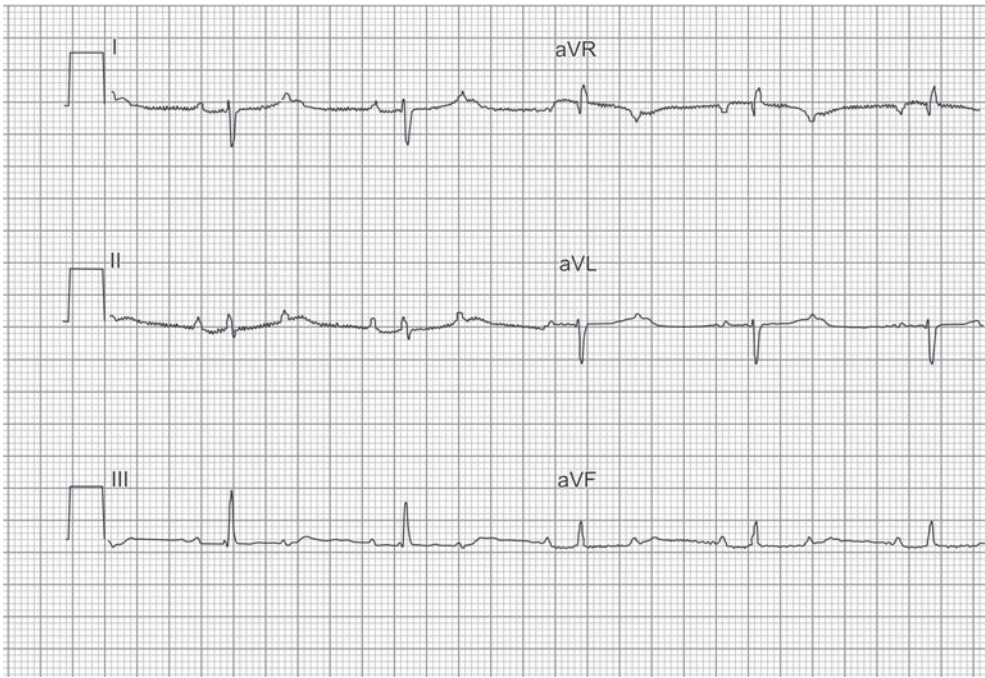


Fig. 8: ECG showing a 2:1 AV block and long QT syndrome in a 2-day-old neonate presenting in bradycardia, QTc was measured to be 490 msec

Table 1: Differential diagnosis of heart failure using CXR and ECG			
ECG	CXR		
	Increased pulmonary blood flow	Pulmonary venous congestion	Decreased pulmonary blood flow
RVH	HLHS CoA Aortic stenosis Interrupted arch truncus arteriosus TAPVC (unobstructed) PDA AVSD ASD	TAPVC (obstructed) Mitral stenosis all with severe heart failure	Pulmonary stenosis Ebstein's anomaly
LVH	PDA Truncus arteriosus aortic stenosis Univentricular connection with unobstructed PBF	Aortic stenosis all with severe heart failure	PAIVS PS hypoplastic RV
BVH	VSD AVSD Truncus arteriosus DORV Univentricular connection with unobstructed PBF	all with severe heart failure	Complex forms of pulmonary atresia

(HLHS: Hypoplastic left heart syndrome; CoA: Coarctation of aorta; AVSD: Atrioventricular septal defect; TAPVC: Total anomalous pulmonary venous connection; DORV: Double outlet right ventricle, PDA: Patent ductus arteriosus; ASD: Atrial septal defect; VSD: Ventricular septal defect; PAIVS: Pulmonary atresia with intact ventricular septum)

ECHOCARDIOGRAPHY

Echocardiography is currently the most commonly used diagnostic modality postnatally for diagnosis and assessment of cardiovascular function in newborns with suspected congenital heart defects. The major advantage of echocardiography is the fact that it is an accurate noninvasive investigation in a newborn which gives both structural and hemodynamic status of congenital heart disease.¹⁷

INDICATIONS FOR ECHOCARDIOGRAPHY IN A NEONATE

- Any neonate presenting in heart failure
- Any neonate presenting in cyanosis or saturation less than 94 percent on routine exam
- Any neonate with a heart murmur
- Any neonate detected to have discrepancy in pulses
- Any neonate with abnormal blood pressure
- Cardiomegaly detected on a chest X-ray
- Neonate with unexplained hemodynamic instability.

An echocardiogram done for the above indications by a pediatric cardiologist or an experienced. Pediatric cardiac sonographer results in pickup of most congenital heart disease.

In a study Rice and her colleagues¹⁸ evaluated the effect of echocardiography in the management of newborns suspected of having congenital heart disease. The results of this study observed that echocardiography improved the management of sick newborns with no increase in morbidity and was accurate when compared to invasive diagnostic modalities such as cardiac catheterization. Leung et al.¹⁹ found that echocardiography had a sensitivity and specificity of 95.5 and 98.6 percent respectively in a study while evaluating 536 cardiovascular anomalies in newborns. The authors concluded that infants could be

correctly managed without cardiac catheterization and several other studies have corroborated these findings.¹⁹

A segmental approach needs to be followed for an accurate diagnosis of congenital heart disease in a neonate by echocardiography. This approach includes sequential analysis of situs, systemic and pulmonary venous drainage, atrioventricular and ventriculoarterial connections, looping of ventricles and associated intracardiac structures and assessment of great arteries their branches and ductus arteriosus. Also important consideration needs to be given to dimensions of the cardiac structures as well as hemodynamic information (measurement of gradients across the valves and pulmonary artery pressure assessment). Following this systematic approach ensures that the diagnoses reached properly explains the presentation as well as the hemodynamics.

With improving access to technology a functional echocardiogram done by a trained neonatologist in suspicious cases helps in pickup of congenital heart disease in a neonate even before they become critical. These will need to be confirmed by a pediatric cardiologist. Certain indicators on echocardiograms in a neonate with cyanosis are illustrated in Table 2. These findings on a functional echocardiogram should arouse considerable doubt leading to swift involvement of pediatric cardiologist and timely pick up and management of critical congenital heart disease.

Echocardiography in hands of a pediatric cardiologist is useful in diagnosing cyanotic congenital heart disease which clinically present as persistent fetal circulation and shows evidence of ventricular dysfunction, dilated right ventricle and presence of tricuspid insufficiency as identified on functional echocardiogram. Echocardiographic features which may help reach the diagnoses in such patients are indicated in the Table 2.

Table 2: Differential diagnosis of a sick newborn presenting with cyanosis

<i>Anomaly</i>	<i>Characteristic echocardiographic findings</i>	<i>Definitive echocardiographic features</i>
Total anomalous pulmonary venous drainage	Dilated right ventricle, small left atrium (bald appearance), interatrial septum bowing into the left, right-to-left atrial shunting	Right-to-left shunting across the interatrial septum
Functional pulmonary valve atresia	Dysplasia of tricuspid valve or Ebstein's anomaly, severe tricuspid insufficiency, dilated right atrium, no or minimal ante grade flow across the pulmonary valve, presence of pulmonary regurgitation	Presence of pulmonary regurgitation
Simple transposition of great arteries	Aorta from right ventricle, pulmonary artery from left ventricle; parallel great arteries, ductus arteriosus easier to visualize in the arch view compared to the parasternal short axis view	Bifurcating great artery arising from the left ventricle
Ebstein's anomaly of the tricuspid valve	Dilated right atrium, small right ventricle, apical displacement of the tricuspid valve attachment, tricuspid insufficiency	A very large right atrium and morphology of tricuspid valve
Dilated cardiomyopathy or myocarditis	Dilatation of the left ventricle with global hypokinesia, presence of mitral and tricuspid regurgitation	Rule out arch anomalies and coronary abnormalities

CONCLUSION

Timely identification of neonate with congenital heart disease especially those who are symptomatic is of paramount importance as when picked up on time and managed the results may be quite good. Institution of appropriate management can really help in improving the long-term survival of newborn with congenital heart disease. High index of suspicion, proper physical examination, institution of protocols in nursery which include blood pressure measurement and pulse oxymetry, use of chest X-ray, ECG and reliable echocardiogram by a pediatric cardiologist help in diagnosis and management of critical congenital heart disease in a neonate.

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Screening for Inborn Errors of Metabolism

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Abstract

Inborn errors of metabolisms (IEMs) are inherited disorders occurring due to block(s) in one or more biochemical pathways in human body. The IEMs are rapidly gaining importance in our country for reasons: (i) IEMs are collectively not uncommon in our country in view of the vast population and prevalence of consanguinity, and (ii) technological revolution and medical advancements leading to reduction in mortality due to infections and perinatal events. The awareness for these disorders is also essential as early detection has potential for treatment, thus prevention of death and irreparable brain damage. This article describes an approach for testing a sick neonate, as well as newborn screening. Diagnostic algorithms for a suspected case of IEMs are given. For newborn screening, the evolving methods are discussed including tandem mass spectrometry.

INTRODUCTION

Inborn errors of metabolism (IEMs) are genetic disorders occurring due to deficiency of an enzyme or co-factor or transporter in any metabolic cascade in our body.¹ This disrupts a biochemical pathway, leading to symptoms and signs due to accumulation of toxic metabolites prior to the block or deficiency of the end product beyond the metabolic block.

Nearly all the inborn errors of metabolism are inherited recessively, mostly autosomal and some X-linked. They are individually rare but collectively numerous.² They are increasingly being recognized because of the advancement in diagnostic facilities like blood gas analysis and automated biochemical tests, coupled with the reduction in mortality related to infections and perinatal asphyxia.³ Other factors that lead to an increased frequency of IEMs in our country are a huge population, high birth rate, and custom of consanguineous marriages among many communities.⁴ Limited studies have been published on the prevalence of IEMs in India.⁵⁻⁸ Nagaraja and Christopher et al reported a prevalence of 3.2 percent with a small molecule disorder (amino acidopathy, organic aciduria, and fatty acid oxidation defect) among a high-risk cohort in South India. At Sir Ganga Ram Hospital, a study of 393 cases suspected to have inborn errors of metabolism resulted in specific diagnosis in 56 (6.7%) cases (Table 1) (personal communication). At our center, we found a wide

range of metabolic disorders through similar screening, and the common disorders prevalent in our cohort were Methyl malonic aciduria, maple syrup urine disease and Citrullinemia type 1.

SCREENING FOR IEMS IN THE NEWBORN

Inborn errors of metabolisms can be broadly categorized into three groups.⁹ The enzyme defects occurring in the

Table 1: IEM: detected in a cohort of patient at Ganga Ram Hospital

Disorders detected	Number of children
Organic acidemias	38
Methyl malonic acidemia	12
Multiple carboxylase deficiency	8
Maple syrup urine disease (MSUD)	7
Glutaric aciduria type II	4
Propionic acidemia	3
3 methylglutaconic aciduria	2
Beta-ketothiolase deficiency	2
Urea cycle disorders	9
Citrullinemia	4
Argininosuccinic aciduria	2
Arginase deficiency	1
Ornithine transcarbamylase deficiency	1
HHH syndrome	1
Other disorders including Tyrosinemia 2	9

metabolism of amino acids, carbohydrates and fatty acids or in the mitochondrial energy metabolism are referred to as 'small molecule disorders'. Clinical manifestations of these disorders are severe and non-specific and occur early in life. In contrast, larger molecule or storage disorders, the symptoms develop gradually due to accumulation of substrates, thus resulting in progressive organomegaly and coarse body features. A third group is that of other miscellaneous disorders of metals (Wilson and Menkes disease), lipoproteins, congenital adrenal hyperplasia and hyperinsulinism.

The focus of this article is on the 'small molecule disorders' which comprise classical IEMs in the neonatal period. These disorders are dynamic, fluctuating with the patient's metabolic state and require early diagnosis for therapeutic intervention to prevent the irreparable brain damage.

APPROACH TO INBORN ERRORS OF METABOLISM

There are two approaches to screening for inborn errors of metabolism. The first is the testing of suspected cases in order to establish diagnosis in a sick neonate or infant. The second approach is to screen all newborns for selected group of disorders. This approach is ideal and an established practice in the developed countries as the babies who are screened positive for a known metabolic disorder then gets preventive treatment and develops normally with no or minimal disability in life. Mass newborn screening however requires huge investments and funding for ongoing expenses of the program. The newborn screening would only be considered successful if appropriate preventative strategies are available to the general citizens, which depend on the cost and effort from the government. Thus, it has yet to take off in India, although pilot studies have been started.¹⁰ Facilities for diagnosis of all IEMs to be included in newborn screening programs are now available in India (at least in the private sector) but the treatment possibility still eludes the average Indian in view of the overpowering costs and difficulty in procuring the special diets and medications. Once these facilities are set up and strong socioeconomic and health infrastructure has been built up, newborn screening should be initiated. Until that time, in our country, screening for high-risk neonate and infants seems the way to go.

SCREENING OF HIGH-RISK (SICK) NEONATES

Enormous strides have been made in the past three decades in the recognition and understanding of metabolic illnesses. The newborn appears to have a limited repertoire of ways to respond to insult, with the result that the clinical features of many inherited metabolic diseases are superficially indistinguishable from that of the commoner acquired conditions, such as infections and intoxications. Moreover, a newborn with an IEM may present

with a proven infection. Thus, a high index of suspicion is required in order to identify the sick neonate with an IEM. The diagnosis of IEMs should be considered along with that of other common illnesses, and should not be a diagnosis of exclusion. This would save the time which is of utmost importance for improving outcomes in these babies.

Pointers to the presence of IEM are:¹⁰

- History of acute deterioration after a period of normalcy after birth. This is so because symptoms are caused by postnatal accumulation of toxic metabolites, which were getting cleared *in utero* by the placenta and maternal metabolism. Examples are urea cycle defects, organic aciduria and galactosemia. However, it is important to note that this period of normalcy may not be always present and obscured by other problems like perinatal asphyxia.
- A family history of consanguinity or similar illness in a sibling.
- Progressive illness showing nonspecific signs of cerebral dysfunction such as poor sucking, limpness, vomiting, irritability, respiratory distress, lip smacking movements and hypothermia.
- Unusual odors may offer an invaluable aid to the diagnosis. In Maple syrup urine disease (MSUD), there is a characteristic odor of maple syrup or burnt sugar. Performing a DNPH test in the urine of such a case can make the diagnosis fairly easily.
- Some IEM are associated with concomitant sepsis and neutropenia like organic aciduria and galactosemia (*E. coli* sepsis).

Initial laboratory investigations (Table 2) should be carried out as soon as possible. Some tests like blood ammonia and lactate are considered crucial for diagnosis of IEMs and thus should be available to every neonatal care unit. Specialized investigations are performed depending upon the clinical features and initial investigations MRI brain is an important modality for diagnosis of some IEMs such as molybdenum cofactor defects, non-ketotic hyperglycinemias, pyridoxine dependent seizures etc, where there may be structural changes in the brain suggestive of the diagnosis.

A simplified algorithm for diagnosis of inborn errors of metabolism in an acutely sick neonate is given in Flow chart 1.

- Metabolic acidosis is an important finding and narrows down the diagnosis to a few disorders including all the organic acidurias and primary lactic acidurias. A diagnostic algorithm is given in Flow chart 2. The common organic acidurias prevalent in our country are methyl malonic aciduria, propionic aciduria, glutaric acidurias, multiple carboxylase deficiency and MSUD.⁸
- Hyperammonemia is a very useful clue, and often associated with encephalopathy and seizures. Urea

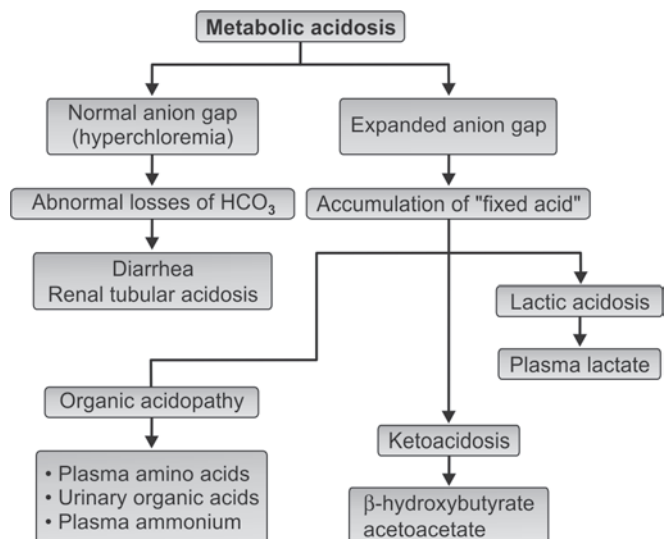
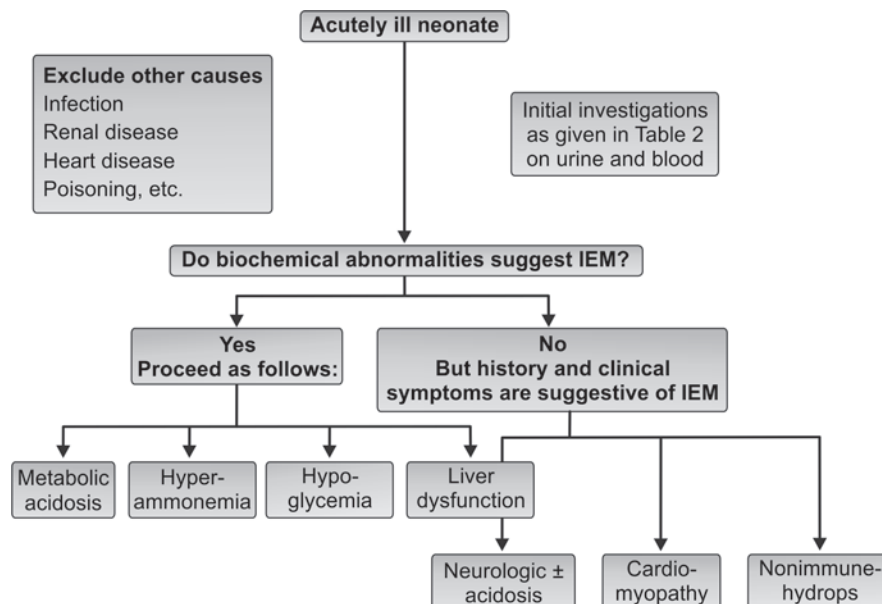
Table 2: Investigations in a suspected case of IEM

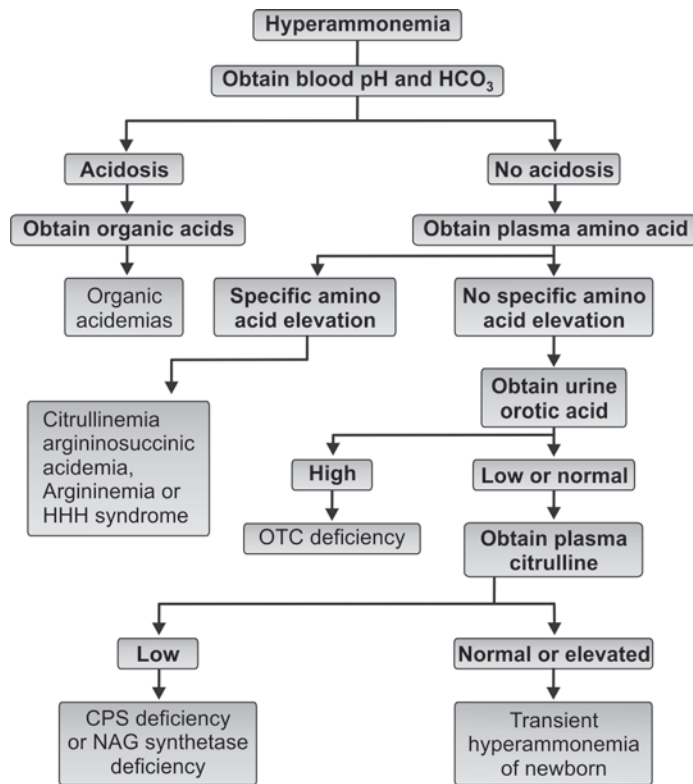
A. Initial investigations	Blood: Hemoglobin, white blood count, platelets Blood gases and plasma electrolytes (anion gap $(\text{Na}^+\text{K}) - (\text{HCO}_3^- + \text{Cl}) =$ normal <20 mmol/L) Glucose Calcium, magnesium Blood urea nitrogen, creatinine Liver function tests (Prothrombin time, liver enzymes, albumin, etc.) Ammonia Lactate Urine: Specific gravity, pH Proteins Sugar, reducing substances (Benedict's and uristix) Ketones, ketoacids (DNPH) Sulfites Microscopy
B. Specialized investigations	Blood: Amino acid analysis, quantitative Galactosemia screening test Carnitine, total and free (Tandem Mass Spectrometry) Plasma for storage at -200°C : 2-5 ml Urine: Organic acids (GC-MS) Succinylacetone Urine for storage at -200°C : 10-20 ml Neuroimaging: CT/MRI brain

Modified from Clarke JTR¹¹

cycle disorders usually occur without metabolic acidosis. These babies require immediate treatment with sodium benzoate or phenyl butyrate if available as delay in initiation is directly related to adverse outcome. Raised ammonia in presence of metabolic acidosis suggests organic aciduria, which can be diagnosed using the approach given in Flow chart 3. Other causes of raised ammonia are lysinuric protein intolerance, liver failure and 'congenital hyperinsulinism with hyperammonemia'.

- Blood glucose is a universal investigation performed on all sick neonates and thus hypoglycemia is commonly encountered. When common causes of hypoglycemia like maternal diabetes, small for gestational

Flow chart 2: Diagnosis of metabolic acidosis**Flow Chart 1:** Diagnosis of IEM

Flow chart 3: Diagnosis of hyperammonemia

age baby and sepsis are ruled out, one can follow the algorithm given in Flow chart 4 to make a diagnosis of IEM. It is a good practice to check urinary ketones in all babies at the time of hypoglycemia.

- Neurologic dysfunction occurs most commonly in newborn in form of lethargy, poor reflexes and seizures. This encephalopathy may or may not be associated with acidosis. While the disorders related to acidosis are given above, the IEMs associated with encephalopathy without acidosis include:
 - Urea cycle disorders
 - Maple syrup urine disease
 - Homocystinuria
 - Pyridoxine dependent seizures
 - Xanthine-sulfite oxidase deficiency/molybdenum cofactor defects
 - Nonketotic hyperglycinemia
 - Electron transport chain disorder or Pyruvate dehydrogenase deficiency
 - Fatty acid oxidation defects
 - Peroxisomal disorders like Zellweger syndrome
- Hepatic involvement manifesting as jaundice, hepatocellular dysfunction and hypoglycemia, is a common presentation of many inborn errors of metabolism. The main disorders here are amino acidopathies—hepatorenal tyrosinemia, disorders of carbohydrate metabolism—hereditary fructose intolerance (HFI)

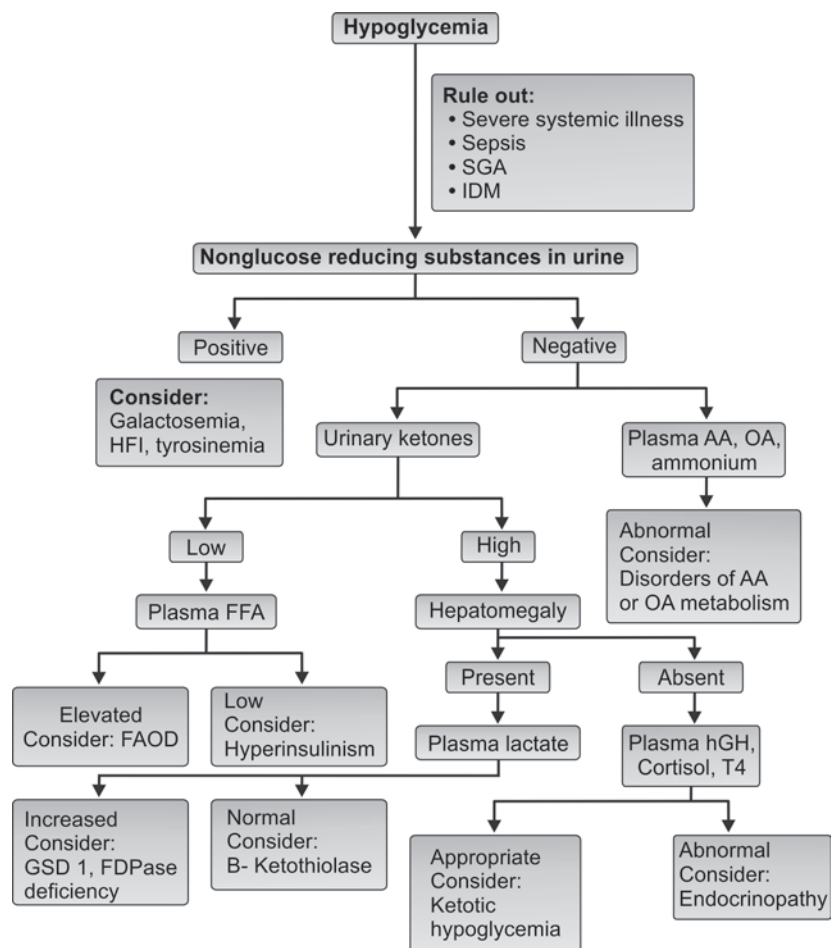
and glycogen storage diseases (GSD), fatty acid oxidation defects—Medium chain acyl CoA dehydrogenase (MCAD), long chain acyl-CoA dehydrogenase (LCAD), carnitine palmitoyl transferase II deficiency (CPT II) and carnitine–acylcarnitine translocase deficiency (CAT).¹⁰ These disorders are diagnosed by tandem mass spectrometry. Mitochondrial energy metabolism—cytochrome C oxidase deficiency and mitochondrial depletion syndromes also present with hepatic symptoms.

- Nonimmune hydrops may be due to IEMs and these should be suspected after exclusion of anemia and hemolysis and in the presence of significant organomegaly. Main IEMs to be looked for are GM1 Gangliosidosis, Gaucher Disease, Niemann-Pick disease, Sialidosis, Galactosialidosis, I-cell disease, Morquio (MPS IV) and Sly disease (MPS VII).
- Cardiac involvement occurs as rhythm disturbances, shock like symptoms, cardiomegaly or cardiomyopathy leading to cardiac failure.² Some IEMs such as glycogen storage disease type 2, fatty acid oxidation defects – MCADD, VLCADD, CPT I and II deficiency, primary carnitine deficiency, tyrosinemia type 1 and mitochondrial electron transport chain disorders may present with cardiac symptoms.

COLLECTION, STORAGE AND TRANSPORT OF SAMPLES

- Urine:** Collect 10 to 15 ml of urine, preferably first morning specimen (sufficiently concentrated). Tests include:
 - Routine biochemical tests, protein, glucose, reducing substances, pH
 - Chemical tests like DNPH, ferric chloride test, Sulfite dipstick test, etc.
 - Amino acid chromatography and quantitative estimation
 - Organic acids (collect on filter paper).
- Blood**
 - For ammonia estimation, a free flowing fresh sample should be drawn in vial and transported directly to lab on ice as soon as possible. This is critical, as ammonia tends to rise falsely if sample is not processed immediately. For lactate and pyruvate, a fluoride vial is used and same precautions as for ammonia are to be taken.
 - Collect in EDTA if plasma is required for testing or for storage.
 - For galactosemia and tyrosinemia testing, heparinised blood is required.
 - For enzyme assays on blood leukocytes, blood sample should be collected in EDTA vial.
 - For tandem mass spectrometry, take fresh blood on filter paper; or 1 ml of blood in heparin or EDTA vial and put on filter paper.

Flow chart 4: Diagnosis of hypoglycemia



Every suspect case of IEM who is very sick should have following samples stored for diagnostic purpose and to carry out prenatal diagnosis in the family's future pregnancies.

- DNA - collect blood in EDTA tube. All gene studies require DNA sample. DNA to be stored at 4 to 8 degree Celsius.
 - Plasma to be stored at –20 degrees Celsius.
 - Urine to be also stored at –20 degrees Celsius.
 - Other body tissues—CSF, liver, muscle, bone biopsy, kidney etc. may be utilized later for diagnostic purpose and therefore should be stored in culture medium for enzyme assays and DNA studies.
- Transport of samples on filter paper (blood spots and urine) and DNA can be done in room air while plasma samples and blood for enzyme assays need to be cooled during transportation.

THERAPY, GENETIC COUNSELING AND PRENATAL DIAGNOSIS

Management of inborn errors of metabolism is out of scope of this article. Books on IEM may be consulted.^{1,2, 9,11,12}

It is essential to make a diagnosis in a given suspected case of IEM for genetic counseling and prenatal diagnosis in the couple's subsequent pregnancies. This holds importance in our country since the burden of these disorders is high in view of the enormous cost of treatment, difficulty in procuring the drugs/diets from abroad and lack of government funding or initiative. Blood and urine sample should be stored in anticipation of an adverse outcome as the diagnosis can be made on these samples later.

Prenatal diagnosis can be offered after an accurate diagnosis by DNA technology or enzyme assay on chorionic villi or cultured amniocytes, as there is a 25 percent risk of recurrence in all the autosomal and X-linked recessive disorders.

NEWBORN SCREENING FOR INBORN ERRORS OF METABOLISM

A novel idea struck Robert Guthrie in 1961 and the world of the newborn transformed like never before. He successfully performed a test on dried blood spots on filter paper for phenylketonuria.¹³ Medical science took a major leap forward and newborn screening emerged as a preventive

health program to prevent mental retardation. Newborn screening is mandatory in many developed countries as part of their public health programs. The time has come to introduce newborn screening programs in India.

WHO task force committee defines newborn screening as a “public health program aimed at the early identification of conditions for which early and timely interventions can lead to the elimination or reduction of associated mortality, morbidity and disabilities.¹⁴ It involves the following components: screening, short-term follow-up, diagnosis, treatment/management, and evaluation”.¹⁵ Thus, it is not just diagnosis but also about treatment to prevent disabilities and reduce the burden of such illnesses. Neonatal screening service involves many professionals such as nurses, laboratory technicians, clinical biochemists, pediatricians, neuropsychiatrists, social workers, obstetricians, medical geneticists but some one is required to coordinate all these activities.

Since the introduction of screening for phenylketonuria, many other disorders have been added for analysis of dried blood spots on filter paper. Newborn screening for congenital hypothyroidism was introduced in 1974 by Dussault et al.¹⁶ Newborn screening for CH has been dealt with elsewhere in the book. The early 90s saw another sea-change in the newborn screening with advent of TMS (tandem mass spectrometry) for detection of many other in-born errors of metabolism. This was different as it changed the paradigm of one test–one disease. Presently as many as 30 disorders amongst the 600 odd IEMs are detectable in one test using the filter paper methodology.¹⁷ Advances have been made further in the new millennium with LC-MS/MS technology being incorporated—providing extra sensitivity to the assays.

PRINCIPLES AND CRITERIA FOR NEWBORN SCREENING

Screening is the application of a test to people who are as yet asymptomatic, with the purpose of classifying them with respect to their likelihood of having a particular disease. Since the tests are carried out on normal individuals, this raises certain ethical issues. The WHO (1968) had outlined certain criteria for a screening program based on principles formulated by Wilson and Junger.¹⁸ These are:

- Clinically and biochemically well-defined disorder
- Known incidence in the population
- Disorder associated with significant morbidity or mortality
- Effective treatment available
- Period before onset during which interventions improves outcome
- Ethical, safe, simple and robust screening test
- Cost-effectiveness of screening is established

Newborn Screening Methodology

The newborn screening methods have evolved over the last 4 decades from the basic bacterial inhibition assay used for phenylketonuria by Robert Guthrie to the more sophisticated tandem mass spectrometry today. Methods such as ELISA and time resolved fluorometry are being used in many countries for newborn screening because of its low cost and rapid analysis of multiple samples. Conditions included in Newborn screening programs are given in Table 3:¹⁴

The various analytes tested for screening of above disorders and the evolving methodologies from time-to-time are enlisted in the Figure 1.¹⁴

Tandem Mass Spectrometry (TMS or MS/MS)

Tandem mass spectrometry is an established method for newborn screening in the developed world in view of its simplicity, rapidity and ability to detect a number of disorders in the one sample. It has its own controversies as it has the ability to screen some disorders also which do not have any treatment at present.¹⁹

Tandem mass spectrometry expands neonatal screening to several disorders in amino acid, fatty acid oxidation and organic acid metabolism, more than 60 in number. TMS can improve the detection of PKU also. A high sensitivity (95.4%) and specificity (99.7%) is reported with a

Table 3: Conditions included in newborn screening program

Common disorders

Phenylketonuria
Endocrine
 Congenital hypothyroidism
 Congenital adrenal hyperplasia (21 hydroxylase deficiency)
G-6-phosphate dehydrogenase deficiency
Galactosemia
MSUD
Biotinidase deficiency
Homocystinuria
Tyrosinemia
Cystic fibrosis
MCAD
Alpha-1 antitrypsin deficiency

Other disorders

Infections
 HIV
 Toxoplasmosis
Tumors
 Neuroblastoma
Ambiental toxicity
 Lead exposure
Sickle cell anemia
DMD
Hypercholesterolemia

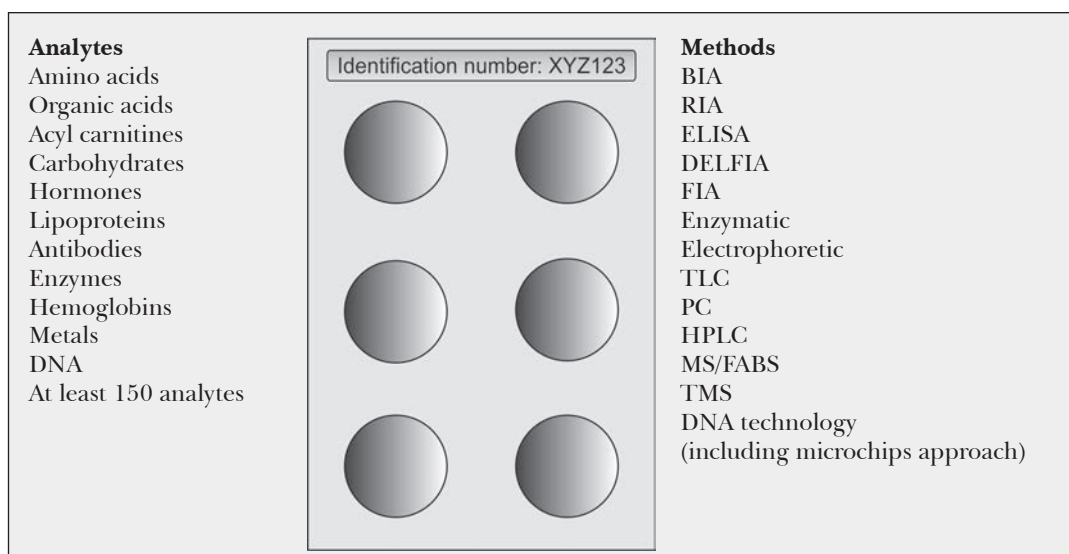


Fig. 1: Analytes that have been determined in dried blood samples collected on filter paper and more frequently employed screening methods¹³

Abbreviations: BIA: Bacterial inhibition assay; RIA: Radioimmunoassay; ELISA: Enzyme linked immunosorbent assay; DELFIA: Delayed europium-linked fluorescence immunoassay; TLC: Thin layer chromatography; MS/FABS: Mass spectrometry/fast atom bombardment mass spectrometry; TMS: Tandem mass spectrometry

combined prevalence of 1:2336 (in Germany).²⁰ Treacy et al argue that after diagnosis using TMS, response to treatment was complete in 12 percent of IEMs, there was no response in 34 percent, and in more than half (54%) there was a partial response, which justifies some intervention.²¹ Another study from Australia showed the benefit of newborn screening in improving outcomes in children with Glutaric aciduria type 1.²² Thus, TMS provides an early diagnosis and facilitates early intervention, so that 'partial benefits' can become 'substantial benefits'. Further, once an IEM is diagnosed in a family, a prenatal diagnosis can be performed to prevent birth of a child if it is a disorder which is not treatable. This perhaps has more relevance in our country with little resources and health care system not being completely state funded.

Indian Scenario

India has progressed immensely in the field of medical technology and health care. Therefore, this is the time to implement a newborn-screening program. Pilot studies conducted hope to give us the exact prevalence of the IEMs in different parts of the country before starting a national program. While the world is moving on to better technologies such as LC-MS/MS or even DNA based screening for newborns (for cystic fibrosis, etc.),²³ India is at a stand still and has a long way to go.

CONCLUSION

It is the fundamental right of a human being to live a disease free life as far as possible. The newborn screening systems can help in achieving this goal. Let us benefit from the medical advancements and give our newborns a disease free life.

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CHAPTER 33

Retinopathy of Prematurity

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INTRODUCTION

Retinopathy of prematurity (ROP) has been recognized as an important cause of childhood blindness. It is a retinal vasculopathy that occurs almost exclusively in preterm infants. An arrest in the development of retinal vessels, triggered by extreme prematurity, sets off a cascade of molecular events which may cause mild, usually transient changes of the peripheral retina to severe progressive vasoproliferation, scarring, and potentially blinding retinal detachment. Retinopathy of prematurity (ROP) refers to all stages of the disease and its sequel.

PATHOGENESIS

Retinopathy of prematurity is a condition confined to the immature retinal vascular system. The likelihood of developing retinopathy is related to the degree of vascular development so that once the retina is fully vascularized, the risk of developing ROP has passed.

Vascularizing proceeds centrifugally from the optic disk, commencing at about 16 weeks of fetal life and is complete in the nasal retina by 32 weeks gestation age (GA) and by about 37 to 40 weeks GA in the temporal retina. Thus, as retinal vascularization proceeds symmetrically from the optic disk to the ora serrata, there is an advancing circumferential border between vascular and avascular retina. It is within this border area that acute ROP develops. This predictable pattern of retinal vascularization was formally recognized by ICROP (International Classification of Retinopathy of Prematurity), which divided the retina into progressive concentric zones. The location of ROP is described in terms of these arbitrarily defined zones. The appearance of the disease at a rather consistent postmenstrual age (PMA), regardless of the elapsed time following preterm birth or subsequent neonatal events, suggests that the innate maturation process

of the retina and its vessels is related to the timing of this disorder's onset and progression.

Both vascular endothelial growth factor (VEGF) and insulin-like growth factor (IGF-1) are implicated in normal vascular development and ROP pathogenesis. A better understanding of the vascular development is an area of current investigation.

RISK FACTORS

Risk factors of ROP include measures of immaturity (low-birth weight and low gestational age), metabolic acidosis and sepsis. Systemic steroids administered to the mother prior to preterm delivery have been shown to reduce the risk of ROP. Surfactants do not significantly alter the proportion of babies at risk who develop severe ROP and the role of systemic vitamin E is controversial. Clinical trials of reduced light exposure in the nursery have shown that this intervention has no impact on the incidence of ROP. The role of genetic factors remains unclear. Norrie disease gene mutations have been found in some infants with ROP, but the significance of this is still to be determined and ethnic factors may have some implications in ROP development.

CLASSIFICATION

The currently used International Classification of ROP (ICROP) describes the location, extent, and severity of the disease.

Location

To delineate location, the retina is divided into three concentric zones, centered on the optic disk (Fig. 1). Zone I, the posterior or inner zone, extends twice the disk-macular distance in all directions from the optic disk. Zone II, the middle zone, extends from the outer edge of zone I to the ora serrata nasally and to the anatomic equator

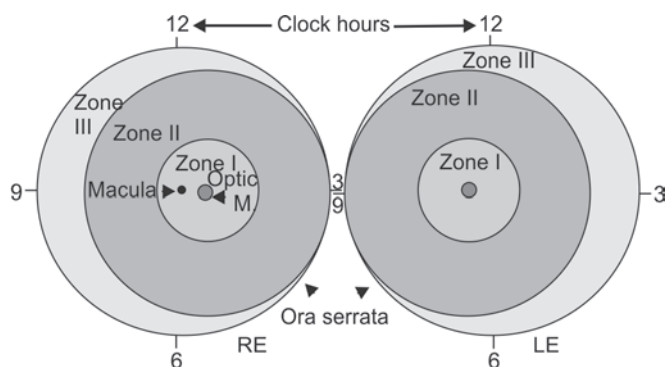


Fig. 1: ROP zones as described in the ICROP classification

temporally. Zone III, the outer zone, is the residual crescent that extends from the outer border of zone II to the ora serrata temporally.

As retinal blood vessels grow progressively across zone 1 through zone 3, the location of normal vascularization or ROP broadly reflects maturity and the progress of retinovascular development. Thus, the extremely immature baby whose retinal blood vessels are still within zone 1 at initial screening is at the greatest risk of the most severe disease. For instance, incomplete vascularization in zone I carries a 54 percent risk of reaching threshold ROP while for zone II this is only 8 percent. The larger baby whose retinal vessels have already grown into zone 3 by the initial exam has an extremely low risk of developing severe ROP, and when it does occur, it is likely to be mild, with a close to zero risk of visual impairment.

Extent

The extent of involvement is described by the number of circumferential clock hours involved.

Stages

The phases and severity of the disease process are classified into five stages:

Stage 1: It is characterized by a demarcation line that separates vascularized from avascular retina. This line lies within the plane of the retina and appears relatively flat and white (Fig. 2).

Stage 2: It is characterized by a ridge; the demarcation line has grown, acquiring height, width, and volume, and extending up and out of the plane of the retina. It may change from white to pink. Vessels may leave the plane of the retina to enter the ridge (Fig. 3).

Stage 3: It is characterized by the presence of a ridge and by the development of extraretinal fibrovascular tissue (Fig. 4).

Stage 4: It has subtotal retinal detachment caused by traction from the proliferating tissue in the vitreous or on the retina. This is subdivided into two phases:

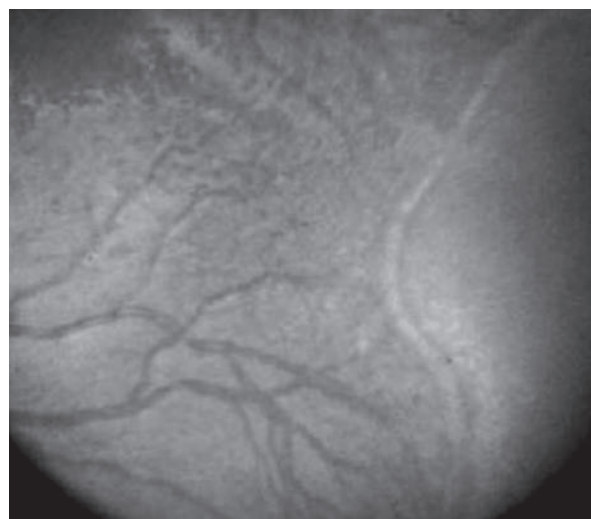


Fig. 2: Stage 1 ROP showing demarcation line
(For color version see plate 2)



Fig. 3: Stage 2 ROP showing a ridge (R)
(For color version see plate 3)

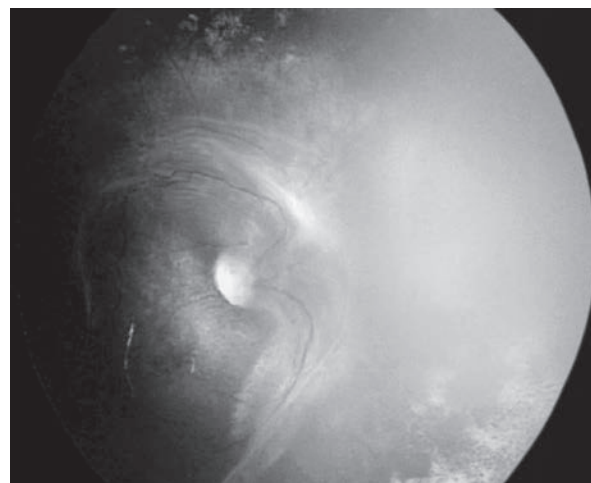


Fig. 4: Stage 3 ROP showing extraretinal fibrovascular proliferation
(For color version see plate 3)

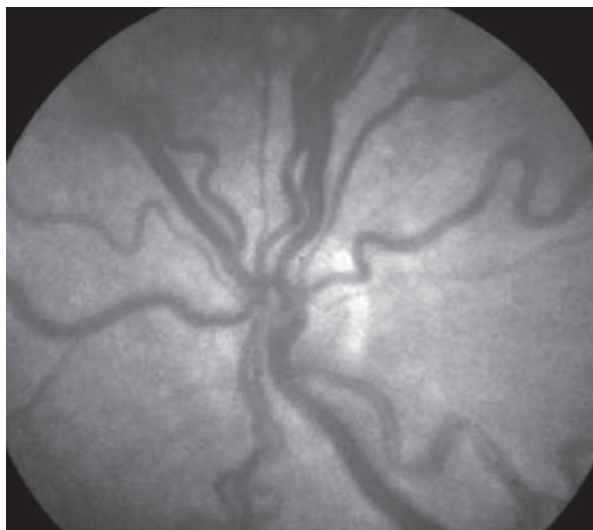


Fig. 5: Plus disease with dilatation and tortuosity of vessels at the posterior pole (*For color version see plate 3*)

- Subtotal retinal detachment not involving the macula (Fig. 5)
- Subtotal retinal detachment involving the macula.

Stage 5: It is total retinal detachment.

Stages 1 and 2 are referred to as mild ROP as they often resolve without visually threatening ophthalmic sequel. Stage 3 ROP is the first ROP stage that presents a significant risk of poor structural or visual outcome and thus represents serious disease. Stage 4 and especially Stage 5 usually result in some permanent visual impairment despite surgical intervention.

Plus Disease

When signs of posterior retinal vascular changes accompany the active stages of ROP, the term *plus* disease is used, characterized by the dilatation and tortuosity of the retinal vessels (Fig. 6) frequently along with the engorgement of the iris vessels, pupillary rigidity and vitreous haze. It is a critical sign of severe ROP and its presence is an important prognostic indicator.

Threshold disease is stage 3 ROP in zone I or II in 5 or more contiguous clock hours or 8 cumulative clock hours [30° sectors] with plus disease. This represented the minimum severity of disease indicating the need for treatment according to the CRYO-ROP study.

Prethreshold disease is less than threshold disease and has been defined by the early treatment of retinopathy of prematurity (ETROP).

SCREENING FOR RETINOPATHY OF PREMATURITY

Goal of Screening

The purpose of screening is to identify preterm infants that require treatment for ROP, while minimizing the number of stressful examinations.



Fig. 6: Stage 4 ROP with subtotal retinal detachment (*For color version see plate 3*)

Age at Onset and Rate of Progression

While the propensity of a baby to develop severe ROP is influenced by many factors such as the degree of prematurity and neonatal events, the time at which it develops appears to be largely independent of these events. This knowledge has proved useful in the design of ROP screening guidelines for it is known that most babies—whatever the degree of immaturity and illnesses—develop ROP at a time which can be predetermined to a significant degree, and which progresses according to PMA.

Screening Guidelines

In more than 90 percent of infants with ROP, the course is one of spontaneous arrest and regression with little or no residual effects or visual disability. In less than 10 percent of infants there is progression toward severe disease, with significant extraretinal vasoproliferation, cicatrization, detachment of the retina, and impairment of vision. Permanent structural and visual damage occurs only in stage IV of ROP. Therefore, adequate treatment should be initiated well before this stage is reached. The aim of screening is to identify all treatable neonates. It is also necessary to keep the screening within a specific protocol so as not to waste resources on low risk neonates.

The disease is considered to be more severe if it is present in zone I, has a “plus” component or involves more clock hours of the retina. ROP in zone III is rarely aggressive and normally regresses (involutes) without adverse consequences. A good screening program ensures early detection and timely intervention. Treatment is done by ablation of the peripheral avascular retina using cryo or laser therapy and should be considered within 48 hours of diagnosis.

Whom to Screen?

Infants with a birth weight of less than 1500 g or with a gestational age of 34 weeks or less, as well as selected infants between 1500 and 2000 g with an unstable clinical course who are believed to be at high-risk by their attending pediatrician or neonatologist, should have at least 2 fundus examinations performed after pupillary dilation using binocular indirect ophthalmoscopy to detect ROP. Nurseries can set up their individual protocols depending on the level of neonatal care available. The location and sequential retinal changes, if any, should be recorded using the International Classification of Retinopathy of Prematurity. One examination is sufficient only if it unequivocally shows the retina to be fully vascularized bilaterally.

When to Screen?

The first examination should normally be performed between 4 and 6 weeks of chronologic (postnatal) age or, alternatively, within the 31st to 33rd week of postconceptional or postmenstrual age (gestational age at birth plus chronologic age), whichever is earlier. As ROP usually develops after 5 to 6 weeks of age, examinations are generally not needed in the first 4 weeks after birth. The timing of the initial screening examination may be adjusted appropriately on the basis of local incidence and onset of ROP or the presence of other recognized risk factors. The initial screening examination and subsequent examinations should be timed to permit sufficient time for treatment. Scheduling of follow-up examinations is determined by the immaturity of the retina and the stage of ROP at the first examination. The crucial window period for the development of ROP is 37 to 42 weeks (Fig. 7). If the retinal vascularization is incomplete but no ROP is detected, follow-up examination should be planned at approximately 2 weeks intervals until vascularization

proceeds into the periphery. Weekly examination is done in mild ROP or if the retinal vasculature is immature with vessels ending in zone I but no ROP in that zone. Any disease in zone I is critical and must be monitored closely. This area is very small and changes can occur very quickly, sometimes within days. Twice weekly examination is recommended for more severe ROP. Parents of infants with ROP should be informed of the nature and possible consequences of this disorder throughout the infant's hospital stay, beginning at the time of first diagnosis and continuing on an ongoing basis with updates on its progression during hospitalization. Responsibility for examination and follow-up of infants at risk for ROP must be carefully defined by each neonatal intensive care unit. Unit specific criteria for examination for ROP should be established for each neonatal intensive care unit by consultation and agreement between neonatology and ophthalmology services. These criteria should be recorded and should automatically trigger scheduled ophthalmology examinations. If hospital discharge or transfer to another neonatal unit or hospital is contemplated before retinal maturation into zone III has taken place, the availability of appropriate follow-up ophthalmologic examination must be ensured and specific arrangement for that examination must be made before such discharge or transfer occurs. If responsibility for arranging follow-up after discharge is delegated to the parents, it must be clearly understood by the parents that blindness is a possible outcome, that there is a critical time window to be met if treatment is to be successful, and that timely follow-up examination is essential to successful treatment.

How to Screen?

Screening should be done in a temperature-controlled room/nursery as premature babies are susceptible to hypothermia, bradycardia, apneic episodes and fall of oxygen saturation. A dilated fundus examination using a 20 diopter and 28 diopter lens, with scleral depression if necessary. Pupillary dilatation is done with phenylephrine 2.5 percent and tropicamide 0.5 to 1 percent instilled 3 times at 10-minute intervals, one hour before examination. The eye examination is stressful for babies, it may cause bradycardia, which can be reduced by nesting.

The first part of the examination should be external, with identification of iris rubeosis, if present. The next part of the examination should be the posterior pole, with identification of any plus disease or straightening of the vascular arcades. The eye is rotated to identify the presence or absence of zone 1 disease (if the ridge and the optic nerve are present in the same view, this usually implies zone 1). If the nasal vessels are not at the nasal ora serrata, this is still zone 2. If the nasal vessels have reached the nasal ora serrata, the eye is in zone 3.

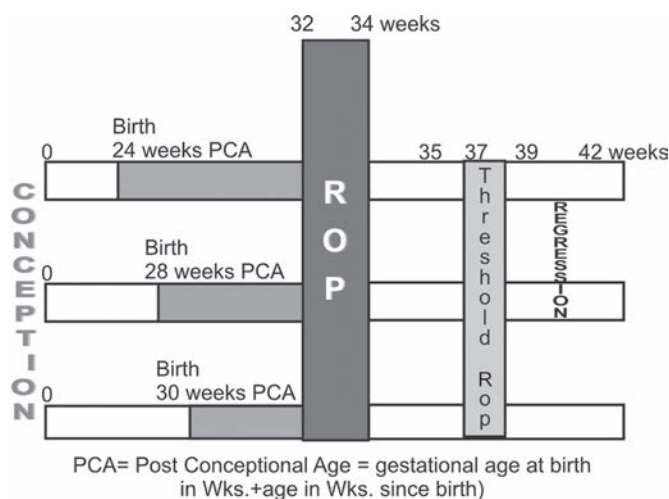


Fig. 7: Occurrence of ROP and subsequent events
(For color version see plate 3)

Table 1: Revised indications for the treatment of ROP

<i>Type 1 ROP (New Threshold)</i>	<i>Type 2 ROP</i>
<i>Administer Peripheral Ablation</i>	<i>Treatment Wait and Watch for Progression</i>
<i>Zone II</i>	<i>Zone II</i>
Plus disease with stages 2 or 3	Stage 3 without plus disease
<i>Zone I</i>	<i>Zone I</i>
Plus disease with stages 1, 2, or 3	Stages 1 or 2 without plus disease
Stage 3 without plus disease	

TREATMENT OF ACUTE ROP

The CRYO-ROP study confirmed the success of cryotherapy treatment versus nontreatment. Over the past decade, cryotherapy has very largely been succeeded by (argon/diode/double frequency YAG) retinal laser treatment. Laser is now the preferred mode since the most severe forms of disease are more easily treated with laser than with cryotherapy. Although more time-consuming, it is less traumatic to the baby (Table 1).

Rationale for Treatment

The stimulus for abnormal vessel growth comes from the peripheral nonvascularized hypoxic retina. The fundamental principle of treatment is to remove, by cryotherapy or laser, the stimulus for vessel growth by ablating the peripheral avascular retina.

Criteria for Treatment

The indication for treatment as reported in the CRYO-ROP study was threshold ROP. The term threshold denotes the ROP stage at which spontaneous and complete resolution is unlikely and the risk of blindness is predicted to be close to 50 percent. However, although the CRYO-ROP study improved outcome in 44.4 percent of eyes with a history of severe ROP, this is far from ideal and the need for more effective approaches to treatment is required. Further studies, such as that published recently by the Early Treatment for Retinopathy of Prematurity Cooperative Group (ETROP), have addressed this issue.

Earlier the indication for treatment was threshold ROP but now the ETROP Study recommends treating eyes before threshold is reached because the outcome of some eyes treated once they have developed threshold disease has been poor. This has resulted in modification of the currently accepted treatment guidelines and offers hope for the most difficult ROP cases. Other reported trials have shown morphological variations in extreme

prematurity that do not follow the previous clinical criteria. These findings may also lead to the need to modify the current guidelines for treatment in extreme prematurity. *What is ETROP?* The Early Treatment for Retinopathy of Prematurity (ETROP) study, published in December 2003, has demonstrated that earlier treatment of selected cases of prethreshold retinopathy of prematurity (ROP) at high-risk to progress to retinal detachments gives better overall ROP outcomes than treatment at threshold severity of the disease.

The study's criteria called for treating patients who fell into these three categories.

Type I ROP

- Zone 1, any stage of ROP with plus disease
- Zone 1, stage 3 without plus disease
- Zone 2, stage 2 or stage 3 with plus disease

The following schedule is used for screening infants who do not yet meet criteria for treatment:

TYPE II ROP

- Twice a week if there is
Zone II, no plus, stage 3
Zone I, no plus, stage 1 or 2
- Every week if the infant is near type 2
Zone II, no plus, stage 2
Zone I, no ROP, immature
- Every 2 weeks if less concerning
Zone II no plus, immature or stage 1

Timing

Timing is critical and should be undertaken within the treatment window. Type 1 ROP should be treated within 24 to 48 h from the identification of ROP reaching a criteria for treatment (Fig. 8).

PREPARING FOR THE PROCEDURE

Preparing the Parents

The parents must be informed about the nature of the disorder, the risk of blindness and the expected success rate.

Preparing the Baby

Close supervision and monitoring throughout the procedure can best be provided in the neonatal unit. Cryotherapy and laser treatment are painful and/or lengthy procedures and a team effort with the support of the neonatologist is required. Full monitoring is essential during the procedure. A separate room, usually in the NICU should be used for laser treatment and safety goggles should be worn by all staff present.

	I	I+	II	II+	III	III+
Zone I	HR	THRESHOLD ROP-TREAT (8 cumulative or 5 contiguous clock hours)	HR	THRESHOLD ROP-TREAT (8 cumulative or 5 contiguous clock hours)	THRESHOLD ROP-TREAT (8 cumulative or 5 contiguous clock hours)	THRESHOLD ROP-TREAT (8 cumulative or 5 contiguous clock hours)
Zone II					HR	THRESHOLD ROP-TREAT (8 cumulative or 5 contiguous clock hours)
Zone III						+/– May treat if follow up is poor (not according to ETROP)

Fig. 8: Treatment and follow-up criteria for ROP according to ETROP

Preparing the Eye

This is similar to the preparation for screening.

Procedure

Cryotherapy is applied externally through the sclera, whereas laser therapy uses both argon-green and diode wavelengths delivered through a portable indirect ophthalmoscope. Systemic complications are rare if treatment is applied with adequate monitoring. Ocular complications can occur with both treatments, but are usually minor and relatively rare.

Postoperative management: No postoperative medication is required following laser treatment. Topical antibiotic ointment is applied for 5 days following cryotherapy. The retina is examined 5 to 7 days later by which time plus disease should show signs of subsiding.

Retreatment

With effective treatment, retreatment is not frequently required, but if it is, it should be undertaken as soon as it is obvious that regression has not started, usually within 7 to 10 days.

Regression: Post-treatment it takes 6 to 12 weeks to regress completely.

LONG-TERM FOLLOW-UP

All infants with stage 3 disease and those who have been treated should be kept under review for at least the pre-school years to monitor the development of vision, refractive status, and ocular motility. The incidence of strabismus is between around 6 percent to over 30 percent. Myopia is a well-known complication of ROP with its onset in infancy and progression during the first year after birth but with relative stability thereafter. Long-term complications include an increased risk of developing retinal detachment, which may occur any time during life.

MANAGEMENT OF ADVANCED DISEASE

Parents will want to know if anything can be done if cryotherapy or laser treatment has failed to stop the progression of the disease. There are a number of aspects to consider.

Vitreoretinal Surgery

Anatomical retinal alignment can be obtained in a significant proportion of cases, but to date the visual results are extremely dismal with almost all infants gaining no improvement with respect to vision. It is critical that during any discussion parents are made aware of the difference between anatomical and functional success. It should be pointed out that complex surgery may put any residual useful vision at risk and leave a painful eye that requires long-term pain control. Multiple operations may be required, which impacts the psychological development of the infant. Stage IV is treated by an encircling band. Stage IV B and stage V are treated by vitrectomy.

THE ROP EPIDEMICS

The literature contains many references to two ROP epidemics. The first occurred in the 10 to 15 years following 1942 and was due mainly to high, unrestricted and unmonitored, oxygen administration. The excessive amounts of oxygen administered at that time almost certainly swamped all other ROP risk factors, even the effect of immaturity, so that in this era blinding ROP affected a wide birth weight range of premature babies. Because the survival of babies under 1000 g birth weight in the 1940s was under 10 percent, most of those babies blinded at this time had a birth weight exceeding 1000 g.

The second 'epidemic' commenced slowly in the 1970s and continues to the present time. Advances in neonatal intensive care, including the meticulous administration and monitoring of oxygen administration, have largely eliminated the risk of severe ROP for the more mature

pre term babies, so that nowadays severe ROP is mostly confined to babies of birth weight under 1000 g. Consequently the second epidemic reflects mainly the increased survival of extremely premature babies. While in high-income countries, increased survival is the main ROP factor, standard of care still contributes to its development. In middle-income countries the prevailing health care environment contains elements of both epidemics, namely increased survival but with limited resources that do not permit the highest quality of neonatal care.

In India, we have all the phases of the epidemic and babies up to 2 kg have been recorded to have ROP stage III. In nurseries with a high quality of care (less sepsis, decreased oxygen use with monitoring, decreased transfusion) ROP is limited to children < 1 kg.

SETTING UP A ROP PROGRAM FOR SCREENING AND TREATMENT

All hospital nurseries, which are managing babies of birth weight < 1500 gm should have a screening program. It is the duty of the neonatologist to send all babies for screening. The neonatologist should identify an ophthalmologist, preferably a retinal surgeon who is well-versed with indirect ophthalmoscopy. The ophthalmologist should be trained in a center where ROP screening is done regularly as it takes time even for a trained retinal surgeon to be well-versed with retinal evaluation in a neonate. The neonatologist and the ophthalmologist should jointly decide the protocol for screening. Initially all children up to 34 weeks and < 1.8 kg maybe examined to assess the incidence of ROP in the nursery and the weight and gestation limit, e.g. if a 1.8 kg and 34 weeks is the biggest child who develops ROP stage I, this should be the limit for screening. The data should be reviewed every year and the screening criteria reduced. As the nursery care improves, the rate of ROP will reduce. In our nursery at Sir Ganga Ram Hospital the criteria have been revised from 34 weeks and 1.5 kg in 1994 to 1.2 kg and 30 weeks in 2005.

The second stage of the program is the treatment part. All hospitals may not have in-house facilities for laser/cryotherapy. With time laser has become more popular in view of less morbidity. If your city has a laser center for ROP, then the neonatologist must coordinate with it. Nowadays laser machines have become portable and can be transferred to the nursery.

The third stage of the program is treatment for stages IV and V. This entails scleral encircling band for stage IV and vitreoretinal surgery for stage V under general anesthesia, and is done in a few specialized centers only. Surgery for stage V ROP is still controversial as the visual results are poor despite anatomical success.

SUMMARY

Blindness due to ROP is preventable. The incidence of ROP will continue to increase with the increasing survival rates of premature babies. Relevant information regarding the screening and treatment of RP needs to be disseminated among neonatologists and ophthalmologists.

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Facility-based Newborn Care

Vikram Datta, Bhanu Bhakhri

BACKGROUND

Reproductive and Child Health (II) Program of the Ministry of Health and Family Welfare, Government of India aims to reduce Infant Mortality Rate (IMR) and Under-Five Mortality Rate (U5MR) in accordance with the fourth Millennium Development Goal (MDG).

In India, IMR was estimated to be 50/1000 live births in year 2009 (SRS 2009). Of these 50 deaths, 35 were attributed to deaths in neonatal period (first 28 days of life) and further, 27 of these 35 were during first 7 days of life (early neonatal deaths). Hence, approximately half of the deaths in first year of life occur during first week of life. Neonatal mortality (NMR) contributes to about two-thirds of infant deaths and nearly half of all under 5 deaths. Though in recent years, a modest decline has been observed in IMR in India, NMR appears to be contributing considerably to U5MR and IMR (Table 1). Hence, there is an increasing need to focus on newborn care and survival for significant reduction in IMR and U5MR.

Prematurity/low birth weight, birth asphyxia and infections, the three major causes of early neonatal death account for majority of all neonatal deaths¹ (Fig. 1).

Most of these morbidities can be managed at household and peripheral health facilities and deaths due to them can be prevented.

Introduction of the Janani Suraksha Yojana (JSY) scheme and Integrated Management of Neonatal and

Childhood Illnesses (IMNCI and F-IMNCI) programs has resulted in an increased number of sick newborns presenting to referral hospitals. Provision and delivery of services for both essential newborn care and care of sick newborns in the existing health facilities at the district and subdistrict level has however been found lacking.

THE NEED OF FACILITY BASED NEWBORN CARE

Facility based newborn care (FBNC) assumes significant importance by aiming at strengthening the care of sick, premature, low-birth-weight newborns at the various levels of facilities right from the moment of birth through the neonatal period. It was conceptualized by Ministry of Health and Family Welfare, Government of India under the National Rural Health Mission (NRHM) and its Reproductive and Child Health Programme (RCH II) and operationalized units started in year 2006. The guidelines for FBNC have been put together based on recommendations of an expert group including experts from medical colleges, professional bodies—National Neonatology Forum (NNF), UNICEF, WHO, USAID and NIPI.²

Table 1: Child mortality indicators: Indian scenario			
	1990	Current (2011)	MDG by 2015
Under 5 mortality rate (U5MR)	107	64	36
Infant mortality rate (IMR)	80	50	27
Neonatal mortality rate (NMR)	53	34	20

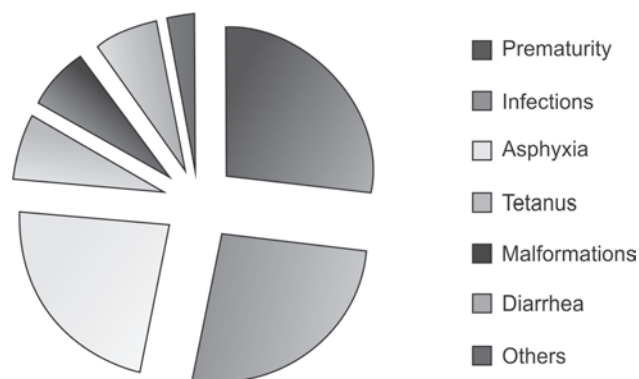


Fig. 1: Direct causes of neonatal deaths (Lancet 2005)

LEVELS OF NEWBORN CARE AT HEALTH FACILITIES

Based upon level of health facility catering to varying magnitude of population 3 levels of centers for neonatal care has been introduced under FBNC (Table 2).

Newborn Care Corner (NBCC)

This is a space within the delivery room in any health facility where immediate care is provided to all newborns at birth. This area is mandatory for all health facilities where deliveries are conducted. The area of about 20-30 feet is equipped with radiant warmer and resuscitation kits. One doctor and one staff nurse (or ANM at subcenter) is designated to NBCC to ensure appropriate functioning of the corner. All the doctors and nurses who attend the deliveries are trained in Navjaat Shishu Suraksha Karyakram (NSSK), a 2-day training program in basic newborn care and resuscitation rolled out with support from the IAP and NNF.

Newborn Stabilization Unit

Newborn stabilization unit (NBSU) is a facility within or in close proximity of the maternity ward where sick and low birth weight newborns are cared for during short periods. All FRUs/CHCs, catering to less than 3000 people, have a neonatal stabilization unit, in addition to the newborn corner. For a 4 bedded NBSU, 2 beds from postnatal wards

are dedicated for rooming in. The NBSU are equipped for provision of resuscitation and temperature maintenance. One trained doctor is stationed at stabilization unit. At least one full-time staff nurse trained in newborn care per shift is available. The staff at NBSU is trained in facility based IMNCI (F-IMNCI).

Newborn presenting with any of the following signs to a facility with neonatal stabilization unit requires admission for initial stabilization and transfer to SCNU:

- Apnea or gasping
- Respiratory distress (Rate >70/ minute with severe retractions/grunt)
- Hypothermia <35.4°C
- Hyperthermia (>37.5°C)
- Central cyanosis
- Shock (Cold periphery, with CFT >3 seconds and weak and fast pulse)
- Significant bleeding that requires blood or component transfusion.

Newborns, who after assessment and stabilization, can be managed at stabilization unit:

- Newborns with respiratory distress, having respiratory rate 60-70/ minute without grunting or retractions (for observation and oxygen therapy)
- Newborns with gestation less than 34 weeks or weight <1800 g (for observation and assisted feeding)
- Newborns with hypothermia and hyperthermia who are hemodynamically stable after initial stabilization

Table 2: Centers for neonatal care under FBNC

Health facility	NBCC	NBSU	SCNU
Health facility	Primary health center (PHC)/Subcenter (SC) identified as MCH Level I	Community health center (CHC)/ First referral unit (FRU) identified as MCH Level II	District hospital identified as MCH Level III
Minimum bed strength (area in sq. ft.)	1 (20-30)	4 (200)	12 (1000)
Minimum trained technical staff	1 doctor and 1 nurse	1 doctor and 4 nurses	3-4 doctors and 12 nurses
Care at birth	Resuscitation, infection control, warm chain, breastfeeding and weighing	Resuscitation, infection control, warm chain, breastfeeding and weighing	Resuscitation, infection control, warm chain, breastfeeding and weighing
Care of normal newborn	Breastfeeding and feeding support	Breastfeeding and feeding support	Breastfeeding and feeding support
Care of sick newborn	Identification and prompt referral Immunization services	Management of infants >1800 gm, neonatal jaundice, sepsis. Stabilization and referral of sick newborns and those <1800 gm at birth Immunization services	Management of infants <1800 gm and all sick newborns (except requiring assisted ventilation or major surgery) Follow-up services Referral services Immunization services
Approximate indicative cost for set up (in INR)	1,05,000	7,50,000	51,00,000

- Newborns with jaundice requiring phototherapy
- Neonates with sepsis who are hemodynamically stable, for observation and antibiotic therapy.

Special Care Newborn Unit (SCNU)

Any facility with more than 3,000 deliveries per year should have an SCNU (most district hospitals and some subdistrict hospitals would fulfill these criteria). The minimum recommended number of beds for an SCNU at district hospital is 12. However, if the district hospital conducts more than 3000 deliveries in a year, 4 beds are added above 12 for every 1000 additional deliveries. Additional one third beds (4 for 12 bedded SCNU) are available for rooming in. Table 3 provides calculation for estimating number of beds required for a SCNU.

A 12-bedded unit is managed by 1 pediatrician trained in neonatology, supported by 2 or 3 medical officers trained in FBNC. Such a unit will also have 3 nurses in each shift, dedicated support staff, round the clock. In addition, a part time lab technician and a data operator are available for the unit. The staff posted at the SCNU undergoes intensive 4 day training focusing on the skills on clinical management, housekeeping and maintenance of the equipment followed by 2 weeks observership at one of the recognized centers. SCNU provides special care (all care except assisted ventilation and major surgery) for sick newborns.

Indications for Admission to the SCNU are:

- Birth weight <1800 g or gestation <34 weeks
- Large baby (>4.0 kg)
- Perinatal asphyxia
- Apnea or gasping
- Refusal to feed
- Respiratory distress (Rate >60/minute or grunt/ retractions)
- Severe jaundice (Appears <24 hrs/Stains palms and soles/lasts >2 weeks)
- Hypothermia <35.4°C, or hyperthermia (>37.5°C)
- Central cyanosis
- Shock (Cold periphery with CFT >3 seconds and weak and fast pulse)
- Coma, convulsions or encephalopathy
- Abdominal distention

- Diarrhea/dysentery
- Bleeding
- Major malformations.

Criteria for Transfer from SCNU to the Step Down

- Babies whose respiratory distress is improving and do not require oxygen supplementation to maintain saturation
- Babies on antibiotics for completion of duration of therapy
- Low-birth-weight babies (less than 1800 g), who are otherwise stable (for adequate weight gain)
- Babies with jaundice requiring phototherapy but otherwise stable
- Babies admitted for any condition but are now thermodynamically and hemodynamically stable.

Criteria for Discharge from SCNU to Home

- Baby is able to maintain temperature without radiant warmer
- Baby is hemodynamically stable (normal CFT, strong peripheral pulses)
- Baby accepting breastfeeds well
- Baby has documented weight gain for 3 consecutive days; and the weight is more than 1.5 kg
- Primary illness has resolved.

Operational Steps for Planning and Rolling Out Facility based Newborn Care in India

- *National collaborative center* for FBNC at Kalawati Saran Children's Hospital, New Delhi, will provide technical expertise and overall support to the government for effective implementation and monitoring of the progress in the states. Its functions will include preparing and updating technical guidelines, norms and protocols, monitoring the progress and quality, analyzing reports, mentoring some regional/state collaborative centers, providing recommendations to the Ministry of Health and Family Welfare to improve the implementation and to build capacity of the regional and state collaborative centers.
- *Regional collaborative centers* are the existing centers of excellence in newborn care (e.g. King Edward Memorial Hospital, Mumbai, PGIMER, Chandigarh and Institute of Child Health, Chennai). They provide technical support in operationalization of newborn care facilities, establishing a monitoring system, and conducting quality assessment.
- In addition, a state medical college is recognized as state collaborative center for capacity building of staff and administrators, establishment of recording and reporting system and operational research.
- Districts with high IMR and high institutional delivery rate are recognized as high priority districts for setting up SCNUs.

Table 3: Number of beds required for SCNU

Average number of live births in last 2 years	A
Number of live births requiring special care	B = (15% × A)
Number of bed days required (average 7-day stay)	C = (B × 7)
Number of special care beds required	D = C/365
An extra allowance of 30% beds for extramural births	E = D × 30%

Table 4: Newborn care facilities a district having one district hospital with more than 3,000 deliveries per year, five FRUs, and twenty 24 x 7 PHCs

Health facility	Services	Numbers
Primary health care/MCH I	Newborn care corners in labor rooms	20
FRU/ Community health center/MCH II	Newborn care corners in labor rooms	5
	Newborn care corners in OT	5
	Newborn stabilization unit	5
District Hospital/MCH III	Newborn care corners in labor rooms	1
	Newborn care corners in OT	1
	Special care newborn unit	1

- Three tiered system of facilities for newborn care in a district is given in Table 4.
- A *multidisciplinary team* composed of doctors, civil work team and biomedical engineers oversee the overall assessment, civil work and refurbishment plans at the district and state level.
- *Record keeping:* Using a standard format, units submit a case record based reports to the state health authorities and collaborative center. The analysis of these reports is used for assessment of the performance of the units which are then provided appropriate feedback.
- Adherence to standard operating procedures for housekeeping and for clinical care of admitted newborns is critical for ensuring quality care at the facilities.
- *Role of NNF*
 - Trainings 4 day FBNC (support, develop pool of national and state trainers)
 - Development and revision of training modules and toolkit
 - Mentoring visits, Quality assurance
 - Handwashing audits, KMC Audits
 - Accreditation of operationalized units under process for linkage with RSBY
 - Equipment trouble shooting guidelines being developed
- *Development of Transport Model:* Free services are provided for transport of pregnant women and sick newborn across the health facilities. The system is regulated by call center based operation and in this context

Shivpuri district of MP has developed a lead model for others' reference.

List of Clinical Protocol Included in FBNC Training Module

- Triage of sick newborns
- Assessment and treatment of newborns displaying emergency signs
- Criteria for admission to SCNU and criteria for transfer to step-down unit and discharge
- Indication of admission to Neonatal Stabilization Unit (NSU)
- Grading and management of hypothermia
- Expression of breast milk
- Assisted feeding of low birth weight neonates
- Intravenous fluid therapy for newborn
- Management of hypoglycemia
- Assessment and management of Jaundice in the newborn
- Assessment and management of respiratory distress
- Assessment of neonatal sepsis
- Administration of commonly used drugs
- Resuscitation algorithm
- Management of the newborn with seizures
- Administration of Dopamine in a newborn with hemodynamic compromise
- Checklist for assessment and management of a newborn requiring special care (remember by mnemonic 'TABCFMFMCF' for temperature, airway, breathing, circulation, fluids, medication, feeding, monitoring, communication and follow-up)
- Identifying Intrauterine Growth Retardation in a newborn
- Assessing gestation of the newborn baby: Expanded New Ballard Score
- Housekeeping protocols
- Breastfeeding.

The detailed discussion of the protocols is beyond the scope of this chapter; interested readers are referred to 'Facility based Newborn care Operational Guide-Guidelines for Planning and Implementation' for further details.

FBNC: VISION AND CHALLENGES

It has been estimated that such health facility based interventions can reduce neonatal mortality by as much as 25 to 30 percent.³ Under the program, so far, 274 SCNUs, 1124 NBSUs and 7413 NCCs have been operationalized till June 2011. Government of India plans to have atleast one SCNU in each district supported by network of NBSU at first referral units, and newborn care corners in each "delivery-point". However, with the expansion of the network, some

of the challenges which have been recognized are integration of obstetric-newborn care, raising a class of trained personnel and mentoring support, maintenance of quality assurance system for delivery of compassionate care at all levels and to strengthen the follow-up of graduates from these facilities for monitoring of the outcomes, as a barometer of the impact of FBNC on the community.

At the preliminary stage, FBNC appears to deliver promising results in certain districts. The replication of the model in other partner states is expected to be an important step to reaffirm community trust in health care system and in turn, strengthen the hopes for achieving the targets of MGD's in India.

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Section 2

Infectious Diseases and Vaccines

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Rational Antibiotic Therapy

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INTRODUCTION

Infections are common in children and fever is a common presentation. Fever does not equate with infection and not necessarily bacterial infection that may justify an antibiotic. After all, viral infections are common in the community and should not be treated with an antibiotic. Further, not all bacterial infections deserve an antibiotic prescription. However, antibiotics are prescribed for majority of children presenting with fever. In fact they may also be prescribed for children who have no infection as in case of cough due to hyperreactive airway disease. Thus antibiotics are often prescribed without proper diagnosis for fear of probable bacterial infection and antibiotics are often changed or multiple antibiotics used due to fear of worsening condition. Misuse of antibiotics in this way leads to increasing drug resistance that has become a major concern today. Besides, irrational use of antibiotic may suppress but not control infection that would pose difficulty in diagnosis with increased morbidity and risk of mortality. Thus, improper antibiotic use is a threat to the community and also to an individual patient. If this trend continues, it may not be long before even a simple infection may not be amenable to drug therapy.

WHEN SHOULD AN ANTIBIOTIC BE PRESCRIBED?

Attempt a Bacteriological Diagnosis

Antibiotic is indicated only in case of bacterial infection. It is ideal to attempt bacteriological diagnosis in every child with suspected bacterial infection. Though it is not practical in routine office practice. However, few conditions demand proof of bacterial infection as in case of urinary tract infection and typhoid fever. UTI in children is a potential serious disease with a risk of permanent renal damage if not properly diagnosed and

treated. Typhoid fever being a bacteremic infection, blood culture is often positive and technically, it is easy to culture *Salmonella typhi*. It is therefore expected that UTI and typhoid fever are bacteriologically diagnosed as often as possible and empirical treatment is not justified. In case culture facilities are not available, at least, circumstantial evidence should be collected before embarking on specific antibiotic therapy.

Circumstantial Evidence of Bacterial Infection

Typical clinical syndrome in an acutely febrile child may strongly suggest bacterial infection that may not need further proof for rational antibiotic prescription. Acute tonsillitis is clinically diagnosed by finding beads of pus on inflamed tonsils and tender submandibular lymph nodes. Loose stools with blood and mucus and abdominal cramps suggest acute bacillary dysentery. Localized chest findings in an acutely febrile child who develops tachypnea denotes bacterial pneumonia that may be confirmed by chest X-ray but even without chest X-ray would justify antibiotic therapy.

Laboratory evidence of bacterial infection should not be considered in isolation without clinical correlation. Neutrophilic leucocytosis and high CRP may favor bacterial infection but not adequate enough by themselves to consider antibiotic therapy.

WHEN THERE IS NO CLUE TO DIAGNOSIS

This is most common situation in routine office practice during first few days of onset of fever. Generally, one can arrive at reasonably correct diagnosis only after disease evolves over few days after onset of symptoms. It means that correct diagnosis is not possible in a febrile child in first few days with exception cited above such as tonsillitis and bacillary dysentery. At such stage, it is important to assess risk of waiting without specific action in an acutely febrile child.

Following situations in acutely febrile child are considered to be at risk of serious bacterial infection that demands urgent specific action:

- Age <3 months
- Severe PEM
- Immunosuppressed state
- Behavioral abnormality—lethargy or extreme irritability
- Significant oliguria or anuria
- Tachycardia and tachypnea disproportionate to degree of fever.

In such situations, laboratory tests should be ordered before starting empirical antibiotic and decision taken for need for hospitalization. Laboratory tests may be prioritized on individual merits and they include CBC, urinalysis, chest X-ray, blood and urine culture and CSF examination.

WHEN THERE IS NO CLUE TO DIAGNOSIS BUT SAFE TO WAIT

In absence of risk factors in a febrile child, it is rational to wait and observe progress without antibiotic therapy. Fever should be controlled with paracetamol. Parents must be counseled about danger symptoms such as behavioral abnormality and reduced urine output that demand reporting to medical facility. Periodic clinical examination is necessary over next few days to pick up clinical clues to diagnosis. Attempt must be made to differentiate acute bacterial infection from acute viral infection. It is possible to a reasonable extent by detailed analysis of history of fever as depicted in Table 1.

Table 1: Look for clues to diagnosis

	<i>Bacterial</i>	<i>Viral</i>	<i>Malaria</i>
Degree at onset	Moderate	High	High
Rhythm	Regular	Regular	Irregular
Response to paracetamol	Average	Good	Good
Interfebrile state	Sick	Normal	Normal
Progress on D3-4	Persisting	Better	Variable
Contact history	None	Positive	None

In case of suspected viral infection, no antibiotic is justified. In case of suspected bacterial infection, consider

relevant laboratory tests before starting empirical antibiotic. Empirical antibiotic selection should be based on local epidemiological observation and experience. In case of suspected malaria, one should look for malarial parasite in blood smear before prescribing antimalarial therapy.

WHEN ANTIBIOTIC FAILS IN SUSPECTED BACTERIAL INFECTION?

Antibiotic rarely fails in routine office practice in case of community-acquired infection in a normal host. One should expect response to antibiotic within 3 to 4 days. If there is no response, it calls for reassessment.

Firstly confirm whether it is infection and if so bacterial infection. This may be done by repeated physical examination supported by repeat laboratory tests. Choice of antibiotic and its route of administration may be a factor responsible for poor response. If bacterial infection and choice of antibiotic are reasonable confirmed, look for complications such as empyema in case of bacterial pneumonia or subdural collection in case of meningitis. At times, poor response may be due to iatrogenic factor such as catheter related infection or nosocomial infection in a hospitalized setting. Only when all such factors are ruled out that one may consider drug resistance. It is ideal even at this stage to send blood culture and then change to best considered empirical antibiotic. However, if this change also fails, bacterial infection is ruled out and one must search for alternate diagnosis. It is not wise to persist with empirical antibiotic trial beyond one change.

SUMMARY

Rational antibiotic therapy is the need of the hour. Empirical antibiotic therapy has a place in routine practice but only with rational approach. It includes assessing risk of waiting, clinically evaluating probable etiology of fever supported by relevant laboratory tests, repeated observation to monitor progress, selecting appropriate empirical antibiotic and reassessment in case of poor response. With indiscriminate antibiotic use, there has been increasing drug resistance and time has come to change this trend lest we are defeated by simple infections.

Adverse Drug Reactions and Pharmacovigilance

DC Dhasmana

INTRODUCTION

Humans are fond of taking medicines for their sufferings since time immemorial. At present, consumption of medicines has become a normal concept of daily life, being used in all trivialities. The huge list of available formulations and drugs coupled with enormous therapeutic advances is tempting to all clinicians to prescribe them. The Druglist continues to grow especially in recent times with a lot of newer entries as a result of high tech pharma products, new vaccines, new dosage forms, newer routes of administration besides new therapeutic claims of existing drugs.

India is a vast and diverse country with almost 1.2 billion population, at present with many diverse characteristics with social, economic and cultural paradigms. As population continues to grow, the disease pattern and magnitude grows in parallel to increased drug consumption in the society. Habitual prescribing, misuse and abuse of drugs are common. Simultaneous growth of nonprescription (OTC) drugs and self-medication contributes heavily to overall drug consumption. With increasing burden of non infectious/degenerative diseases, poly pharmacy is a common practice inviting drug-drug interactions. Many alternative therapies, herbal medications, nutritional supplements added to complicate the issue of drug interactions further.

Indian Pharmaceuticals, worth Rs. 90,000 crore, are growing at a pace of 12 to 14 percent per annum with ~25 percent export growth per year according to one estimate. They are competing in finding a share of the market by infusing many new combinations and formulations with special physical/ technological properties. India, in fact has established a global pharmacy of generic drugs, producing quality drugs at affordable prices. More over India is coming up as global hub for clinical trials in drug discovery programs too.

Harmful effects of drugs as referred to adverse drug reactions (ADRs) are as old as medicinal use. In fact, a common dictum is 'a drug that does not produce an ADR is not a drug at all'. Incidence of ADR's is contributed by poly pharmacy, OTC drug use, alternative medications/ nutritional supplements equally. ADRs *per se* are one of the leading causes of morbidity and mortality worldwide. ADRs may range from mere inconvenience to serious disability and may contribute to 3 to 6 percent of hospital admissions and death (2-12%).¹ They commonly occur in hospital setting where more serious patients are managed with multiple drug therapies. Further, managing ADRs put a huge financial burden on the health care delivery and the total cost involved may be more than the individual cost of managing cardiovascular, diabetes, cancer and HIV disorders.²

Small group of widely used drugs accounts for a disproportionate number of ADRs. Almost 50 percent of drugs produce unusual and unpredictable serious ADRs only after marketing. Moreover, newly marketed drugs need more care on ADRs as they are not exposed to large number of patients in a variety of situations, over a long period of time for want of their remote manifestations. Full range of ADRs may not be known until the drug is already in use for many-many years. Thus, the irony is that long-term safety of drug use and rare ADRs are practically unknown at the time of its introduction in the market. Further, the special population of patients, i.e. pediatric, elderly, pregnant and lactating women, patients with multiple disorders etc. make them more prone to develop ADRs. Spectrum and severity of ADRs also varies as the disease pattern, patient population characteristics, prescribing habits, availability of drugs and their quality vary from region to region.

A large number of ADRs (almost more than 50%) could be prevented, if we are aware of them and know

about their mechanisms and predisposition. This is possible only by a close and continual watch on ADRs, their understanding and reporting. Monitoring ADRs is a challenging job in the current scenario for which a robust program is needed. At times, such observed ADRs in the past led to withdrawal of many drugs from the market with big surprises among the public, i.e. Cloquinol, practolol, Benoxaprofen, suprofen, Tacyinafen, Zomepirac, Troglitazone, cerivastatin, lomefloxacin, grepafloxacin, gatifloxacin, Rofecoxib, Astemizole, Terfenadine, alos-etron, phenylpropanolamine, fenfluramine, sibutramine, mibefradil, cannabinoid receptor antagonist—rimonabant, Tegaserod and change in labeling of cisapride, isotretinoin, and many others. To conclude, ADRs, must be predicted, recognized, reported, their mechanism be understood and prevented at all cost keeping in mind the huge economic loss in managing them.

TERMINOLOGIES USED IN ADRS

The following terminologies are used as per WHO recommendations:³

Adverse drug reaction: A response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function.

Unexpected adverse reaction: An adverse reaction, the nature or severity of which is not consistent with domestic labeling or market authorization, or expected from characteristics of the drug.

Adverse event/adverse experience: Any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment.

Side effect: Any unintended effect of a pharmaceutical product occurring at doses normally used in man which is related to the pharmacological properties of the drug.

Signal: Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information.

CLASSIFICATION OF ADRs/TYPES

Workable classification includes:

Type-A: are those that are dose dependent, predictable and are the extension of known pharmacological actions of drugs.

Type-B: are those that are nonpredictable and not so dose dependent and are not explained by the known pharmacological actions of the drugs.

A more elaborate classification is based on Type-A (dose dependent known pharmacological effect), Type-B (non dose dependent; bizarre sensitivity reactions—allergic or idiosyncratic reactions), Type-C (cumulative chronic toxicity-chronic organ damage), Type-D (delayed—carcinogenicity, teratogenicity), Type-E (end of the use effect) and Type—F (negative effect or the failure of the drug efficacy).⁴

FREQUENCY⁵

Frequency of ADRs can be assessed as follows in terms of fractions and percentage:

Very common	>1/10	(>10%)
Common (frequent)	1/100-1/10	(1-10%)
Uncommon (infrequent)	1/1,000-1/100	(0.1-1%)
Rare	1/10,000-1/1,000	(0.01-0.1%)
Very rare	<1/10,000	(<0.01%)

SEVERITY

“Severity” is used to describe the intensity of a specific event/reaction as mild, moderate, severe or lethal; the event itself, however, may be of relatively minor medical significance, i.e. such as severe headache.⁶ Severity assessment can be done by Hartwig et al scale.⁷

VARIABLES THAT DETERMINES THE INCIDENCE AND SEVERITY OF ADRs

Many variables influence the incidence and severity of ADRs as both intrinsic and extrinsic factors play a role. Age being one of the important predisposing factors—both elderly and pediatric age (neonates, infants) being vulnerable.⁸ Others could be sex, immunological, genetic, environmental, socioeconomic, prescribing factors, drug factors, i.e. route, formulation and duration of therapy. Determinants must be explored to understand ADRs leading to their preventability, i.e. Gray baby syndrome due to chloramphenicol in infants and neonates.

SERIOUSNESS³

A serious adverse event or reaction is any untoward medical occurrence that at any dose:

- Results in death
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is life-threatening

PREVENTABILITY

ADRs almost more than 50 percent are preventable provided that they are anticipated in a clinical situation.⁹ Under reporting due to misconceptions and failure to

disseminate the information because of lack of knowledge as to where, when and how to report the ADRs contributes to nonpreventability. Prior considerations of factors/variables known to modify drug actions often make it possible to prevent ADRs.⁷ Unfortunately despite increased vigilance in western world the number of preventable ADRs remains constant over four decades.¹ Pharmacogenomics may add new dimensions to boost the prevention of ADRs in near future.

DRUG SAFETY ISSUES RELATED TO PEDIATRICS

There is a limited knowledge of drugs in terms of drug dosage, and their safety in neonate, premature neonate, infants, children and adolescents compared to adults. Kinetics and dynamics of drugs are least certain in this age group where there is a rapid transition in physiology, anatomical and functional development over time. Moreover off-label use of drugs is high (~43%) in pediatric age group, increasing particularly the serious ADRs burden.¹⁰

Sulfanilamide elixir dissolved in diethylene glycol deaths, thalidomide disaster, gray baby syndrome, Reye's syndrome being the typical historical examples. Ethambutol causing visual impairment, fluoroquinolones linked to arthropathy, increased phenothiazines sensitivity for extrapyramidal syndromes, sulfa drugs predisposition to kernicterus, tetracyclines causing dental staining, valproic acid induced hepatotoxicity, steroid induced growth and development problems, and antiepileptic induced mental retardation are other examples that are specific in this age group. Study by Ufer et al¹⁰ in Sweden showed anti-asthmatics and antibiotics on top of ADRs producing drug list in pediatrics and most common manifestations were psychiatric and the mucocutaneous inflammatory reactions. Thus, this age group is bound to be most vulnerable to unpredictability of drug actions and their consequences.

PHARMACOVIGILANCE

The early experiences of thalidomide and high oral estrogen contraceptives led to stringent safety requirements during drug development and establishment of spontaneous ADRs reporting system in 1960s.¹¹

Detection of ADRs is a complex issue. Their detection is inefficient due to difficult clinical situations, difficulty in clinical monitoring, diagnostic imprecision, low index of suspicion and nonreporting of ADRs by the clinicians.¹² Early experiences with a new drug are poor predictors of unknown, rare, and long term ADRs in the looser context of their use in the society. To keep a watch on such ADRs, continual post marketing surveillance/pharmacoepidemiological studies are needed for which observational/descriptive designs must be adopted, i.e. cohort studies, prescription event monitoring, case control studies, case

reports, case series and spontaneous reporting system, etc. so as to refine rational use and socioeconomic impact of drugs with possible regulatory changes. The lower cadre of observational studies yields most in detection of ADRs after drug marketing. In this way, the importance of spontaneous ADRs monitoring system is tremendous in surfacing new and previously unrecognized ADR leading to awareness and even regulatory changes or withdrawal of the drug from the market. There is no substitute for such a system in detecting ADRs though even with spontaneous ADRs monitoring system, the occurrence of new and unexpected ADRs after marketing remains unabated that raises questions on the methodology and implementation of predicting ADRs.¹¹

WHO took up the issue of grave public and professional importance of ADRs and came out with a systematic spontaneous reporting system at Uppsala, Sweden in 1968.¹³ The initiative has created a whole new discipline of pharmacovigilance that can be defined as: the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problems. It is the collection of information on ADRs in a systematic manner to draw meaningful conclusions. The primary aim of pharmacovigilance program (PVP) is to detect early warning signals that are unknown to drug previously. A robust PVP has educative, managerial and regulatory roles to play. ADRs reported to national PVP globally looks to be the most efficient system in generating data on ADRs¹¹ with the help of all stake holders, i.e. Pharma industry, academic and private institutions, practicing physicians, nurses, pharmacists, media, consumers and regulators. The ambit of PVP has lately increased further to cover the food, herbal, biological products including vaccines and medical devices. This is the way one can protect the patients and ensure unsafe drugs to be weeded out of market.

In fact, most of the recent reporting on ADRs leading to withdrawal or change in labeling were the results of such successful national programs worldwide like sibutramine by Italian and Rofecoxib by Canadian PVPs. Even, at times, the spontaneous AEs database through PVP may lead to identification of unanticipated drug benefits for therapeutic exploration.¹²

HOW TO DETECT ADRs?

The physician must exert efforts and keep his eyes and ear open to see and report an ADR. To collect and collate ADRs, all the health care persons/pharmaceuticals and regulatory bodies have to integrate their efforts to generate high quality data as an obligatory national priority. It is to foster the culture of reporting adverse events for which voluntary cooperation of health professionals is a must. A prepared mind with strong index of suspicion is desired in every practicing physician.

CAUSALITY ANALYSIS³

Causality assessment is crucial in PVP as it reflects into safety aspects of drug. It is the causality assessment that makes an adverse event to adverse drug reaction. WHO's direct introspection method is the most common method for this purpose, although many decisional algorithms have also been described in the literature to predict the causality with their own merits and demerits. Basic concept lies in describing, challenge, dechallenge, and rechallenge, previous knowledge and confounding other drug's contribution for suspected ADR in reported adverse event.

As per WHO³, following criteria are used:

Certain: A clinical event, including laboratory test abnormality, is occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure, if necessary.

Probable/likely: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.

Possible: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.

Unlikely: A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.

Following noncausality terms are also used:

Conditional/unclassified: A clinical event, including laboratory test abnormality, reported as an adverse reaction, about which more data is essential for a proper assessment or the additional data are under examination.

Unassessible/unclassifiable: A report suggesting an adverse reaction which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified.

PHARMACOVIGILANCE PROGRAM OF INDIA

Unlike western countries, there is a dearth of ADRs monitoring in India. Pharmacovigilance program of India I is

still in infancy, in spite of large number of tertiary care centers, a fleet of well trained and skilled healthcare manpower and a blooming pharmaceutical industry. Here, most of the ADRs go under reported.

The regulatory frame work must ensure drug safety of Indian population at all cost. To protect the interest of consumers, the DGHS, Government of India has mandate to facilitate availability of safer and effective drugs and to keep unsafe ones off the market. Presently, this task is given to Indian Pharmacopoeia Commission as National Coordinating Center (NCC) to ensure PVP in India from 2010 onwards. Earlier, PvPI was started in India with the support of WHO in 2004-2008 under DGHS. Realizing its importance, this program is now being indigenously run by the DGHS. The whole idea of PvPI is to generate independent data on Indian population through designated frame work of peripheral centers all over India and then provide evidence based recommendations to industry, the healthcare prescribers, to incorporate in regulatory framework of DGHS and to be the part of the data linkage at Uppsala global monitoring center of WHO as per the agreement. It is a continuous program that has strategic advisory committee, a steering committee, the NCC with signal review committee, core training committee and a quality review panel to look into the whole gamut of ADRs monitoring in India.

Basically, it is an active process of spontaneous ADRs monitoring system that has been given a robust footing to capture all possible meaningful data by new signals generated at the earliest, since we are the major consumers of drugs globally but right now contributing very little towards assurance of safety both nationally and globally.

CONCLUSION

Success of any health care delivery depends heavily on availability of safe, effective and quality drugs at an affordable and reasonable price at all time and all places as per the essentiality of drugs in the area. It is a national priority in the interest of the society to protect the population from potential harm. We cannot escape from ADRs but certainly reduce their occurrence at the same time we can not handle ADRs that are not known beforehand. ADRs must be anticipated in any situation of drug use. A high index of suspicion, good communication and reporting every drug reaction hallmark the quality of the physician. Responsibility of identifying and reporting rests with the practicing physician by careful observation of the drug effects in real world. The facilitatory support for ADRs monitoring can be provided by the system.

Scientifically weaker observational studies, i.e. case reports are more suitable for detecting new unexpected ADRs unlike therapeutic trials and act as whistle blowers. Big hospitals become a hub for detecting ADRs where the

newer drugs are used in all diverse situations. These ADRs can further be put to test by more systematic analysis and quantifying risk. Spontaneous ADRs monitoring looks to be the best suited program for continuous and robust database for any country. Active assistance boosts up the level of reporting and sensitizes and encourages the clinicians to report them. The national program of PvPI has already been made operational to this effect.

To conclude, we all have the concern, responsibility and obligation to strengthen the ADRs reporting program. The fruition of medical practice lies in realizing that each individual is unique and treatment needs to be individualized to suit best under the circumstances.

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Newer Antibiotics: New Drugs and New Challenges in Primary Care

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INTRODUCTION

Today, the primary care physician is faced with a bewildering array of new antimicrobials to treat common infections. These agents promise to be extremely effective as replacements for time-honored drugs, as prophylaxis, and for the treatment of infections previously requiring prolonged intravenous therapy. The overuse of the newer antibiotics may prove to be ecologically and economically costly. It is feared that the selective pressure from these broad-spectrum agents may burden society with an even greater problem of community-acquired pathogens that are resistant to multiple antibiotics. The specific therapeutic and economic advantages and disadvantages of each class should be considered and the decision to employ these agents should be highly individualized. Several antibiotics have arrived in the market over the past few years. Should they be widely used, or are they best saved for use in exceptional situations by tertiary care specialists?

Each year, Drug Controller of India approves a few new antimicrobial agents. Occasionally, one is quickly

recognized as a potential blockbuster. More often, though, the new drugs are either similar to some already on the market, or they may occupy an important but narrow treatment niche. Methicillin-resistant *Staphylococcus aureus* (MRSA) infections, which were once acquired only in health care settings, are now widespread in communities across the nation. Vancomycin-resistant enterococci (VRE) are present in many tertiary care facilities. Investigators associated with a study of geographic and temporal trends in antibiotic resistance in *Streptococcus pneumoniae* predicted in 2003 that by July 1, 2004, 41 percent of the pneumococci at the CDCs active bacterial core surveillance sites would be resistant to both penicillin and erythromycin.¹ In contrast, they added, only 5% will be resistant just to penicillin, and another 5% would be resistant to erythromycin only.

ANTIBIOTICS

Pathogenic bacteria have demonstrated an unparalleled ability to adapt to changing environments. Of particular concern has been the rapid development of resistance to multiple front-line antibiotics which has severe consequences on patient care and outcomes. Many of these organisms have become important sources of nosocomial infections further adding to morbidity and mortality in already sick individuals. *The Infectious Diseases Society of America* recently published a hit list of bacterial pathogens² whose antibiotic resistance severely impacts the ability to treat infections in the US hospital setting. This list is comprised of *Staphylococcus aureus*, *Enterococcus faecium*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Enterobacter spp.* Such data are not available on a large-scale multicenter level in our country as yet. However, the presence of these resistant organisms in our health care institutions due to the lack of coherent guidelines on antibiotic use is an open secret.

Drugs discussed in this article

Daptomycin	Telithromycin
Linezolid	Oritavancin
Ranbezolid	Dalbavancin
Eperezolid	Telavancin
Ertapenem	Iclaprim
Doripenem	Cefditoren
Quinupristin-dalfopristin	Ceftobiprole
Tigecycline	Ceftaroline
Gemifloxacin	

The goal of this chapter is to update primary care clinicians about new antibiotics, their appropriate use and also, importantly, when not to use them. Antibacterials are discussed below, antifungal and antiviral agents are discussed in separate chapters.

A brief review of some new antibiotics is presented below. Several of these recently approved or soon to be approved antibiotics may have a role in primary care practice, while others will probably find more use in tertiary care facilities. In the discussion that follows we have reviewed the more widely used newer antibiotics in some detail. Brief information has also been provided about some drugs which are at the cusp of approval or advanced stages of development.

Daptomycin

Class

Cyclic lipopeptide

Initially discovered in 1980's but clinical development was ceased due to toxicity concerns. It was approved only in 2003 by the US FDA.

Mechanism of Action

Rapidly bactericidal by apparently inserting into the cytoplasmic membrane of targeted Gram-positive pathogens, where it undergoes structural changes associated with binding of calcium ions, which in turn leads to pore formation, as well as depolarization of the membrane and inhibition of amino acid transport and peptidoglycan formation.^{3,4}

Indications

Primarily active only against Gram positive organisms.

- The treatment of complicated skin and skin-structure infections caused by susceptible strains of the following organisms:
 - *S. aureus* (including methicillin-resistant strains)
 - *Streptococcus pyogenes*
 - *Streptococcus agalactiae*
 - *Streptococcus dysgalactiae* (subspecies *equisimilis*)
 - *Enterococcus faecalis* (vancomycin-susceptible strains only).
- *Staphylococcus aureus* bloodstream infections (including right-sided infective endocarditis).

Daptomycin can be used in combination regimens when infection with a gram-negative or anaerobic organism is either suspected or confirmed. This drug's action is rapidly bactericidal.

Off-label or Investigational Use

Daptomycin is active against VRE.

Utility in Primary Care

This parenteral agent is unlikely to be used widely in primary care practice, although it is one possible alternative for the treatment of patients with resistant, aerobic,

gram-positive pathogens, including MRSA. It is approved only for specific indications at present. Application in the treatment of respiratory tract infections is very limited which is mainly attributed to inactivation of the drug by pulmonary surfactant.⁵ Researchers are considering daptomycin as a possible alternative to vancomycin, linezolid, and the fluoroquinolones for the treatment of MRSA infections. It may also be useful in the treatment of VRE infections, especially if these become more widely disseminated in the community. *Also*, it constitutes an attractive option for the treatment of neutropenic patients, and investigations in this direction are ongoing.⁶ At this time, specialists do not consider it more effective than linezolid or vancomycin.

Although daptomycin is available only for administration via the parenteral route, it is administered once daily, making it possible to deliver it in an ambulatory care setting. Daptomycin is well-tolerated, but it has been associated with myopathy and myositis. While uncommon, these adverse reactions can be severe.

Potential Problems

Dosing more than once a day may lead to elevations of creatine phosphokinase levels. Pseudomembranous colitis is a risk, as it is with all antibacterial agents.

Patients receiving this drug should be assessed for the development of muscle pain or weakness and creatine phosphokinase levels should be determined weekly. Clinicians should be aware that daptomycin has been confused with the similarly named anticancer agent dactinomycin.

Dosage

It is administered @ 4 mg/ kg over a 30 minute period by IV infusion in 0.9 percent sodium chloride injection once every 24 hours for 7 to 14 days. Adults with renal impairment characterized by a creatinine clearance of less than 30 ml/ min (including patients who are undergoing hemodialysis or continuous ambulatory peritoneal dialysis), dose modification is indicated (4 mg/ kg once every 48 hours).

Linezolid

Class

Oxazolidinones; represent a new class of synthetic antibacterials which are unrelated to any currently marketed agent. It was first approved for clinical use by the FDA in 2000.

Mechanism of action

Unique mechanism of bacterial protein synthesis inhibition involving interference with the binding of mRNA to the ribosomes at the initiation phase of translation.⁷ It binds to the 50s subunit of the bacterial ribosome.

Indications

Treatment of patients with:

- Vancomycin-resistant *Enterococcus faecium* infections, with or without concomitant bacteremia
- Nosocomial pneumonia caused by *S. aureus* (methicillin-resistant and -susceptible strains) or *S. pneumoniae* (penicillin-susceptible strains and only some resistant strains)
- Complicated skin and skin-structure infections, including diabetic foot infections without concomitant osteomyelitis caused by *S. aureus* (methicillin-resistant and methicillin-susceptible strains), *S. pyogenes*, or *S. agalactiae*
- Linezolid could be of particular value in the treatment of infections caused by MRSA producing the Panton-Valentine leukocidin (PVL) toxin, which are commonly community-acquired and involve mainly the skin and soft tissues or the lower respiratory tract.⁸
- Uncomplicated skin and skin-structure infections caused by *S. pyogenes* or methicillin-susceptible strains of *S. aureus*
- Community acquired pneumonia (CAP) caused by methicillin-susceptible strains of *S. aureus* or penicillin-susceptible strains of *S. pneumoniae*, including patients with concomitant bacteremia.
- Combination therapy may be required if infection with a gram-negative organism is suspected.
- Also, active against atypical bacteria.

Off-label or Investigational Use

Linezolid has not been tested in patients with decubitus ulcers but could be useful in that situation. As it is available for oral administration, it may be clinically useful in the treatment of infections requiring prolonged antibiotic therapy, such as endocarditis⁹ or osteomyelitis.^{10,11}

Utility in Primary Care

Linezolid is available for oral and parenteral administration, which facilitates the transition from inpatient to outpatient care. This valuable agent is active against gram-positive organisms, as well as VRE and MRSA.^{12,13} The use of linezolid has been restricted at some institutions because the drug has been prescribed as a first-line agent for the treatment of patients with staphylococcal infections when the presence of MRSA was possible, but not confirmed. Linezolid is also considerably more expensive than alternative agents, including vancomycin.

Accumulated evidence from large clinical studies comparing vancomycin and linezolid in patients with MRSA infections has shown little difference in efficacy. Hospital-acquired pneumonia caused by MRSA seems to be an exception, however, with linezolid producing a better outcome and lower mortality than vancomycin.¹⁴ These data

were derived from a subgroup analysis, however, so specialists would like to see the findings replicated elsewhere. For other forms of suspected MRSA infection, vancomycin is still used in most institutions as first-line treatment.

Once MRSA is confirmed and the patient is ready for discharge, therapy can continue with linezolid, with its predictable activity against MRSA. Note, however, that the newer fluoroquinolones with good activity against gram-positive organisms, such as gemifloxacin, moxifloxacin, and gatifloxacin, as well as TMP-SMX, may also be effective alternates for oral therapy and are less expensive than linezolid. The microbiological data are crucial in MRSA infections, however. Use of a fluoroquinolone or TMP-SMX to treat MRSA is not advisable until the antibiotic sensitivities of the organism are confirmed. In most situations, of course, confirmation of MRSA and the sensitivity data become available at the same time. The bottom line is that if the infection is life-threatening, vancomycin or linezolid use is recommended. For skin or soft-tissue infections that can be treated orally another antibiotic may be considered.

Potential Problems

To prevent the development of resistance to linezolid, experts in this field urge clinicians to avoid using it to treat methicillin-sensitive staphylococcal infections or enterococcus infections that are sensitive to other antibiotics. Disturbances of gastrointestinal function (diarrhea, nausea, and vomiting) were the most commonly observed side effects. Severe rashes and lactic acidosis have also been reported in patients taking linezolid. Prolonged administration of linezolid carries an increased risk for the development of specific types of adverse events, such as myelosuppression (primarily thrombocytopenia) or peripheral neuropathy that may not be reversible.^{9,10}

Drug Interaction

Probenecid

Dosage

Children 10 mg/kg q12 h IV or PO, adults 600 mg IV or po, q12 h for 10 to 14 days.

Other Oxazolidinones

Ranbezolid (RBX 7644)

It has been tested on pneumococcal and staphylococcal strains.¹⁵ Activity against pneumococci was similar irrespective of the strains' —lactam, macrolide, or quinolone susceptibilities. The MIC values for coagulase-negative staphylococci were lower than those for *S. aureus*. The compound also showed very good *in vitro* activity against both gram-negative and -positive anaerobes.

Eperezolid- It is active orally or intravenously against multi-drug-resistant, gram-positive bacteria. There is a uniform susceptibility in sensitive bacteria independent of resistance to other antibiotics.

Ertapenem

Class

Carbapenem. It was first approved by the USFDA for clinical use in 2001.

Mechanism of Action

It acts by inhibiting peptidoglycan synthesis. Carbapenems are primarily bactericidal.

Indications

The treatment of adults with one of the following:

- Complicated intra-abdominal infection due to *Escherichia coli*, *Clostridium clostridioforme*, *Eubacterium lentum*, *Peptostreptococcus* species, *Bacteroides fragilis*, *Bacteroides distasonis*, *Bacteroides ovatus*, *Bacteroides thetaiotaomicron*, or *Bacteroides uniformis*.
- Complicated skin and skin-structure infections caused by *S. aureus* (methicillin-susceptible strains only), *S. pyogenes*, *E. coli*, or *Peptococcus* species
- Community-acquired pneumonia (CAP) caused by *S. pneumoniae* (penicillin-susceptible strains only), including cases with concomitant bacteremia, *Haemophilus influenzae* (beta-lactamase-negative strains only), or *Moraxella catarrhalis*
- Complicated urinary tract infections, including pyelonephritis due to *E. coli*, including cases with bacteremia, or *Klebsiella pneumoniae*
- Acute pelvic infections, including postpartum endomyometritis, septic abortion, and postsurgical gynecologic infections caused by *S. agalactiae*, *E. coli*, *B. fragilis*, *Porphyromonas asaccharolytica*, *Pepto-streptococcus* species, or *Prevotella bivia*.

Utility in Primary Care

Ertapenem has a narrower spectrum of activity than other carbapenems, which may be an advantage in some clinical situations. It is not active against *Acinetobacter* or *Pseudomonas* species, but it is very effective against other gram-negative, gram-positive, and anaerobic organisms. Some experts think of ertapenem as a combination of ceftriaxone and metronidazole. It has excellent activity against enteric organisms and is administered once a day. It is an appropriate choice in a situation in which ceftriaxone might otherwise be used, but coverage against anaerobes was also sought—for example, a patient admitted for treatment of pneumonia but at risk of aspiration because a seizure disorder, drug overdose, or alcohol abuse.

Daily dosing makes it convenient for treating patients with pneumonia who reside in long-term care facilities. Ertapenem can be administered parenterally to patients in the emergency department (ED) and then continued at a long-term care facility.¹⁶ High-dose ampicillin/sulbactam might be an alternative in this setting, but it must be administered several times a day.

Very-broad-spectrum antibiotics such as piperacillin/tazobactam, ticarcillin/clavulanate, imipenem, or meropenem are often prescribed for patients with very severe pneumonia. More important, the anti-pseudomonal activity of these drugs is usually unnecessary in this clinical setting and may contribute to resistance among gram-negative organisms.

Potential Problems

It may be prudent to monitor renal function in elderly patients, as ertapenem is excreted largely by the kidney. As with most antibiotics, pseudomembranous colitis has been reported in association with ertapenem use.

Dosage: 1 g either given once daily for up to 7 days IM or up to 14 days IV.

Other Carbapenems

Doripenem

This is a new parenteral carbapenem that has bactericidal activity against many gram-positive and gram-negative aerobic organisms encountered in patients with HAP. It has a broad spectrum of antimicrobial activity, including Gram-negative, Gram-positive and anaerobic bacteria; MRSA and VRE are excluded, however. Doripenem appears to be more active *in vitro* against *P. aeruginosa* than imipenem.¹⁷ Doripenem appears to be equally or slightly more active against *P. aeruginosa* than meropenem.^{18, 19} It was approved by the FDA in 2007 for the treatment of complicated intra-abdominal infections and complicated urinary tract infections, including pyelonephritis. Apart from these indications, doripenem has been favourably compared with piperacillin/tazobactam and imipenem/cilastatin in two multicenter open-label randomized clinical trials in patients with nosocomial pneumonia and ventilator-associated pneumonia, respectively.^{20, 21}

Quinupristin-dalfopristin

Class

Streptogramins. These antibiotics are produced naturally by *Streptomyces* species, but the therapeutic use of the natural compounds is limited. Quinupristin-dalfopristin is a 30:70 combination of a type B and a type A streptogramin.²² It is a water-soluble injectable preparation and was approved by the USFDA in 1999.

Mechanism of Action

The two components target the late and early stages of bacterial protein synthesis, respectively, and thus have a synergistic inhibitory effect. They inhibit bacterial growth by disrupting the translation of mRNA into protein. Individually, the two components are bacteriostatic, but the combination has bactericidal activity against most gram-positive bacteria.

Indications

Active *in vitro* against various pathogens, including MRSA (commonly exhibiting bactericidal activity) and vancomycin-resistant *E. faecium* (commonly exhibiting bacteriostatic activity), but is typically inactive against *E. faecalis*. Currently approved indications are-

- Vancomycin-resistant *E. faecium* infections.
- Complicated skin and skin-structure infections caused by methicillin-susceptible *S. aureus* or *Streptococcus pyogenes*.
- *Quinupristin-dalfopristin is considered to be one of the few potential treatment options for endocarditis caused by isolates of E. faecium that exhibit resistance to vancomycin, penicillin and aminoglycosides.*²³

Utility in Primary Care

Extremely limited. Mainly indicated for use in tertiary care centers for infections by specific organisms that are resistant to multiple antibiotics.

Potential Problems

It has a relatively high rate of reported adverse events with use. Development of phlebitis at the injection site has been reported, which may be avoided by administration via a central line.

Variable numbers of patients have developed myalgias and/or arthralgias that may be severe. These events are more likely to occur in patients with chronic liver disease, in liver transplant recipients, or those receiving cyclosporine or mycophenolate.²⁴ The clinical utility of quinupristin-dalfopristin is further limited by numerous drug interactions: the drug inhibits the cytochrome P450 3A4 isoenzyme and therefore can increase the serum levels of drugs that are metabolized by this enzyme, e.g. astemizole, cisapride, cyclosporine, disopyramide, lidocaine, midazolam, nifedipine, quinidine, and terfenadine.²⁵

Dosage

This drug is administered intravenously at a dose of 7.5 mg/kg every 8 hours.

Tigecycline

Class

Glycylcycline. It is derived by modification of the nine-position of minocycline. Tigecycline was first approved by the USFDA for clinical use in 2005.

Mechanism of Action

These antibiotics are bacteriostatic, and they act by binding to the bacterial 30s ribosomal subunit and by blocking entry of amino-acyl tRNA molecules into the A site of the ribosome. Amino acid residues are prevented from becoming incorporated into elongating peptide chains, which leads to inhibition of protein synthesis.

Indications

It is active against VRE strains and MRSA, as well as certain Enterobacteriaceae and anaerobes.²⁶ Resistance to tigecycline by *P. aeruginosa* and reduced susceptibility among *Proteus* species has been noted. The current indications for use include (each caused by specific pathogens):

- Complicated skin and skin-structure infections
- Complicated intra-abdominal infections
- Community-acquired pneumonia.

Tigecycline may also be active, although not consistently, against a substantial proportion of isolates of multidrug-resistant or carbapenem-resistant *Acinetobacter baumannii*. In this regard it constitutes one of the few potential therapeutic options against carbapenem-resistant *A. baumannii*.²⁷

Utility in Primary Care

It probably has limited use in primary care practice. Clinicians need to prescribe tigecycline appropriately, to avoid the emergence of resistant strains. As a single antimicrobial agent, tigecycline confers broad antibiotic coverage against vancomycin-resistant enterococci, methicillin-resistant *S. aureus*, and many species of multidrug-resistant gram-negative bacteria.

Potential Problems

The main adverse reactions are nausea and vomiting. As with tetracyclines, tigecycline may cause permanent tooth discoloration, so it should not be taken by young children or pregnant women. Drug interactions have not been observed.

Dosage

It is available as an intravenous formulation. An initial loading dose of 100 mg is followed by 50 mg every 12 hours for 7 to 14 days.

Gemifloxacin

Class

Fluoroquinolone. Gemifloxacin was approved in 2003 by the USFDA.

Indications

It has enhanced *in vitro* activity compared with ciprofloxacin against gram-positive pathogens, particularly

S. pneumoniae, including penicillin resistant and multidrug-resistant isolates.²⁸

It has been used for the treatment of acute bacterial exacerbation of chronic bronchitis (AECB) caused by *S. pneumoniae*, *H. influenzae*, *Haemophilus parainfluenzae*, or *M. catarrhalis* and mild-to-moderate CAP caused by *S. pneumoniae* (including multidrug resistant strains of pneumonia [MDRSP]), *H. influenzae*, *M. catarrhalis*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, or *K. pneumoniae*. Note that MDRSP refers to *S. pneumoniae* strains that are resistant to at least 2 of the following drugs or drug classes: penicillin, second-generation cephalosporins, macrolides, tetracyclines, and trimethoprim/ sulfamethoxazole (TMP-SMX).

Off-label or Investigational Use

Gemifloxacin is active against some *Enterobacteriaceae*. In addition, it exhibits *in vitro* minimal inhibitory concentrations (MICs) of 0.25 mcg/ ml or less against at least 90 percent of strains of 2 gram-positive organisms—*S. aureus* and *S. pyogenes*—and several gram-negative ones, including *Legionella pneumophila* and *Proteus vulgaris*. The clinical significance of these *in vitro* data is unclear.

Utility in Primary Care

Gemifloxacin has strong activity against gram-positive bacteria, most importantly *S. pneumoniae* and *S. aureus*, distinguishes it from other fluoroquinolones.^{29,30} Otherwise, its spectrum of activity is quite similar to those of levofloxacin, gatifloxacin, and moxifloxacin. Unlike ofloxacin, levofloxacin, and ciprofloxacin, however, gemifloxacin is not active against mycobacteria. This is not a common use for these drugs, however. Gemifloxacin is not as useful as ciprofloxacin or levofloxacin against *Pseudomonas aeruginosa*, a factor, which may limit its usefulness in patients with cystic fibrosis.

The blood levels of gemifloxacin are lower than those achieved by moxifloxacin and levofloxacin, and its half-life is shorter. Nonetheless, its *in-vitro* anti-pneumococcal activity is excellent and is estimated to be 4 times that of moxifloxacin and 10 to 100 times that of levofloxacin. Whether these *in vitro* differences are clinically important is unclear.

Pneumococcal resistance to levofloxacin has been reported in Canada, and some resistance has been seen in the United States, and treatment failures have also been reported with ciprofloxacin. Gemifloxacin could be a treatment option in this situation. Experts in this field recommend considering gemifloxacin if drug-resistant pneumococcal infection is suspected because of a documented resistant isolate, or because the patient is vulnerable as a result of frequent antibiotic use or recent or frequent hospital stays. Overuse of gemifloxacin could render it less useful, however, so specialists caution against prescribing without a good reason. Also consider that levofloxacin is

inexpensive and well-tolerated. Gemifloxacin is expected to be an excellent choice for patients with CAP and AECB, but it may not be any more effective than some other fluoroquinolones or antibiotics in other classes.

Gemifloxacin may ultimately be extremely useful in patients with MRSA, and a certain percentage of MRSA isolates are sensitive to fluoroquinolones. Until recently, MRSA was not considered a risk in community-acquired infections and nafcillin, for example, could be safely used in a patient with endocarditis and a history of IV drug use. It is no longer safe to make this assumption. Community acquired MRSA infections, especially skin and soft-tissue infections are increasing in prevalence. In fact, infectious disease specialists often recommend that when a patient is hospitalized with a staphylococcal infection, even if it was acquired in the community, that it be treated with an agent that is active against MRSA. Risk factors for MRSA include frequent contact with EDs, hospitals, and frequent use of antibiotics. While this is true nationwide, there are geographic differences in the prevalence of community-acquired MRSA.

Some of the newer fluoroquinolones are active against anaerobes, organisms which are cause for concern among patients with CAP who may have aspirated oropharyngeal secretions. Moxifloxacin has shown good *in vitro* activity against anaerobes, but no studies have demonstrated its clinical efficacy against anaerobic infections. Gemifloxacin is less likely to be useful in this situation.

Potential problems

Overuse of gemifloxacin is a possibility. It is considerably more expensive than levofloxacin, however, which should reduce the amount of over prescribing. Side effects may include diarrhea, rash, and nausea. The incidence of rash is 2.8 percent but ranges from 1 to 32 percent, so this drug should not be considered for first-line treatment. As with many fluoroquinolones, there can be prolongation of the QTc interval.

Dosage

AECB- 320 mg/d for 5 days; CAP- 320 mg/ d for 7 days.

Telithromycin

Class

Ketolides. They are semisynthetic derivatives of macrolides.³¹ It was first approved by the USFDA in 2004.

Mechanism of Action

Telithromycin has the ability to bind to the bacterial ribosome more tightly than erythromycin; this is attributed to binding of telithromycin not only to domain V of the 23s rRNA (the binding site for macrolides), but also to domain II.

Indications

As telithromycin binds to an additional site on the bacterial ribosome it is active in vitro against erythromycin-resistant and multidrug resistant isolates of *S. pneumoniae*.³² It is also active against other common respiratory pathogens.³¹ Telithromycin has very good oral bioavailability and a favorable pharmacokinetic profile in respiratory tract infections.³³ Initial approval was given for clinical use in community-acquired pneumonia, acute bacterial exacerbation of chronic bronchitis, and acute bacterial sinusitis. However, following postmarketing surveillance reports of rare but severe adverse events, particularly of hepatotoxicity, the latter two indications were retracted.³³

Utility in Primary Care

Ketolides are the latest structural derivatives of erythromycin to be added to the macrolide family. This oral agent was developed to help manage the problem of macrolide-resistance in the pneumococcus and multidrug-resistant gram-positive bacteria in general, and it may become a first-line agent for that purpose in certain geographical areas, where pneumococcal resistance to macrolides has reached significant levels. Telithromycin is active against *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, and *S. pyogenes*. In addition, it is active against some atypical respiratory pathogens, including *C. pneumoniae*, *L. pneumophila*, and *M. pneumoniae*.³⁴

Telithromycin can be taken without regard for meals and requires no dosage reduction in elderly patients or those with hepatic impairment. It is well absorbed after oral administration and achieves rapid penetration into respiratory tissues and fluids.

Potential Problems

The most common adverse effects associated with telithromycin include diarrhea, nausea, headache, and dizziness. Prolongation of the QTc interval is a possibility and the drug interacts with ketoconazole and itraconazole and is a statin inhibitor. Scattered but severe adverse events, especially hepatotoxicity warrant careful use of this drug, and only in approved indications.

Dosage

800 mg once daily for 5 to 10 days.

Glycopeptides and Derivatives

New glycopeptide derivatives undergoing clinical development include oritavancin (a derivative of the glycopeptide chloroeremomycin), as well as the lipoglycopeptides dalbavancin and telavancin (derivatives of teicoplanin and vancomycin, respectively).

Oritavancin

It has potent bactericidal activity against MRSA and VRE,³⁵ and has mainly been evaluated in clinical trials for the treatment of complicated skin and skin-structure infections.³⁶ In addition to inhibiting peptidoglycan synthesis, a second recently identified mechanism, involves the rapid disruption of both membrane potential and permeability. These combined activities provide oritavancin with potent activity against a wide spectrum of gram-positive organisms. Oritavancin demonstrates activity against both MSSA and MRSA.³⁷ Importantly, oritavancin possesses activity against VISA and VRSA isolates.³⁸

In vitro it has been noted to cause alterations in animal lysosome activity suggesting oritavancin has the potential to cause a mixed-lipid storage disorder; however, the clinical significance to humans is unknown.³⁹ Other adverse effects reported include transient elevations in hepatic transaminases and injection site reactions.

Dalbavancin

It is a lipoglycopeptide. Dalbavancin binds to the terminal D-alanyl-D-alanine of the pentapeptide chain, which inhibits peptidoglycan cross-linking and leads to cell death. It is active solely against Gram positive organisms.

Dalbavancin exhibits bactericidal activity against pneumococci, regardless of penicillin sensitivity.⁴⁰ It has slow bactericidal activity against *S. aureus*, both methicillin-sensitive and -resistant.⁴¹

This drug is active in vitro against MRSA; however, similarly to teicoplanin, it is not active against vancomycin-resistant *E. faecium* with the van A genotype.⁴² It has a prolonged serum elimination half-life that allows for a dosing interval of 1 week, thereby rendering this agent an appealing option for outpatient parenteral antimicrobial therapy. It has mainly been evaluated in clinical trials for the treatment of complicated skin and skin-structure infections and catheter-related bacteremia.^{43, 44}

Approximately one third of dalbavancin is excreted unchanged in the urine, suggesting non-renal routes of elimination. No dosage adjustment is required for patients with mild to moderate renal impairment. The most commonly reported adverse events included pyrexia, headache, and gastrointestinal symptoms. No auditory or vestibular toxicity, or “red man” syndrome was observed in study subjects. Dalbavancin has been shown to be devoid of major ecologic effects on normal intestinal microflora.⁴⁵

Telavancin

This drug is also an investigational lipoglycopeptide. It inhibits cell wall synthesis by binding to peptidoglycan precursors containing the terminal D-ala-D-ala residue and preventing cross-linking. It is active and bactericidal against

MRSA and has greater activity than clinically available glycopeptides against VRE, particularly against those carrying the vanB genotype.⁴⁶ It has mainly been evaluated clinically for the treatment of patients with complicated skin and skin-structure infections and nosocomial pneumonia.^{47,48}

The primary elimination route is renal, and the elimination half-life is 8 to 9 hours. It is anticipated that patients with moderate to severe renal dysfunction will require dosage adjustments. Reported adverse events from clinical trials include taste disturbances, nausea, headache, and insomnia.

Iclaprim

Class

A synthetic diaminopyrimidine, a racemic mixture of two equipotent enantiomers.

Mechanism of action

It is a selective inhibitor of the enzyme dihydrofolate reductase (DHFR), similar to trimethoprim. Iclaprim prevents the production of tetrahydrofolic acid by interrupting the bacterial biosynthetic pathway.⁴⁹ As a specific and selective DHFR inhibitor, iclaprim preferentially prevents the synthesis of bacterial DNA and RNA.⁵⁰ Currently being developed as monotherapy in view of its potent intrinsic activity.⁵¹

Indications

Iclaprim has *in vitro* activity against *S. aureus*, including MRSA, and a single VRSA strain.^{52,53} Against penicillin-sensitive and penicillin-resistant pneumococci, it demonstrates more potent activity than trimethoprim.^{54,55} Iclaprim is also active against trimethoprim-resistant staphylococci and pneumococci.⁵⁵ Iclaprim is active against the respiratory pathogens *H. influenzae* and *Moraxella catarrhalis*. Unlike trimethoprim, it exhibits activity against the intracellular pathogen *C. pneumoniae*.⁵⁶ In addition, this drug is active against the atypical pathogen *Legionella pneumophila*.⁵⁷ The activity of iclaprim against Enterobacteriaceae is generally comparable to trimethoprim.⁵⁸

- Data suggest iclaprim achieves the necessary respiratory concentrations to be efficacious for the treatment of pneumonia.
- Early preclinical data suggest iclaprim may have a role in the treatment of HAP due to gram-positive pathogens, and clinical trials are under way.
- May also have a role in the therapy of complicated skin and skin-structure infections (cSSSI).

An oral formulation is also under trial and this makes iclaprim an attractive option for an IV to PO switch.

NEWER CEPHALOSPORINS

Cefditoren

Cefditoren is a newer third-generation cephalosporin that is available for oral administration. It was approved by the USFDA in 2001, and is currently indicated for use in patients with various types of respiratory tract infections (CAP, acute bacterial exacerbation of chronic bronchitis, and pharyngitis/tonsillitis) and uncomplicated SSSI. Cefditoren appears more active *in vitro* than other third-generation oral cephalosporins against penicillin-non-susceptible *S. pneumoniae*.^{59, 60}

Ceftobiprole

Ceftobiprole is an investigational “fifth”-generation cephalosporin with a broad spectrum of activity encompassing both gram-positive and gram-negative organisms. Like other β -lactam antibiotics, ceftobiprole prevents cell wall formation by binding to and inhibiting penicillin binding protein (PBPs). Due to specific changes brought about by structural engineering its structure ceftobiprole has bactericidal activity against methicillin-sensitive and -resistant *S. aureus*.⁶¹ Ceftobiprole is also active *in vitro* against VISA and VRSA.⁶² The strong binding affinity of ceftobiprole to PBP-2x provides enhanced activity against penicillin sensitive and -resistant *S. pneumoniae* and other streptococci.⁶³

Ceftobiprole generally exhibits potent activity against Enterobacteriaceae with the exception of *Proteus vulgaris*.⁶¹ The anti-pseudomonal activity of ceftobiprole is similar to cefepime. Like other cephalosporins, ceftobiprole is inactive against ESBL-producing isolates.⁶⁴ Ceftobiprole also lacks activity against many nonfermentative gram-negative bacilli, including *Acinetobacter* spp., *Burkholderia cepacia*, and *Stenotrophomonas maltophilia*.⁶⁵

This drug has recently completed phase III trials for treatment of cSSSIs, CAP and HAP (including VAP).

Ceftobiprole was generally safe and well tolerated in clinical studies. Frequently reported adverse effects included taste disturbances, nausea, and vomiting. Ceftobiprole is predominantly excreted unchanged in the urine, has an elimination $t_{1/2}$ of 3 to 4 hours, and requires dosage adjustment for renal impairment.⁶⁶

Ceftaroline

Ceftaroline is another broad-spectrum cephalosporin with activity against MRSA. Like ceftobiprole, ceftaroline inhibits bacterial cell wall synthesis and has enhanced binding affinity for PBP-2a resulting in anti-MRSA activity. Ceftaroline possesses potent bactericidal activity against many staphylococci, including both MSSA and MRSA.^{67,68} In addition, ceftaroline retains activity against VISA. It is active against *S. pneumoniae*, including penicillin-intermediate and -resistant strains.⁶⁷

Ceftaroline is active against many common gram negative respiratory pathogens, including *H. influenzae*, *E. coli*, *Salmonella spp.*, *Citrobacter freundii*, *Morganella morganii*, *Proteus mirabilis*, and *Klebsiella pneumoniae*.^{67, 68} Importantly, ceftaroline does not possess activity against *P. aeruginosa* and exhibits reduced activity against *E. cloacae*, *P. vulgaris*, and *Providencia spp* compared with ceftobiprole.⁶⁷

Phase III studies for the treatment of community-acquired pneumonia and cSSSIs are currently under way. It may have a role as monotherapy in serious CAP or HAP infections where MRSA is a potential etiologic organism.

The major route of elimination is renal excretion. In patients with mild renal impairment, no dose adjustment is necessary.

12 Steps to Prevent Antimicrobial Resistance in Hospitalized Patients

Prolonging the usefulness of new and older antibiotics should be a prime goal of every health care provider. Many antibiotic resistance problems originate in hospitals and other health care facilities. The CDC offers the following 12 steps as a means of preventing the development of resistance in hospitalized patients. Most of these points have application in office practice, as well.

PREVENT INFECTION

Step 1: Vaccinate

- Give influenza and pneumococcal vaccines to at-risk patients before discharge
- Get your own influenza vaccine every year.

Step 2: Get the Catheters Out

- Use catheters only when essential
- Use the correct catheter
- Use proper insertion and catheter-care protocols
- Remove catheters when they are no longer essential.

DIAGNOSE AND TREAT INFECTION EFFECTIVELY

Step 3: Target the Pathogen

- *Culture the patient.*
- Target empiric therapy to likely pathogens and local antibiogram.
- Target definitive therapy to known pathogens and antimicrobial susceptibility test results.

Step 4: Access the Experts

- Consult infectious diseases experts for patients with serious infections.

USE ANTIMICROBIALS WISELY

Step 5: Practice Antimicrobial Control

- Engage in local antimicrobial control efforts.

Step 6: Use Local Data

- Know your antibiogram
- Know your patient population.

Step 7: Treat Infection, not Contamination

- Use proper antisepsis for blood and other cultures
- Culture the blood, not the skin or catheter hub
- Use proper methods to obtain and process all cultures.

Step 8: Treat Infection, Not Colonization

- Treat pneumonia, not the tracheal aspirate
- Treat bacteremia, not the catheter tip or hub
- Treat urinary tract infection, not the indwelling catheter.

Step 9: Know When to say No

- Treat infection, not contaminants or colonization
- Fever in a patient with an intravenous catheter is not a routine indication for vancomycin.

Step 10: Stop Antimicrobial Treatment

- When infection is cured
- When cultures are negative and infection is unlikely
- When infection is not diagnosed.

PREVENT TRANSMISSION

Step 11: Isolate the Pathogen

- Use standard infection control precautions
- Contain infectious body fluids (follow air-borne, droplet, and contact precautions)
- When in doubt, consult infection-control experts.

Step 12: Break the Chain of Contagion

- Stay home when you are sick
- Keep your hands clean
- Set an example.

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Newer Antiviral Agents

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INTRODUCTION

Chemotherapy using antiviral agents has a long history, but it has been only recently that a large number of effective antiviral agents have been available. Many early antiviral agents were associated with serious side effects. This is because viral infection of a cell is dependent upon intimate relationship between virus and host cell replication machinery, so that using antiviral agents to target particular viral replication functions also causes changes in normal cellular functions, which the virus has used for its own growth. With further progress in virology, molecular biology and clinical nature of viral infections a more targeted approach can be developed.

Advances in antiviral drug development and in rapid diagnostic methods like shell vial cultures, polymerase chain reactions, antigen detection assays have lead to effective management strategies, particularly for infections due to herpes simplex virus, varicella zoster virus, cytomegalovirus, Influenzae A and B and chronic hepatitis B and C. Moreover, rapid diagnostic tests permitted the introduction of a new preventive strategy termed as preemptive treatment which consists of initiating antiviral treatment only after documenting viral infection to prevent disease due to that virus.

Human Herpes Virus Group

Human herpes viruses are among the most frequent causes of viral disease. Following primary infection, the virus remains latent and reactivates intermittently especially during periods of profound immunosuppression. Treatment strategies have been established for infections due to herpes simplex virus^{1,2} cytomegalovirus and varicella-zoster virus.

Acyclovir

One of the most commonly used antiviral drugs, it is primarily used for the treatment of herpes simplex virus infections, as well as in the treatment of varicella-zoster (chickenpox) and herpes zoster (shingles). It is a synthetic analog of 2-deoxyguanosine and must be activated to its active form by phosphorylation, which takes place intracellularly. It is commonly marketed as tablets (200 mg, 400 mg, 800 mg and 1 gram), topical cream (5%), intravenous injection (25 mg/ml) and ophthalmic ointment (3%).

Valaciclovir and Famciclovir

Both Valaciclovir and Famciclovir are oral drugs.

Valaciclovir is the L-valyl ester of acyclovir, and is rapidly converted to acyclovir after oral administration.¹ The bioavailability of valaciclovir is 3 to 5 times greater than that of oral acyclovir.^{1,2} Famciclovir has a bioavailability of 77 percent, and is an oral prodrug of penciclovir, which has a similar antiviral spectrum to acyclovir.³⁻⁵ Penciclovir is a nucleoside deoxyguanosine analog that inhibits the DNA synthesis of herpes viruses. Because it is very poorly absorbed orally, famciclovir was developed to orally treat herpes virus infections. Penciclovir enters all the cells of the body, both virus-infected and uninfected cells. In the virus-infected cells only, penciclovir is phosphorylated to its active form first by the viral thymidine kinase, which adds the first phosphate and then by a cellular enzyme, which completes the activation. In this way, penciclovir in its active triphosphate state is confined to the virus-infected cells. Once formed, penciclovir triphosphate has a very long intracellular half-life when compared with acyclovir triphosphate. Penciclovir triphosphate is now free to insert in the viral DNA as it is being formed in place of

the nucleotide guanine and terminate the sequence, thus inhibiting replication of the virus. It is not recommended for children under 18 years of age, pregnant or nursing mothers, and its effects have not been studied in immunocompromised patients (although intravenous penciclovir produced no harmful effects). Side effects of intravenous penciclovir (seen in comparable rates in placebo) may be headache, abdominal pain, increased serum lipase, nausea, dyspepsia, dizziness, and hyperbilirubinemia.⁶

The advantage of valaciclovir and famciclovir over acyclovir is their high oral bioavailability, which permits less frequent dosing when treating HSV or VZV disease.^{7,8} These drugs were shown to be well-tolerated and safe in large populations of patients.⁹

Ganciclovir

Ganciclovir has antiviral activity against all members of the human herpes virus group, but is considerably more potent than acyclovir or penciclovir against CMV.¹⁰ Ganciclovir requires intracellular phosphorylation for activation. Conversion to ganciclovir monophosphate is catalyzed by an UL97-encoded phosphotransferase of CMV. Ganciclovir-triphosphate blocks CMV replication by inhibiting the viral DNA polymerase and by being incorporated into the DNA chain, thereby reducing the rate of DNA chain elongation.¹⁰ Ganciclovir is hematotoxic, and thus requires dose reduction or discontinuation of treatment in up to one-third of immunodeficient patients.¹⁰ The oral bioavailability of <10 percent makes intravenous administration of ganciclovir necessary for most indications.¹⁰ An alternative approach is the use of an intraocular sustained-release ganciclovir implant combined with oral ganciclovir, which delays progression of retinitis and reduces the incidence of new CMV disease by about 40 percent over 1 year compared to the implant alone.¹¹

Valganciclovir

Valganciclovir is a monoethyl ester prodrug that, when administered orally, is rapidly hydrolyzed to the active compound ganciclovir. The absolute bioavailability of ganciclovir from valganciclovir is 60 percent.¹² The serum levels of ganciclovir achieved with valganciclovir use are four-fold higher than those with oral ganciclovir because of valganciclovir's superior oral bioavailability. Because the hematologic side effects of ganciclovir are in part dose-dependent and the drug is renally excreted, doses of valganciclovir and both forms of ganciclovir must be reduced in patients with renal dysfunction. Valganciclovir was approved by the US Food and Drug Administration (FDA) for a single indication: treatment of CMV retinitis in patients with acquired immunodeficiency syndrome. Although retinitis is the official indication, the drug is used to treat CMV infections at all sites.¹³

Cidofovir

Cidofovir is a nucleotide analog (nucleoside phosphonate) and is therefore independent from virus-encoded enzymes for activation.²⁹ Cellular enzymes mediate phosphorylation of cidofovir to its active metabolite that selectively inhibits viral DNA polymerase. The long half-life of the active metabolite permits infrequent administration of cidofovir, which needs to be given intravenously because of poor oral bioavailability (<5%).¹⁴ Cidofovir shows potent *in vitro* and *in vivo* activity against CMV and other herpes viruses, and against adenovirus and papilloma virus. The substantial nephrotoxic potential of cidofovir can be lowered by concomitant hydration and administration of probenecid.

Maribavir

1263W94 [maribavir; 5,6-dichloro-2-(isopropylamino)-1, beta-L-ribofuranosyl-1-H-benzimidazole], a novel benzimidazole compound, had been demonstrated to potently and selectively inhibit human cytomegalovirus replication *in vitro* and to have favorable safety profiles in animal species. The mechanism by which maribavir inhibits HCMV replication is by inhibition of an HCMV encoded protein kinase enzyme called UL97 or pUL97.

Maribavir showed promise in Phase II clinical trials and was granted fast track status, but failed to meet study goals in a Phase III trial.¹⁵

Bay 38-4766

The nonnucleosidic BAY 38-4766 was identified as a highly selective inhibitor of human cytomegalovirus (HCMV). The compound selectively inhibits not only HCMV strains, including ganciclovir-resistant, ganciclovir/foscarnet and ganciclovir/cidofovir double-resistant clinical isolates, but also a number of monkey and rodent cytomegaloviruses. In a murine cytomegalovirus (MCMV) pathogenicity model in mice, antiviral efficacy and excellent tolerability were demonstrated. BAY 38-4766-resistant HCMV and MCMV strains are not cross-resistant to the nucleoside analogs ganciclovir and cidofovir or the pyrophosphate analog foscarnet, indicating a different mode of action. Mechanistic studies demonstrated that the high selectivity of this drug class is most likely due to the inhibition of a late stage of the viral replication cycle. Sequence analyses of resistant HCMV and MCMV strains revealed mutations in UL89 and UL104, proteins known to be involved in viral DNA cleavage and packaging. Consequently, the drug is highly specific for the viral as opposed to cellular functions, since UL89 is related to a bacteriophage terminase and no human equivalent exists. In addition, because some of the genes of the viral DNA cleavage and packaging complex are highly conserved among herpes viruses, development of broad-spectrum agents covering

additional human herpes viruses might be possible using this approach.¹⁶

Hepatitis B and C Viruses

Interferon-alpha IFN- α is a lymphokine produced by B-lymphocytes and monocytes, and has antiviral activities that result in decreased viral load and immunomodulatory effects, which assist eradication of virus.¹⁷ IFN- α can be administered subcutaneously or intramuscularly. After initial doses, fever, chills, myalgias, fatigue, nausea, and vomiting may occur, but these symptoms typically improve with subsequent injections and are dose-related.¹⁷ Transient bone marrow suppression may be observed during the first weeks of therapy, and requires close monitoring of blood counts.

Lamivudine

Lamivudine is an oral nucleoside analog, which requires intracellular phosphorylation for activation. The active triphosphate derivative blocks virus replication by terminating the nascent proviral DNA chain, and by interfering with the reverse-transcriptase activity of hepatitis B virus and HIV. The oral bioavailability of 80 percent and the long intracellular half-life permit once daily dosing for therapy of chronic hepatitis B.¹⁸ The incidence of adverse events in patients treated for chronic hepatitis B is similar between lamivudine and placebo.¹⁹

Ribavirin

Ribavirin has antiviral properties against a broad-spectrum of DNA and RNA viruses, and requires activation by intracellular phosphorylation. Ribavirin monophosphate interferes with the synthesis of guanosine triphosphate and thus nucleic acid synthesis, and ribavirin triphosphate inhibits the capping of viral messenger RNA and specifically influenza transcriptase activity. The drug is used in aerosolized form for treatment of respiratory syncytial virus infection in children and immunocompromised hosts, and an oral formulation has beneficial effects in the therapy of chronic hepatitis C.²⁰ Oral ribavirin is generally well-tolerated, and infrequent side effects include hemolysis, anxiety, irritability, fatigue, chronic upper respiratory symptoms, and pruritus.

Chronic Hepatitis B

Until recently, IFN- α was the only approved therapy of chronic hepatitis B. Predictors for a good response to IFN- α treatment are aminotransferase levels >100 IU/ml, the presence of HBV DNA in serum but at a level <200 pg/ml, detectable serum hepatitis B e antigen (HBeAg), a liver biopsy with moderate to severe inflammatory activity, and compensated liver disease.²⁰ With a standard 4-month course of IFN- α , one-third of patients have a virologic

response as compared to 12 percent of untreated controls, and only 5 to 10 percent of those with a seroconversion have reactivation of infection within the next 10 years.²⁰

Oral lamivudine may be used as alternative to IFN- α for therapy of chronic hepatitis B. In a randomized trial, a 1 year-treatment with oral lamivudine at a dose of 100 mg once daily was superior to placebo with regard to seroconversion (16 vs 4%; defined as loss of HBeAg, development of antibody to HBeAg, and undetectable HBV DNA), of sustained normalization of alanine aminotransferase levels (72% vs 24%), and of patients with improved hepatic necroinflammatory activity/ (56% vs 25%).¹⁸ The optimal duration of lamivudine therapy and the effects of combined lamivudine plus IFN- α for treatment of chronic hepatitis B require further study. Moreover, the clinical importance of HBV mutants that emerge during lamivudine therapy needs to be determined.¹⁸

Other Drugs

Adefovir

Adefovir is an acyclic analog of deoxyadenosine monophosphate (dAMP), which has just been approved by the Food and Drug Administration (FDA) for use in chronic hepatitis B. Adefovir has been shown to inhibit the amplification of cccDNA although the *de novo* formation of cccDNA cannot be prevented in duck HBV-infected hepatocytes. In Phase I/II studies, treatment with adefovir results in significant reduction of HBV DNA within 1 to 2 weeks. In a Phase III placebo-controlled trial, adefovir 10 mg daily given for 48 weeks in 171 patients was associated with significantly better histological improvement, a higher rate of HBeAg seroconversion, a three logarithmic reduction of HBV DNA levels and a higher chance of normalization of ALT levels when compared with 167 patients receiving placebo.²¹ Importantly, adefovir is also active against lamivudine-resistant YMDD mutants. Severe renal toxicity has been observed in patients receiving higher doses (60–120 mg daily) of adefovir in trials for patients infected with human immunodeficiency virus (HIV). The renal toxicity is mediated through the human renal organic anion transporter 1 (hOAT1) and may result in proximal renal tubular dysfunction. To date, no clinical renal toxicity has been observed with the 10 mg daily dose.

Tenofovir Disoproxil Fumarate

Tenofovir disoproxil fumarate another acyclic nucleoside analog similar to adefovir, has been approved for the treatment of HIV. *In vitro* studies show that this drug is also effective in suppressing replication of lamivudine-resistant HBV.²² In HIV patients coinfecting with lamivudine-resistant HBV, it causes HBV DNA reduction by 4.5 log. However, to date, no studies have been reported in patients with HBV infection alone.

Entecavir

Entecavir is a carbocyclic deoxyguanosine analog. It is highly effective in inhibiting the priming of the HBV polymerase by guanosine triphosphate during the initiation of HBV replication. Entecavir has been shown to reduce the viral antigens and DNA levels in liver samples of HBV infected woodchucks. The Food and Drug Administration (FDA) has announced the approval of entecavir (Baraclude) tablets and oral solution for the treatment of chronic hepatitis B in adults.

The major adverse events associated with the use of entecavir include severe, acute exacerbation of hepatitis B after discontinuation of entecavir; headache, abdominal pain, diarrhea, fatigue, and dizziness. Entecavir is also effective against lamivudine-resistant HBV although a higher dose of 1 mg daily may be required.

*β -L-2'-Deoxythymidine (Telbivudine)*²³

β -L-2'-Deoxythymidine is one of three L-nucleosides that specifically inhibit HBV replication. The other two members are β -L-2'-deoxycytidine and β -L-2'-deoxyadenosine. The anti-HBV activities are conferred by the common hydroxyl group in the 3'-position of the β -L-2'-deoxyribose sugar of the molecules. Eight logarithmic reduction of viral DNA levels has been demonstrated in the woodchuck model with β -L-2'-deoxythymidine. In Phase I/II clinical trials, β -L-2'-deoxythymidine shows marked dose-proportional antiviral activities with 4 weeks of the 800 mg daily dose causing a 4 log reduction in median HBV DNA levels. No side effects have been observed. The lack of side effects may be related to the L-configuration of the molecule. Clinical trials have shown it to be significantly more effective than lamivudine or adefovir, and less likely to cause resistance.

Chronic Hepatitis C

Therapy of chronic hepatitis C is recommended for patients who have detectable HCV RNA in serum, elevated serum aminotransferase levels, and chronic hepatitis on liver biopsy. Factors predicting a favorable response to treatment with IFN- α include low HCV RNA serum levels, viral genotypes 2 or 3 (by contrast to genotype 1), the absence of cirrhosis, low hepatic iron stores, short duration of liver disease, and younger patient age.²⁴ However, IFN- α monotherapy for up to 48 weeks results in sustained virologic response (defined as undetectable HCV RNA levels in serum 24 weeks after the end of therapy) in <20 percent of patients. Several recent randomized studies comparing the combination of pegylated IFN- α and oral ribavirin to IFN- α alone for a treatment duration of 24 or 48 weeks showed higher rates of sustained virologic response (up to 70%) with the combination therapy, both for patients who received initial treatment and for those who relapsed after initial response to therapy.²⁵ Moreover, combination

therapy administered for 48 weeks was more effective than when given for only 24 weeks.²⁵ Peg interferon alpha-2a and Ribavirin are now being used for children with benefit. Other protease compounds (for hepatitis C) in development include TMC-435, vaniprevir, BI-201335, BMS-650032, and danoprevir. For more details see the Chapter on Hepatitis C.

Influenza Viruses

Influenza A and B viruses are responsible for seasonal epidemics that cause significant morbidity in the general population, and mortality in elderly and immunocompromised patients. Antiviral drug treatment of influenza can be done with amantadine and rimantadine. Both amantadine and rimantadine have an antiviral activity that is restricted to influenza A virus. These agents (M2 inhibitors) are amines that inhibit viral replication by targeting the M2 surface protein of the virus, thereby interfering with the uncoating process.²⁶ In Europe, only amantadine is licensed. Treatment with both drugs is associated with neurological and gastrointestinal side effects, and with the rapid emergence of virus resistance, which limits their usefulness.²⁶

Neuraminidase Inhibitors

The neuraminidase of influenza viruses plays an essential role in allowing virus release from the surface of infected cells by cleaving sialic acid residues of the cell membrane. The active site of the neuraminidase is highly conserved among both influenza A and B strains. Neuraminidase inhibitors have been developed that block the interaction of this enzyme with the sialic acid residues by fitting into the shallow pocket of the neuraminidase active site.

Zanamivir (GG167)

Zanamivir is a potent inhibitor of the neuraminidase of both influenza A and B viruses.²⁷ Because of its low oral bioavailability (about 2%), this drug is used topically. Among patients who were treated within 48 hours of onset of influenza-like disease and who had laboratory-confirmed influenza virus infection, inhaled zanamivir reduced the median time to alleviation of major influenza symptoms by 1 day compared to placebo.²⁷ In patients who began treatment within 30 hours of disease onset, median time to resolution of influenza symptoms was shortened by 3 days.²⁷ Similar results were obtained in another randomized comparison of inhaled zanamivir versus placebo. Of note, the proportion of patients with influenza-like symptoms who had laboratory-confirmed influenza in the two studies was 63 and 71 percent, respectively, and the majority of these infections were due to influenza A virus (56 and 67%, respectively). Topical zanamivir in both trials was well tolerated, including among patients with asthma.²⁷

Oseltamivir (GS4104)

Oseltamivir (Tamiflu) is the oral prodrug of compound GS 4071, which inhibits influenza A and B virus neuraminidase.²⁸ After oral administration, this prodrug is rapidly converted to GS4071, which has a half-life of approximately 8 hours that permits twice daily dosing.²⁸ When therapy was initiated within 36 hours of febrile respiratory illness, a 5-day course of oseltamivir resulted in shortening of disease duration in influenza virus-infected patients by 30 percent compared to placebo, and this effect was similar whether twice daily doses of 75 or 150 mg were used. If therapy was initiated within 24 hours of symptom onset, the duration of the illness was reduced by 40 percent. Recent data suggest that neuraminidase inhibitors may also have a role in the prevention of influenza among healthy adults and in the postexposure prophylaxis among household contact.²⁹ Moreover, issues under study with neuraminidase inhibitors are the determination of their therapeutic and prophylactic efficacy against influenza viruses in high-risk populations. The emergence of antiviral resistance to these agents, although rare, was described, and requires careful surveillance. Of concern, only about two-thirds of infections among patients with febrile respiratory disease during the influenza season are due to influenza viruses, which suggest that one-third of patients may be erroneously treated with neuraminidase inhibitors if rapid diagnosis cannot be made. Rapid and sensitive detection assays for influenza viruses that can be performed by primary care physicians or the patients themselves are needed for the judicious use of these new anti-influenza drugs. As of December 2010, the World Health Organization (WHO) reported 314 samples of the prevalent 2009 pandemic H1N1 flu tested worldwide have shown resistance to oseltamivir.

Laninamivir (CS-8958)

It is a neuraminidase inhibitor which is being researched for the treatment and prophylaxis of influenza virus A and influenza virus B. It is currently in phase III trials.

Advances in understanding the mechanisms involved in influenza virus replication have revealed a number of potential targets that might be exploited in the development of new agents. Among these agents are T-705 (Favipiravir), a polymerase inhibitor, and DAS181, an attachment inhibitor.

T-705 (favipiravir; 6-fluoro-3-hydroxy-2-pyrazinecarboxamide) has antiviral activity against seasonal influenza viruses and a mouse-adapted H5N1 influenza virus derived from a benign duck virus. However, its efficacy against highly pathogenic H5N1 viruses, which are substantially more virulent, remains unclear.

DAS181 is an investigational antiviral medication with preclinical activity and against parainfluenza and influenza viruses. The receptor for both parainfluenza and

influenza on airway epithelial cells is sialic acid. DAS181, a recombinant sialidase fusion protein, removes sialic acid residues from airway epithelium, thereby preventing both the initial step in PIV and IFV infection and the spread of existing infection. DAS181 is currently being studied in a Phase II clinical trial.

SUMMARY

A lot of newer antiviral agents are being developed to meet the demand especially to tackle the emergence of viral infections in immunosuppressed host and emerging resistance to older drugs. They have better bioavailability, lesser side effects and better tolerated. Further studies are required to document their efficacy in pediatric age group.

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Newer Antifungal Agents: A Promising Road Ahead

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The number of agents available to treat fungal infections has increased by 30 percent since the year 2000, yet still only 15 agents are currently approved for clinical use. The greater number of medications now available allows for therapeutic choices; however, differences in antifungal spectrum of activity, bioavailability, formulation, drug interactions, and side effects necessitates a detailed knowledge of each drug class.

POLYENES

Amphotericin B (AMB) and nystatin are the currently available polyenes, although differing safety profiles have limited nystatin to topical use.¹ The polyenes bind to ergosterol present within the fungal cell wall membrane. This process disrupts cell wall permeability by forming oligodendromes functioning as pores with the subsequent efflux of potassium and intracellular molecules causing fungal death.² There is also evidence that AMB acts as a proinflammatory agent and further serves to stimulate innate host immunity. This process involves the interaction of AMB with toll-like receptor 2 (TLR-2), the CD14 receptor, and by stimulating the release of cytokines, chemokines, and other immunologic mediators. It has been suggested that AMB may interact with host humoral immunity after the observation of synergistic activity of AMB and antibodies directed at heat shock protein 90 (hsp90), although further confirmatory data are needed.²

When AMB resistance occurs, it is generally attributed to reductions in ergosterol biosynthesis or the synthesis of alternative sterols with a reduced affinity for AMB. Resistance to AMB is common in *Aspergillus terreus*, *Scedosporium apiospermum*, *Scedosporium prolificans*, *Trichosporon* spp, and *Candida lusitanae* (Table 1). Resistance has been reported with several other species.³

The peak serum level to mean inhibitory concentration (MIC) ratio is the best pharmacologic predictor of

outcomes with polyene therapy. Drug levels are infrequently measured, nor are they necessary, and they are typically available only in the research setting.⁴

AMB is primarily used intravenously (IV) or through the inhalational route. In attempts to avoid the nephrotoxicity seen with amphotericin B deoxycholate (AmBd; Fungizone) several other formulations have been developed. The lipid preparations include: liposomal amphotericin B (L-AMB; Ambisome), amphotericin B lipid complex, (ABLC; Abelcet), and amphotericin B colloidal dispersion (ABCD; Amphotec, Amphocil). All currently available formulations are highly protein bound (>95%, primarily to albumin) and have long half-lives. AMB exhibits poor cerebrospinal fluid levels (<5% of concurrent serum concentration); however, this agent remains the treatment of choice for cryptococcal meningitis.⁵ Previous reports have described the use of intrathecal AMB in an attempt to circumvent the poor cerebrospinal fluid (CSF) penetration; however, this practice is seldom used because of the difficulty of administration, poor patient tolerability, and availability of alternative agents for use in the salvage setting of invasive mycoses. AMB also has low vitreous penetration (0–38%) and intraocular injections may be required to achieve appropriate levels during therapy of deep ophthalmologic fungal infections, including candidal endophthalmitis.^{6,7} The exact route of elimination of AMB is not known and despite the well-known nephrotoxicity, dosing need not be adjusted in patients who have a decreased glomerular filtration rate.

The broad antifungal spectrum and experience with the use of amphotericin B accounts for its continued use despite toxicity concerns. Liposomal amphotericin B remains the recommended antifungal during the treatment of neutropenic fever after an open-label, randomized international trial comparing L-AMB to voriconazole. Although fewer breakthrough infections (including those caused by *Aspergillus* spp.) occurred in patients receiving

Table 1: Antifungal spectrum of activity against common molds and yeast

Organism	AMB	FLU	ITR	POS	VOR	ANI	MFG	CAS	5FC
<i>Aspergillus fumigatus</i>	+	–	+	+	+	+	+	+	–
<i>A. flavus</i>	+/-	–	+	+	+	+	+	+	–
<i>A. terreus</i>	–	–	+	+	+	+	+	+	–
<i>A. niger</i>	+	–	+/-	+	+	+	+	+	–
<i>A. nidulans</i>	+	–	+/-	+	+	+	+	+	–
<i>Candida albicans</i>	+	+	+	+	+	+	+	+	+
<i>C. glabrata</i>	+	+/-	+/-	+	+	+	+	+	+
<i>C. krusei</i>	+	–	+/-	+	+	+	+	+	+/-
<i>C. tropicalis</i>	+	+	+	+	+	+	+	+	+
<i>C. parapsilosis</i>	+	+	+	+	+/-	+/-	+/-	+	+
<i>C. Guillier mondii</i>	+	+	+	+	–	–	–	+	+
<i>C. Lusitaniae</i>	–	+	+	+	+	+	+	+	+
<i>Cryptococcus</i> spp	+	+	+	+	–	–	–	+	+
<i>Blastomycosis</i>	+	+	+	+	+	+/-	+/-	+/-	–
<i>Histoplasmosis</i>	+/-	+	+	+	+/-	+/-	+/-	–	–
<i>Coccidioidomycosis</i>	+	+	+	+	–	–	–	–	–
<i>Fusarium</i> spp	+/-	–	–	+	+	–	–	–	–
<i>Phaeohyphomycosis</i> ^a	–	+	+	+	+	+	+	–	–
<i>Pichia</i> spp	+	+	+/-	+	+	+	+	+	+
<i>Saccharomyces</i> spp	+	+	+	+	+	+	+	+	+
<i>Scedosporium apiospermum</i>	+/-	+	+	–	–	–	–	–	–
<i>Scedosporium prolificans</i>	–	+/-	+/-	–	–	–	–	–	–
<i>Trichosporon</i> spp	+/-	+	+	+	–	–	–	+	+
<i>Zygomycetes</i>	+/-	–	–	+	–	–	–	–	–

(+) Implies antifungal activity against isolates, (–) implies no or limited activity against isolate, (+/-) implies variable activity against isolates.

Abbreviations: AMB: amphotericin; ANI: anidulafungin; CAS: caspofungin; FLU: fluconazole; ITR: itraconazole; MFG: micafungin; POS: posaconazole; VOR: voriconazole; 5FC: flucytosine.

^a Infection requires debridement in almost all circumstances.

voriconazole, predetermined non-inferiority criteria were not reached.⁸ Additionally, a recent meta-analysis suggested L-AMB may be associated with lower mortality than AmBd during the empiric treatment of neutropenic fever.⁹ AMB was previously the preferred first-line agent during the treatment of invasive aspergillosis; however, a greater therapeutic response and survival have been demonstrated when voriconazole is administered in this setting—relegating AMB to second-line or salvage therapy during the treatment of invasive aspergillosis.¹⁰

AMB does remain the agent of choice when the Zygomycetes are encountered. In fact, a delay in the prescribing of an AMB formulation in patients infected with one of the Zygomycetes resulted in a twofold greater risk for death.¹¹ Discriminating between invasive zygomycosis and aspergillosis is difficult, but the differences in the choice of antifungal agents and outcomes mandate an aggressive diagnostic strategy and prompt initiation of antifungal agents.

Before the development of alternative agents, AMB was the recommended first-line agent for invasive candidial infections.¹² AMB in combination with flucytosine remains the drug of choice in the treatment of cryptococcal meningitis and in most cases a lipid formulation is preferred because of the decreased incidence of nephrotoxicity.⁵ Severe infection caused by the endemic mycoses (i.e. histoplasmosis, coccidioidomycosis, blastomycosis, and sporotrichosis) should be treated with an AMB formulation histoplasmosis remains the only infection for which a lipid formulation of AMB (L-AMB) has demonstrated greater efficacy than the conventional form.¹³

In attempts to avoid the potential nephrotoxicity of systemic administration and to deliver higher local concentrations, different formulations of AMB have been given by way of the inhalational route. The deoxycholate used to solubilize AMB acts as a detergent and may affect alveolar surfactant. Lipid preparations are thus preferred for inhalation delivery, although no decline in pulmonary

lung function from AmBd has been documented. AmBd is often difficult to effectively administer in an aerosol form because of foaming caused by the solubilizing agent.^{11,14-16} Aerosol delivery has been found effective in the prevention of pulmonary fungal infections in lung transplantation and in bone marrow transplant recipients, although data supporting its efficacy in other settings are limited.

Inhaled L-AMB has been found protective against development of invasive aspergillosis when given twice weekly to neutropenic patients who have cancer.¹⁶ Inhalation delivery is also an attractive option in the treatment of lung transplant patients and a recent retrospective series reported nebulized ABLC provided effective prophylaxis against invasive aspergillosis in 98.3 percent of all patients.¹⁴

The recommended dose of IV AmBd is between 0.7 and 1 mg/kg and only recently have clinical data emerged evaluating higher doses of lipid formulations of AMB to potentially improve efficacy. The AmBi Load trial evaluated the efficacy of higher initial doses of L-AmB (3 mg/kg versus 10 mg/kg) in the treatment of invasive aspergillosis. Treatment success rates were similar in both treatment arms although there was a greater incidence of nephrotoxicity in those receiving the higher dose of L-AmB.¹⁷

AmBd infusion is associated with infusion related reactions, such as fever, chills, rigors, myalgias, bronchospasm, nausea and vomiting, tachycardia, tachypnea, and hypertension.¹² These events are less likely to occur when one of the lipid formulations is used; however, ABCD has been associated with the development of dyspnea and hypoxia and L-AMB has been associated with back pain during infusion.⁶ Amphotericin B has been associated with acute kidney injury and nephrotoxicity in many studies and is a well known potential complication of therapy occurring in up to 30 percent of patients. This toxicity is believed secondary to vascular smooth muscle dysfunction with resultant vasoconstriction and ischemia.¹⁸ For this reason most advocate ensuring adequate volume status before administration. Lipid preparations of AMB have a lower incidence of renal toxicity, and studies have shown that when AmBd is replaced by a lipid formulation after the development of creatinine elevation, renal function stabilizes or improves in a significant proportion of patients.¹⁹ The avoidance of AmBd and use of a lipid formulation has been met with skepticism by some because of the vast price difference in compounds. The reduction in hospital days when toxicity is avoided, however, has proven the lipid formulations more cost effective than AmBd.¹⁹

TRIAZOLES

The triazoles also exert their effects within the fungal cell membrane. The inhibition of cytochrome P450 (CYP)-dependent 14- α -demethylase prevents the conversion of lanosterol to ergosterol. This mechanism results in the

accumulation of toxic methylsterols and resultant inhibition of fungal cell growth and replication (Fig. 1). This class of agents has demonstrated species- and strain-dependent fungistatic or fungicidal activity in vitro and the area under the curve (AUC) to MIC ratio is the primary predictor of drug efficacy. The indirect immunomodulatory effects are poorly understood because of the complex interaction of triazoles and phagocytic cells. Evidence suggests that ergosterol depletion increases fungal cell vulnerability to phagocytic oxidative damage²⁰ and voriconazole has been shown to induce the expression of TLR2, nuclear factor- κ B, and tumor necrosis factor- α .² Azoles differ in their affinity for the 14- α -demethylase enzyme and this difference is largely responsible for their varying antifungal potency and spectrum of activity. Cross-inhibition of several human CYP-dependent enzymes (3A4, 2C9, and 2C19) is responsible for most of the clinical side effects and drug interaction profiles that have been described with this class. Itraconazole and posaconazole act primarily as inhibitors of 3A4 and 2C9 with little effect on 2C19. Voriconazole acts as both an inhibitor and a substrate on all three isoenzymes providing ample opportunity for drug-drug interactions because of this frequently shared metabolic pathway. Comprehensive lists of triazole drug interactions can be found elsewhere. Briefly, caution should be used when these agents are concurrently administered with: most HMG-CoA reductase inhibitors, benzodiazepines, phenytoin, carbamazepine, cyclosporine, tacrolimus, sirolimus, methylprednisolone, buspirone, alfentanil, the dihydropyridine calcium channel blockers verapamil and diltiazem, the sulfonylureas, rifampin, rifabutin, vincristine, busulphan, docetaxel, trimetrexate, and the protease inhibitors ritonavir, indinavir, and saquinavir.²¹⁻²⁷

The triazoles have also been associated with QTc prolongation²⁸ and co-administration with other agents known to have similar effects (cisapride, terfenadine, astemizole, mizolastine, dofetilide, quinidine, and pimozide, amongst others) should be avoided.²⁹⁻³¹ The triazoles are additionally embryotoxic and teratogenic and are secreted into breast milk, and thus administration should be avoided during pregnancy or while lactating.^{28,32,33}

FLUCONAZOLE

Fluconazole remains one of the most frequently prescribed triazoles because of its excellent bioavailability, tolerability, and side effect profile. More than 80 percent of ingested drug is found in the circulation, and 60 percent to 70 percent is excreted unchanged in the urine. Oral absorption remains unchanged in patients receiving acid suppressive therapy (proton pump inhibitors, H₂-blockers). Only 10 percent of fluconazole is protein bound.³⁴ Fluconazole also exhibits excellent tissue penetration. CSF levels are 70 percent of matched serum levels, and levels reported in saliva, sputum, and other sites are well

within therapeutic ranges. The half-life is 27 to 34 hours in the presence of normal renal function allowing once-daily dosing. In patients who have a reduced creatinine clearance the normal dose should be reduced by 50 percent. Fluconazole serum levels are rarely necessary. Currently 50-, 100-, 150-, and 200-mg tablets are available and IV formulations exist in 200- or 400-mg doses.

Fluconazole is active against most *Candida* spp. with the exception of *C. krusei* and *C. glabrata* isolates. If a *C. glabrata* isolate is found susceptible to fluconazole higher doses (12 mg/kg/d) should be used.^{7,35} There is no appreciable activity against *Aspergillus*, *Fusarium*, *Pseudoallescheria*, or the *Zygomycetes*.

Although fluconazole has substantially fewer drug-drug interactions than other triazole compounds, caution remains necessary because of increases in the serum levels of phenytoin, glipizide, glyburide, warfarin, rifabutin, and cyclosporine.

Fluconazole levels are reduced in the presence of rifampin. Fluconazole is well tolerated by most patients, even if chronic therapy is necessary.³⁶ Headache, alopecia, and anorexia are the side effects most common (10%) with transaminase elevation in less than 10 percent.

Fluconazole remains the drug of choice in the treatment of oropharyngeal candidiasis (OPC) (6 mg/kg/d for 7-14 days).⁷ Newer data suggest a one-time dosing for the treatment of OPC with equivalent relapse rates to standard therapy.³⁷ Patients who have frequent relapse should remain on chronic suppressive fluconazole until immune reconstitution has been documented. Fluconazole has also been used for prophylaxis in those at high-risk for invasive fungal infections.

Initiation of 6 mg/kg/d of fluconazole for the first 75 days after bone marrow transplantation has been found effective in reducing cases of candidemia.³⁸ Preemptive therapy within ICUs remains controversial. The high incidence of invasive candidiasis within this setting (1-2% of all patients) makes prophylaxis an attractive option; however, the largest randomized, multicenter, blinded clinical trial comparing empiric fluconazole therapy in ICU patients with several risk factors for invasive candidiasis to placebo showed no clear benefit to fluconazole therapy.³⁹

Although recent data has accrued regarding the use of high-dose fluconazole monotherapy during the induction course of cryptococcal meningitis, this practice should be used only in resource limited settings and not when AMB is available.⁴⁰

Fluconazole is also useful for infections caused by *Coccidioides immitis*. In cases of meningitis or disseminated infection high-dose fluconazole is often necessary.⁴¹

ITRACONAZOLE

Itraconazole is currently available as capsules and as an oral solution suspended in hydroxypropyl cyclodextrin

(HPCD). Unfortunately, the IV preparation of itraconazole is no longer commercially available. Itraconazole capsules depend on an acidic environment for maximal absorption, and the concomitant administration of H_2 -receptor antagonists, proton pump inhibitors, or antacids causes erratic and unpredictable drug absorption; it is thus recommended that itraconazole capsules be taken with food or a cola beverage.^{42,43} Itraconazole solution allows for greater oral bioavailability and the AUC and peak concentrations are both increased by 30 percent when itraconazole solution is taken in the fasting state.^{44,45} The cyclodextrin carrier has minimal absorption and no systemic side effects have been attributed to its use in the oral formulation.⁴⁶

With once-daily dosing, steady state is reached in 7 to 14 days, although oral loading allows for more rapid attainment of therapeutic serum levels.⁴⁷ Itraconazole is also highly protein bound with less than 1 percent available as free drug and has a relatively high volume of distribution.

Itraconazole is extensively metabolized by the liver and its major metabolite, hydroxy-itraconazole, does possess antifungal activity similar to that of the parent drug. Despite similar antifungal efficacy, hydroxyl-itraconazole is not measured during serum drug level determination by high performance liquid chromatography, although the active metabolite is detected by bioassay.⁴⁸

The development of newer and more effective antifungal agents (i.e. voriconazole) has relegated itraconazole to second-line therapy during the treatment of invasive aspergillosis. Itraconazole does, however, remain the drug of choice for those who have mild to moderate infection caused by histoplasmosis and is the mainstay of secondary prophylaxis in patients who have HIV with a history of histoplasmosis before immune reconstitution with antiretrovirals.⁴⁹ Itraconazole is also approved for allergic bronchopulmonary aspergillosis.¹⁰

The recommended dosage of oral itraconazole in adults is 400 mg/d (capsules) and 2.5 mg/kg twice daily (HPCD solution).¹⁰ Steady-state levels can be more rapidly attained, however, when administered as 200 mg three times daily for 3 days and then 200 mg twice daily for the duration of therapy. Considerable concern remains regarding adequate oral absorption and oral itraconazole is not recommended in seriously ill patients or patients who have life-threatening disease. Dose adjustment is not indicated when the oral formulation of itraconazole is used in patients who have renal insufficiency or those receiving hemodialysis/continuous ambulatory peritoneal dialysis. The half-life of itraconazole is prolonged in patients who have hepatic dysfunction and drug dose adjustment, liver function testing, and drug interactions need to be carefully assessed.⁵⁰ Itraconazole is usually well tolerated and although adverse reactions have been observed in up to 39 percent of patients no fatalities and only rare toxicity

requiring discontinuation of therapy were reported. The most frequent side effects include: nausea and vomiting (<10%), hypertriglyceridemia (9%), hypokalemia (6%), liver enzyme elevations (5%), skin rashes/pruritus (2%), headache and dizziness (<2%), and pedal edema (1%).⁵¹ Gastrointestinal intolerance (46%) is exceedingly common with the oral HPCD solution at doses greater than 400 mg/d with vomiting the most frequent complaint.⁵²

The myocardial depressant effects of itraconazole are also well known and cases of congestive heart failure have been reported.⁵³

POSACONAZOLE

Posaconazole is a lipophilic second-generation antifungal triazole with a similar molecular structure to that of itraconazole. The spectrum of activity of posaconazole includes agents of the *Zygomycetes*, and it has improved activity against *Aspergillus* spp compared with itraconazole.⁵⁴

Posaconazole is insoluble in water and no IV formulation has yet been developed. It is thus administered as a cherry-flavored suspension using polysorbate 80 as the emulsifying agent.⁵⁵ Optimal dosing of posaconazole is obtained when given as two to four divided doses administered with food or a liquid nutritional supplement.^{56,57} Although initial studies suggested that changes in gastric acidity do not affect posaconazole absorption subsequent work has shown H₂-receptor antagonists and proton pump inhibitors may decrease posaconazole serum levels and if possible coadministration should be avoided.^{32,55,58,59}

Posaconazole has demonstrated dose-dependent pharmacokinetics with saturable absorption greater than 800 mg/d; thus oral loading is not possible and steady state is typically achieved after 7 to 10 days of therapy.⁶⁰ This prolonged time required to reach steady-state levels may affect the use of posaconazole as primary therapy for invasive fungal infections. This agent also has a large volume of distribution despite its high protein binding and a half-life of approximately 24 hours. Peak serum concentrations have shown considerable interpatient variability for reasons that remain unclear. Some have proposed genetic polymorphisms within P-glycoprotein to play a role because posaconazole is both a substrate and inhibitor, but this remains unproven.⁶¹ Glucuronidation plays a minor role in posaconazole metabolism and single nucleotide polymorphisms within UGT (uridine diphosphate glucuronyl transferase) have also been proposed to account for these differences but confirmatory studies are lacking.⁶² This unpredictable variation in serum posaconazole levels has heightened interest and the necessity of therapeutic drug monitoring (TDM).

Posaconazole is hepatically metabolized and undergoes minimal glucuronidation. Renal clearance plays a minor role in the clearance of posaconazole, which is

predominantly eliminated fecally. Oral posaconazole has proved effective in the prevention of proven or probable invasive aspergillosis in neutropenic patients who have acute myelogenous leukemia and in hematopoietic stem cell transplant recipients who have graft versus host disease.^{63,64} The efficacy and safety of posaconazole in the treatment of invasive fungal infections has also been assessed, and although this study predates the development of echinocandins and voriconazole the statistically significant success rate of posaconazole compared with other agents allows for its use during salvage therapy.⁶⁵ Currently, 200 mg three times daily is recommended for prophylaxis, and 800 mg divided in two or four doses is recommended in the salvage setting. For patients not tolerating food, a liquid nutritional supplement has been recommended to increase absorption.⁶¹ Pediatric dosing schedules have yet to be established.¹⁰ Dose adjustment by age, sex, race, and hepatic or renal insufficiency is not necessary given the minimal glucuronidation and renal clearance of posaconazole.⁶⁶

Posaconazole is usually well tolerated and infrequently requires discontinuation because of adverse events. The most frequent side effects of posaconazole therapy are gastrointestinal (14%), with transaminase elevation and hyperbilirubinemia occurring in 3 percent.⁶⁴ In one trial, however, more serious adverse events were reported in patients treated with posaconazole than with fluconazole. Three cardiac events were reported among those possibly related to posaconazole treatment, including decreased ejection fraction, QTc prolongation, and torsades de pointes.⁶³ For most patients posaconazole is well tolerated and even long-term therapy (>6 months) is frequently without toxicity.⁶⁷ Posaconazole is not significantly metabolized through the cytochrome P450 system and serum levels are unlikely to be increased by concomitant administration of P450 inhibitors.

VORICONAZOLE

Voriconazole is a low molecular weight water soluble second-generation triazole with a chemical structure similar to fluconazole. Voriconazole exhibits a broad spectrum of activity against molds with the exception of the *Zygomycetes*.⁶⁸ Voriconazole is available in oral and IV formulations. Similar to itraconazole, the IV form depends on sulfobutyl ether β -cyclodextrin for solubility.⁶⁸ When 3 to 6 mg/kg of daily voriconazole is administered, steady-state levels are reached in 5 to 6 days. If IV loading is given, however, steady state can be reached within 1 day.⁶⁹ The oral formulation obtains steady-state levels within 24 hours if appropriate loading is administered; however, fatty foods have been found to reduce bioavailability by 80 percent.⁷⁰ Although voriconazole in children has demonstrated linear pharmacokinetics, in adults nonlinear metabolism is observed, likely secondary

to saturable metabolic enzymes required for drug clearance.⁶⁹ Interpatient serum concentration differences have been attributed to polymorphisms within CYP2C19, the major metabolic pathway for voriconazole.⁶⁸ Up to 20 percent of non-Indian Asians have low CYP2C19 activity and voriconazole serum levels are thus up to four times higher than those found in white or black populations in which the “poor metabolizer” status is uncommon.⁷¹ The unpredictability of patient enzymatic activity has generated an increased interest in the routine use of voriconazole serum level determination. For IV administration 6 mg/kg twice daily on day one, followed by 4 mg/kg IV twice daily for the duration of therapy is recommended. The oral dosages in adults are also weight based. For those weighing greater than 40 kg, 400 mg twice daily on day one, followed by 200 mg twice daily until completion of therapy is suggested, whereas those weighing less than 40 kg should receive 200 mg twice daily for one day followed by 100 mg twice daily.⁶⁸ Pediatric patients are known to hypermetabolize voriconazole and for this reason an IV dose of 7 mg/kg twice daily and oral dosing of 200 mg twice daily without loading is recommended.³³ In patients who have liver dysfunction standard loading doses should be given, but the maintenance dose is reduced by 50 percent. The safety of voriconazole use in severe liver disease remains uncertain. No dosage adjustment is required if oral drug is given to patients who have renal insufficiency.

The presence of a cyclodextrin vehicle within the IV formulation has caused concerns about vehicle accumulation in renal insufficiency or dialysis dependence and IV administration is best avoided in patients who have a creatinine clearance less than 50 mL.⁶⁸

Voriconazole is typically well tolerated, and the side-effect profile is similar to other triazoles with few exceptions. Most of those experiencing a reported adverse reaction to voriconazole describe abnormal vision (up to 23%) that is transient, infusion related, and without sequelae. This unique effect typically occurs 30 minutes after infusion and abates 30 minutes after onset. Other well-known effects of voriconazole therapy include skin rash and transaminase elevation.⁷² Baseline evaluation of hepatic function has been recommended before and during treatment, and rare cases of hepatic failure during voriconazole use have been reported.⁷³ Elevated voriconazole serum levels have been attributed to most side effects encountered in clinical practice, and higher levels (>5.5 mg/L), although associated with favorable outcomes, have also been suggested to be responsible for the uncommon potential side effects of encephalopathy or hallucinations.⁷⁴⁻⁷⁶

Voriconazole has become the drug of choice for most cases of invasive aspergillosis based on recent data comparing voriconazole to conventional amphotericin B, followed by other antifungal therapy in patients who have invasive aspergillosis.⁷⁷ Voriconazole has also been

evaluated in the treatment of neutropenic fever. Although, voriconazole did not meet predetermined non inferiority criteria, there were significantly fewer breakthrough infections (including those caused by *Aspergillus* spp.) in patients receiving voriconazole.⁸

Voriconazole has also been evaluated for use during infection caused by *Fusarium* and *Scedosporium* spp. A retrospective series evaluated its use in these infections and reported a favorable response in 63 percent of patients treated with voriconazole.³³

ECHINOCANDINS

Echinocandins (caspofungin, micafungin, anidulafungin) are synthetic compounds that inhibit the synthesis of β -1,3 glucan, by inhibiting the activity of glucan synthase. This mechanism impairs cell wall integrity and leads to osmotic lysis.⁷⁸ Their clinical use is primarily limited to *Candida* spp. and *Aspergillus* spp. and they lack activity against the *Zygomycetes*, *Cryptococcus* spp, and other clinically important molds (Table 1). Although activity is observed against all *Candida* spp, the MICs are elevated (>1 mg/mL) when *Candida parapsilosis* and *Candida guilliermondii* are encountered and susceptibility differences between the different agents in this class are minimal.⁷⁹ Echinocandins also have immunomodulatory effects. By exposing β -glucan by the disruption of fungal cell wall mannoproteins, additional antigens are exposed for antibody deposition and fungal recognition by the host immune system.⁸⁰ Echinocandin efficacy is predicted by peak to MIC ratios, and optimal fungicidal activity is obtained when peak concentrations exceed MICs by 5 to 10-fold.⁶ TDM of echinocandins is seldom required, however, and not routinely recommended. Echinocandin resistance is uncommon but may develop during therapy.⁸²

Multiple *in vitro* studies have confirmed a paradoxical effect of the echinocandins. In this circumstance, above a certain concentration of drug decreased antifungal activity is observed. The exact mechanism responsible for this phenomenon has not been fully elucidated and the clinical significance remains uncertain.⁸⁵

Echinocandins have poor oral absorption and current agents are available only in the IV formulation. Echinocandins are highly protein bound (anidulafungin 84 percent, caspofungin 97 percent, and micafungin 99%) and have a half-life of 26, 30, and 15 hours, respectively. Their vitreal and CSF penetration is negligible and this point is of clinical significance during the treatment of candidemia if endophthalmitis is also observed.

Caspofungin was the first available agent of this class, and is metabolized by both hepatic hydrolysis and N-acetylation. Inactive metabolites are subsequently eliminated in the urine. Severe hepatic dysfunction thus mandates caspofungin dose reduction.⁶ Caspofungin has several

drug interactions with agents metabolized through the cytochrome P450 system and serum levels are reduced in the presence of rifampin and may increase levels of sirolimus, nifedipine, and cyclosporine.⁶ Micafungin is metabolized by nonoxidative metabolism within the liver and anidulafungin undergoes nonenzymatic degradation within the kidney. Both agents are eliminated in stool. These agents therefore do not require dosage adjustment with hepatic impairment.⁶

The side effect profile of the echinocandins is minimal and these agents are typically well tolerated. An infusion-related reaction has been described if rapid administration is given, with tachycardia, hypotension, or thrombophlebitis.

The increased incidence of triazole-resistant *Candida* spp and the fungicidal activity of the echinocandins (caspofungin, micafungin, anidulafungin) has prompted some authorities to recommend these agents as first-line therapy for invasive candidiasis. Additionally, their proven efficacy, infrequency of side effects, and favorable drug interaction profiles make them attractive options over other available antifungals.^{12,83–85} Comparative trials have found the echinocandins equally efficacious and better tolerated than AMB in the treatment of candidemia.¹² In one such trial, caspofungin (70 mg loading dose followed by 50 mg daily) was compared to amphotericin B deoxycholate (0.6–1 mg/kg) in the treatment of invasive candidiasis. Although *C. albicans* was more common in the AMB arm, modified intention to treat revealed similar survival in each group, with a trend toward increased survival and a statistically significant decrease in drug side effects in those receiving caspofungin.¹²

Similarly, micafungin (100 mg IV daily) has been compared to L-AMB 3 mg/kg IV daily in an international, double-blind trial. In this study assigning patients to 14 days of IV treatment, successful treatment was equivalent in each group. There were fewer treatment-related adverse events, including those that were serious or led to treatment discontinuation, with micafungin than there were with liposomal amphotericin.⁸³

It is common practice from the results of these trials for local resistance patterns and the severity of infection to be taken into account and echinocandins are frequently used as first-line therapy.

After clinical improvement is obtained or the absence of fluconazole resistance documented, therapy is often changed to a triazole, such as fluconazole. As noted previously, CNS and intraocular infections should not be treated with echinocandin monotherapy because of their poor penetration into these sites.

Although clinical trials have been primarily limited to patients who have candidemia, observational data have shown efficacy in candidal osteomyelitis, peritoneal infections, and abdominal abscesses.⁸⁶ Additional retrospective

data have also shown a potential role for the echinocandins in infective endocarditis caused by *Candida* spp.⁸⁷

The echinocandins have also been found efficacious in the treatment of invasive aspergillosis, although they are fungistatic against this agent. The growing number of patients who are at risk for this infection has prompted a greater interest in the use of other agents that may be of clinical use against this devastating infection. The known toxicity of AMB and its different formulations and the potential for voriconazole-induced drug-drug interactions or toxicity has also increased interest in the echinocandins for use during treatment of IA.⁸⁸

Caspofungin as a potential first-line agent has been evaluated only in limited settings and although acceptable responses have been observed, data are not sufficient to recommend caspofungin for first-line use during the treatment of IA.¹⁰ Patients who are unresponsive or intolerant to voriconazole may benefit from a change to caspofungin.⁸⁸ *In vitro* studies and limited clinical data have also shown the potential role for combination therapy (an echinocandin plus AMB or an azole) and prospective studies are ongoing.

ANTIMETABOLITES

Flucytosine

Flucytosine (5FC) is deaminated to 5-fluorouracil by fungal cytosine deaminase. 5-fluorouracil is further converted to 5-fluorodeoxyuridylic acid, which interferes with DNA synthesis.

Mammalian cells lack cytosine deaminase allowing for a selective inhibition of fungal organisms.⁹⁹ This agent may be either fungistatic or fungicidal depending on fungal species and strain. Activity has been observed against most fungal pathogens, including *Candida*, *Cryptococcus*, *Cladosporium*, *Phialophora*, and *Saccharomyces* spp. *Aspergillus* spp, the *Zygomycetes*, dermatophytes, and the endemic mycoses are all resistant to 5FC.

Additionally, resistance commonly develops when 5FC is used as monotherapy even in susceptible organisms and it should not be used as such except during the treatment of chromoblastomycoses or during the treatment of localized candidal infections when alternative agents are unavailable or contraindicated. 5FC has excellent oral bioavailability with greater than 80 to 90 percent absorption. Peak serum levels occur 1 to 2 hours after ingestion (30–45 mg/ml) of a single dose. The volume of distribution of 5FC is 0.6 to 0.9, yet bone, peritoneal, and synovial fluid 5FC levels have been demonstrated and urinary levels are several-fold higher than concurrent serum levels. Greater than 95 percent of 5FC is eliminated unchanged in the urine. 5FC is typically administered by mouth at 100 or 150 mg/kg/d divided in four doses.

Side effects of therapy include rash, diarrhea, hepatic transaminase elevation, and bone marrow suppression. The marrow suppressive effects are more common if blood levels exceed 100 to 125 mg/mL.⁹⁰ In the presence of prolonged therapy (>7 days) or with alterations in renal function serum drug monitoring is recommended. Other less common side effects, such as abdominal pain or diarrhea, are frequently indirect markers of elevated flucytosine levels and therapy is typically stopped in these circumstances. 5FC is teratogenic and should not be administered during pregnancy.

5FC is primarily used only in the treatment of *Cryptococcus* (combined with AMB) and chromoblastomycosis. Despite concerns for additive toxicity the synergistic effects of dual therapy in *Cryptococcus* allow for more rapid CSF clearance.⁹¹

SUMMARY

The incidence of infection with invasive mycoses continues to increase with the increasing immunosuppressed patient population. The recently expanded antifungal armamentarium offers the potential for more effective and less toxic therapy and these agents offer distinct pharmacologic profiles and indications for use.

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CHAPTER 40

Approach to the Child with Fever of Unknown Origin

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INTRODUCTION

Fever of unknown origin (FUO) is best defined as fever without obvious source on initial clinical examination and then classified into acute (illness of ≤ 1 week's duration) and prolonged (>7 to 10 days' duration).¹

Most of the fevers of unknown origin result from atypical presentations of common diseases whose definitive diagnosis can be established only after prolonged observation. This is especially true in connective tissue disorders where one has to let time uncover the true facet of the disease as initial clinical examination and laboratory results can be normal.

ETIOLOGY

The most common etiology of fever of unknown origin (FUO), both acute and prolonged is infection.²

Infections contribute to 40 to 50 percent cases of FUO followed by collagen vascular disease (15-20%) and malignancy (5-10%). In about 10 to 20 percent cases, a definite diagnosis is never established.

It is useful to recognize that uncommon manifestations of common diseases are more likely than are rare diseases.

Approach to a Child with FUO

All toxic-appearing infants and children and all febrile infants less than 28 days of age should be hospitalized for evaluation and initiation of prompt parenteral antibiotic therapy after sending blood culture. Toxic appearance is a clinical presentation characterized by lethargy, poor perfusion, marked hypo/hyperventilation and cyanosis.

Febrile infants and young children have, by tradition, been arbitrarily assigned to different management strategies by age group: neonates (birth to 28 days), young

infants (29 to 90 days), and older infants and young children (3 to 36 months).³

In all neonates, a complete septic screening which includes CSF with prompt initiation of antibiotic therapy should be done.

The two most important steps in evaluating any child with FUO is a good history and a thorough physical examination.

History

The importance of a good history in evaluating a FUO cannot be overstressed. The history should elicit the details of onset of fever, intensity, pattern, if associated with chills/rigors and other associated symptoms. Many a times, the caretaker may give a history of ten days fever but only after digging properly into the history, the physician may realise that the child had fever for two days a week back and has again got fever since a day after a brief normal afebrile interval. This pattern associated with back to back inter-current viral illnesses is not uncommon in practice.

Many a times, in cases of undocumented fever, the child may be afebrile but the caretaker may wrongly perceive fever due to warm head and palms as compared to the rest of the body.

In neonates and small infants, there may be increased temperature due to overbundling and on recording temperature after removing excess clothes, the child may be found to be afebrile.

Immunization history is important especially in view of era of vaccines available against Hib, *Pneumococcus*, enteric fever, hepatitis A, B, influenza.

Travel history, exposure to pets, consumption of unpasteurised dairy products, family history, contact history with active tuberculosis and drug history need to be asked.

Physical examination

The first aim of a physical examination is to judge whether the illness is acute or chronic and the severity of the illness for any needed prompt action. Vitals should be recorded and a thorough general and systemic examination should be done. Lymphadenopathy, hepatosplenomegaly or rash may not help to pinpoint the system involved but at least will indicate some systemic illness. However, a repeated daily physical examination looking for new signs like rashes, murmur, joint involvement, etc is the best strategy as many of the conditions that cause FUO may have an absolutely normal physical examination to begin with.

Investigations

It is not wise to run a long battery of tests blindly in a FUO. The investigations should be guided by the most probable differentials resulting out of proper history and examination. The decision of the investigations to be carried out is also influenced by the host factors like age and local endemic diseases like malaria, chikungunya, etc.

It is also important that the most common etiology should be ruled out first before proceeding for tests for a lesser probable cause.

The initial investigations should include a complete blood count with a good look at the peripheral smear, a routine urine examination, blood culture, an X-ray chest and a CSF examination in any signs of neurological involvement. A Mantoux test may be useful additional tool to rule out tuberculosis. Similarly, a normal ESR count though nonspecific, is unlikely to be present in rheumatological or malignant conditions. Sometimes multiple blood cultures may be required to establish a diagnosis of subacute endocarditis or osteomyelitis.

CBC is not a sensitive and specific test to differentiate between viral or bacterial infections and may be even normal at the onset of a chronic illness. However, a total leukocyte count of $<5000/\text{mm}^3$ may rule against a serious bacterial infection except in typhoid fever or in neonates. Similarly, a total leukocyte count greater than $15000/\text{mm}^3$ with increase in nonsegmented polymorphonuclear leukocytes $> 500/\text{mm}^3$ indicates a serious bacterial infection. Though a lot of progress has been made in diagnostic tools to detect serious bacterial infections in young like CRP, procalcitonin, interleukin-6, unfortunately there is still no single marker available to diagnose a serious bacterial infection.

It is necessary to look at serial CBCs to detect rise or fall in platelet count or other changes in the differential counts. It is known that parasites like malaria may not be picked up in a single smear examination.

Further investigations like imaging/ 2D echocardiography/serology tests may be carried out depending on the

emergence of new signs or symptoms and on the basis of the results of primary investigations.

Major difficulties in the management of FUO in children in developing countries include constraints in the availability and reliability of laboratory tests, cost, misuse of antibiotics and difficulties encountered in the diagnosis of malaria and typhoid fever.⁴ Of these, irrational antibiotics in terms of the choice, duration and compliance results in the menace of both partially treated infections and atypical course of the infection with the worst scenarios of producing multi drug resistance. To add to the woes is immune mediated fevers triggered by many illnesses ranging from a simple viral fever to malaria or enteric fever, where fever continues even after the underlying infectious process is controlled.

Infections

Among infections, since viral illnesses are usually self limiting, bacterial infections are more common agents resulting in a FUO. *The bacterial infections may be localized for example: abscess, chronic mastoiditis, sinusitis, osteomyelitis, septic arthritis, pyelonephritis, endocarditis or generalized like tuberculosis, salmonellosis, brucellosis.*

Many times prolonged presentations of common viral diseases may also present as a FUO. *Other viral illnesses can cause FUO are cytomegaloviral infections, Hepatitis virus, Infectious mononucleosis and HIV.*

Other common infective causes are parasitic (malarial, amoebiasis, toxoplasmosis), rickettsial, chlamydial and fungal infections.

In a hospital based, prospective, observational study on children between 3 years and 12 years, it was found that a diagnosis was reached in 88 percent cases of FUO. Infections were the predominant cause of FUO in 69 percent. Enteric fever was the most common infection, followed by visceral leishmaniasis and tuberculosis.⁵

One study found that about 34 percent of cases of prolonged FUO caused by infections, bacterial meningitis and urinary tract infection accounting for about 6.5 percent and 11.4 percent, respectively.⁶

The investigations for infectious etiology should be guided by the history of local endemicity, travel history to endemic areas of malaria, etc. consumption of unpasteurised milk (brucellosis), contact history with active tuberculosis (for tuberculosis).

Malignancies

Since most of the childhood cancers are curable, it is very crucial that they are diagnosed at an early stage. Unfortunately, there can be delays in the diagnosis because the signs and symptoms of malignancy may be initially misdiagnosed as infection. A study which tried to evaluate this

initial misdiagnosis of malignancy as infection found that seventy-one percent of the children in the study had fever (most of which were subsequently diagnosed with leukemia).⁷

To look for any signs of malignancy particular attention should be paid during the physical examination to the four Bs—"blood, brain, belly and bone".

*The most common childhood malignancies are acute lymphoblastic leukemia, central nervous system (CNS) tumors and lymphomas.*⁸

Fever may be low grade in leukemia. Leukemia should be suspected if fever is accompanied by evidence of weight loss, abnormal bleeding, bone pain, lymphadenopathy or hepatosplenomegaly.

It has been suggested that paraneoplastic fevers may be more responsive to nonsteroidal anti-inflammatory drugs than are nonneoplastic fevers, and use of the "Naprosyn test" may offer some direction towards the diagnosis of malignancy.

The presenting symptoms of a brain tumor may include elevated intracranial pressure, nerve abnormalities and seizures. In children, lymphoma may present as one or more painless masses, often in the neck, accompanied by signs and symptoms resulting from local compression, as well as signs and symptoms of systemic disturbances, such as fever and weight loss. It is not necessary to see blast cells in peripheral smear and many times leukemia may only have blast cells in their bone marrow.⁸

Bone marrow should be done in clinical suspicion with laboratory findings of anemia, especially if accompanied by reticulocytopenia or a high mean corpuscular volume, thrombocytopenia, leukopenia or leukocytosis. Leukemia may also be considered in a child with high ESR count but a normal platelet count.

Imaging will be diagnostic in detecting solid tumors.

Collagen Vascular Diseases

Five to twenty percent of FUOs in childhood are caused by collagen vascular disease. *The most common rheumatic diseases to present with fever in childhood are systemic onset juvenile arthritis, systemic lupus, and Kawasaki disease.* The diagnosis of rheumatological conditions is usually based on a set of defined criteria rather than a single test.⁹

Systemic Onset Juvenile Arthritis

The fever in systemic onset juvenile arthritis is characteristically quotidian with high once or twice daily spiking fever, $>39^{\circ}\text{C}$, which returns to baseline. The fever spikes occur in the afternoon or evening. The child appears normal during the afebrile intervals. Each fever spike is associated with an evanescent linear or circular salmon pink

macular rash on the trunk and proximal extremities which may elicit a koebner phenomenon. Other features like arthritis, hepatosplenomegaly, lymphadenopathy or pericarditis may be present. The complete blood count may reveal anemia, leukocytosis, thrombocytosis and a high ESR but are nonspecific. The rheumatoid factor and anti-nuclear antibody tests are usually negative. The diagnosis is made easier by the American College of Rheumatology Classification for juvenile arthritis.

Systemic Lupus Erythematosus SLE

Systemic lupus erythematosus should be suspected specially in girls above 8 years of age with mild-moderate fever associated with multisystem involvement. The systemic involvement may be in the form of weight loss, arthritis, malar rash, nephritis, pericarditis, pleuritis or seizures. The complete blood count may suggest anemia, leukopenia, lymphopenia, or thrombocytopenia. Urine may show proteinuria, hematuria or cellular casts. A positive ANA is a hallmark, anti-DNA antibodies and other autoantibodies like rheumatoid factor, antiphospholipid antibodies may also be positive.

Kawasaki Disease

It is the most common febrile vasculitis which can present as FUO especially in younger children. Fever is characteristically high (104°C F or higher), remittent and unresponsive to antibiotics. The fever may even persist for 3 to 4 weeks without treatment. In a classic presentation of Kawasaki, there should be persistence of fever for at least 5 days, with either of the following 4 features like bilateral bulbar conjunctival injection without exudates, mucosal changes in lips and oral cavity, polymorphous exanthema, cervical adenopathy and changes in extremities like edema, rash or periungual peeling (in second/third week).

The diagnosis is mainly clinical. Lab findings reveal systemic inflammation but are nonspecific. The acute phase is characterized by a leukocytosis with a neutrophilic predominance, mild anemia and elevated acute phase reactants. Mildly elevated liver enzymes and a sterile pyuria can also be seen. Thrombocytosis typically develops in the second week, sometimes exceeding $10,00,000/\text{mm}^3$. Antinuclear antibody tests and rheumatoid factors are negative. 2D echo is of utmost importance to evaluate the coronary artery abnormalities.

The diagnostic challenge occurs in atypical or incomplete Kawasaki disease where there may be persistent fever but fewer than four features. Recognition depends on the knowledge of the characteristic features and a high index of suspicion.

This condition is treated with IV immunoglobulins and high dose aspirin.

MISCELLANEOUS

Drug Fever

Drug fevers usually have a constant elevation of fever and disappears within 72 hours of discontinuation of the offending drug. The most common are beta-lactam antibiotics, procainamide, isoniazid, alpha-methyldopa, quinidine and diphenylhydantoin. Slowly metabolised drugs like which contain iodides can cause fever up to one month of discontinuing it.

Periodic Fever's Syndrome

These are rare syndromes where the child presents with episodes of high grade fever lasting for several weeks to months followed by fever free periods of variable duration. Several genes have been identified to be responsible for the familial variety of periodic syndromes. These children may respond poorly to antipyretics.

Prognosis of Fever of Unknown Origin

The prognosis of childhood FUO depends on the underlying etiology. However in comparison to mortality rate of 25 to 40 percent in adults, the mortality in children due to FUO is low (10%).²

Conclusion

In spite of the best advancements for diagnosis of the etiology for fever, the golden strategy remains that of the basic art of medicine, i.e. a good history and repeated clinical examination.

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INTRODUCTION

Sepsis is a clinical syndrome subsequent to invasion of the blood stream by microbes triggering off a systemic inflammatory response, the severity of which determines the clinical manifestations ranging from early signs of circulatory compromise to shock, multiorgan dysfunction and death. The infection can be caused by bacteria, viruses, fungi, parasites or the toxic products of these microbes. Globally sepsis is a major health problem with a high mortality and appears to be increasing¹⁻³ in view of the sizeable susceptible population especially the immunocompromised, awareness and advances in pediatric intensive care and emerging and drug resistant bacteria. The incidence is inversely related to the age of the child. Early recognition and intervention holds the key to a favourable outcome. The mortality reported varies from 10 to 40 percent being higher in resource poor developing countries.

ETIOLOGY

Infection leading to sepsis can be caused by a myriad of bacteria, viruses, fungi, parasites. The infection per se or the toxic products of these microbes together with the numerous host factors can start the cascade of inflammatory response leading to the clinical syndrome.

Bacteria like *S. pneumoniae*, *H. influenzae B*, *N. meningitidis*, *S. aureus* and *Salmonella* are important in community while gram-negative bacilli like *E. coli*, *Klebsiella*, *Pseudomonas*, *Enterobacter*, *Acinetobacter*, *Serratia* and *Burkholderia* are important nosocomial infections.

Dengue virus is an emerging pathogen in the developing world. *Candida* especially *nonalbicans* is an emerging nosocomial fungal organism.

Malaria is an important parasite leading to sepsis syndrome.

PREDISPOSING FACTORS

- Immunocompromised (primary or secondary affecting the T cells, B cells, complement)
- Hemoglobinopathies esp. Sickle cell
- Genitourinary anomalies
- Congenital cardiac malformations
- Infected trauma and burns
- Splenic dysfunction/splenectomy
- Hematologic or solid organ malignancy and chemotherapy
- Hospitalization in intensive care settings
- Indwelling catheters/prosthetics and devices

PATHOGENESIS

Systemic inflammatory response syndrome (SIRS) triggered by infection is a necessary cause of sepsis spectrum (Fig. 1). SIRS can also be triggered by chemical, trauma, malignancy, autoimmunity and idiopathic insults. The inflammatory cascade that ensues is a complex process that involves humoral and cellular responses, complement, and cytokine cascades. The relationship has been aptly summarized by Bone et al as a three stage process⁴ (Flow chart 1).

Stage I: In response to an insult, local cytokine production recruits the reticuloendothelial system to contain the noxious stimulus.

Stage II: Small quantities of local cytokines are released into circulation which recruits the macrophages and platelets. The proinflammatory mediators and the acute phase response is checked by stimulation of anti-inflammatory mediators like interleukin (IL)-4, 6, 10, PGE2, protein C, Lipoxins, GM-CSF, TGF and IG-1RA to achieve homeostasis.

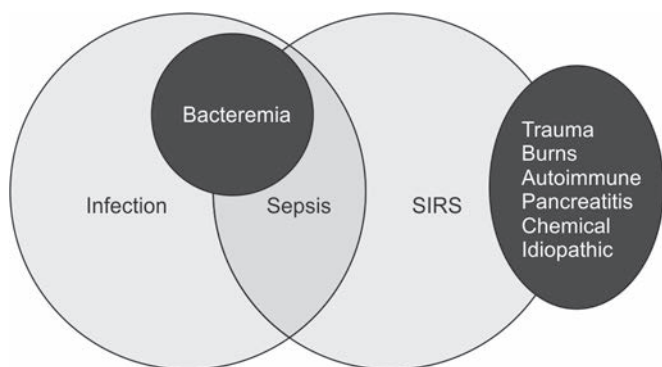
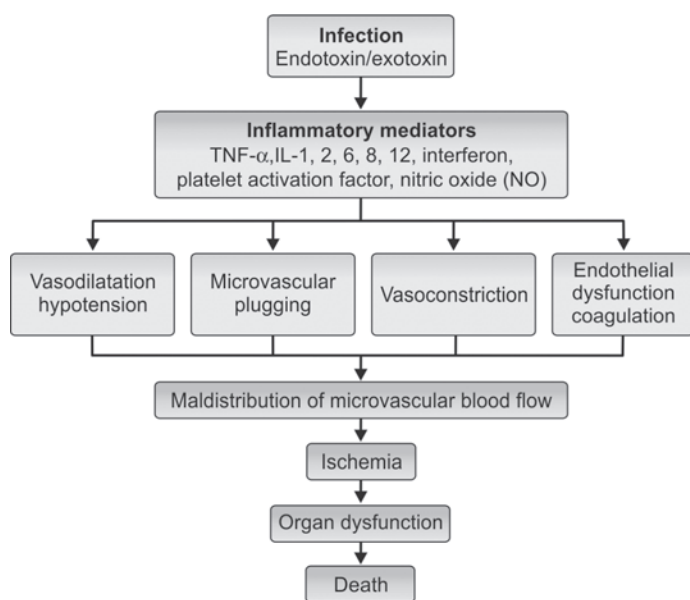


Fig. 1: Infection and SIRS

Flow chart 1: Pathophysiology of systemic inflammatory response syndrome



Stage III: If homeostasis is not restored, a significant systemic reaction occurs. The surge of proinflammatory cytokines TNF- α , IL-1, 6, 8, platelet activating factor, interferon gamma, PGE, leukotrienes and nitric oxide (NO) leads to loss of capillary integrity and maldistribution of microvascular blood flow leading to organ injury and dysfunction.

The inflammatory cascade in infections is often initiated by endotoxin or exotoxin of the invading microbe. TNF- α , IL-1 and the microbial endotoxin or exotoxin lead to cleavage of the nuclear factor- κ B (NF- κ B) inhibitor. Once the inhibitor is removed, NF- κ B is able to initiate the production of mRNA, which induces the production of other proinflammatory cytokines. Both TNF α and IL-1 can be released in large amounts within minutes of an insult and cause fever, hypotension, lung injury and release of stress hormones (norepinephrine, vasopressin, activation of the renin-angiotensin-aldosterone system). IL-6 stimulate the release of acute-phase reactants such

as C-reactive protein (CRP) and procalcitonin. Activation of the coagulation cascade, complement cascade, and the release of nitric oxide, platelet-activating factor, prostaglandins, and leukotrienes is both the cause and effect of cytokine surge. Prostaglandins and leukotrienes incite endothelial damage, leading to multiorgan failure. Polymorphonuclear cells are inhibited to prevent excessive inflammation losing their microbicidal potential.⁵

The procoagulant state mediated via endothelial damage by TNF- α and IL-1 is critical for disease progression. Tissue factor mediated production of thrombin, impaired fibrinolysis due to plasminogen activator inhibitor 1 mediated by TNF α and IL-1, inhibition of anti-inflammatory mediators antithrombin and activated protein-car critical for microvascular thrombosis causing organ dysfunction.

The counter inflammatory response syndrome (CARS) mediated through anti-inflammatory IL-4, IL-10, and antagonists to TNF- α and IL-1 receptor is often overwhelmed by SIRS resulting in an unfavorable outcome. It is believed that because of CARS, agents used to inhibit proinflammatory mediators can deleterious immunosuppression.

DEFINITIONS

The widely followed definitions of pediatric sepsis spectrum have been given by international consensus conference, 2005 and are given in Tables 1 and 2.⁶

CLINICAL PRESENTATION

The importance of a detailed history of the child from a reliable source cannot be undermined. Fever is the most common presenting symptom of children with sepsis syndrome along with fast heartbeats, rapid or labored breathing, cool extremities, or color changes. The child's activity, refusal of feeds, urine output and exposures to infectious illnesses and other sources of insult are important. Verify immunization and drug allergy statuses. A complete physical examination of the infant or child with suspected SIRS is most important. Subtle changes in vital signs (e.g. minimal tachycardia, widened pulse pressure, minimal tachypnea, and minimally delayed capillary refill) may be the first signs of impending SIRS. Hypotension, mental status changes, and anuria are late signs of SIRS. Hypothermia is often a more ominous sign than fever. If SIRS is identified and reversed early, the subsequent inflammatory cascade can often be avoided or mitigated. However, in some situations, further damage occurs because the insult or the resultant host immune response is too great. This damage can result in increased cardiac output, peripheral vasodilatation, increased tissue oxygen consumption, and a hypermetabolic state (warm shock). As the severity increases, cardiac output may fall, peripheral vascular resistance may increase, and shunting of blood may ensue (cold shock). This results in tissue hypoxia, end-organ

Table 1: Definition of sepsis

A. Systemic inflammatory response syndrome (SIRS)	
The presence of at least two of the following four criteria, one of which must be abnormal temperature or leucocytes count:	
<ol style="list-style-type: none"> 1. Core (oral or rectal) temperature of $>38.5^{\circ}\text{C}$ or $<36^{\circ}\text{C}$. 2. Tachycardia, in the absence of external stimulus, chronic drugs, or painful stimuli; or otherwise unexplained persistent elevation over a 0.5 h time period or for children <1 year old: bradycardia, in absence of external vagal stimulus, β-blocker drugs or congenital heart disease or persistent depression over a 0.5 h time period. 3. Tachypnea for an acute process not related to underlying neuromuscular disease. 4. Leukocytes count elevated or depressed for age (not secondary to chemotherapy-induced leukopenia) or $>10\%$ immature neutrophils. 	
B. Infection	
A suspected or proven infection caused by any pathogen or a clinical syndrome associated with a high probability of infection. Evidence of infection includes positive findings on clinical examination, imaging, or laboratory tests (e.g. leukocytes in a normally sterile body fluid, perforated viscus, chest radiograph consistent with pneumonia, petechial or purpuric rash, or purpura fulminans) or a positive culture, tissue stain or polymerase chain reaction test.	
C. Sepsis	
SIRS in the presence of or as a result of suspected or proven infection.	
D. Severe sepsis	
Sepsis plus one of the following: cardiovascular organ dysfunction or acute respiratory distress syndrome or two or more other organ dysfunctions. Organ dysfunctions are described in (Table 2).	
E. Septic shock	
In a child with sepsis presence of; hypotension (systolic BP <70 mm Hg in infant; $<70 + 2 \times \text{age}$ after 1 year of age) or need for vasoactive drug to maintain BP above fifth centile range (dopamine >5 mcg/kg/ min or dobutamine, epinephrine or norepinephrine at any dose) or signs of hypoperfusion—any three of the following: decreased pulse volume (weak or absent dorsalis pedis pulse), capillary refilling time $>3\text{s}$, tachycardia heart rate, core (rectal/oral) to peripheral (skin-toe) temperature gap $>3^{\circ}\text{C}$ and urine output <1 ml/kg/h (<20 ml/h in >20 kg child) or sepsis and cardiovascular organ dysfunction as defined in (Table 2)	
F. Multiple organ dysfunctions	
The detection of altered organ functions in the acutely ill patient constitutes multiple organ dysfunction syndrome (MODS; two or more organs involvement).	

dysfunction, metabolic acidosis, end-organ injury and/or failure, and death.

A meticulous search for localizing signs of infection should be done. A petechial or purpuric rash associated with fever is seen in meningococcal and some hemorrhagic viral infections. Increased effort of breathing with bilateral wheeze or crepitations and unequal breath sounds are pointers toward primary lung pathology or early ARDS. Tense abdomen with a localized guarding or rigidity is due to an abdominal localization of infective focus. Frequent reassessment for and during interventions is the key to success.

The cardinal signs:

- Fever
- Leukocytosis
- Tachypnea
- Tachycardia
- Reduced vascular tone
- Organ dysfunction
- Mental alertness

INVESTIGATIONS

The laboratory evaluation is essential for:

- Etiology and the source of infection
- Evaluation of organ systems
- Monitoring

Cultures of blood, urine, all available body fluids and secretions including skin and cellulitic areas may give a clue to the offending microbe and the source of infection. CSF must be evaluated as and when the clinical condition is stabilized. The positive yield from the culture is invariably around 45 percent.⁷ Viral infections are often not amenable to culture and serology is often relied upon. Newer nonculture based molecular diagnostics like PCR are becoming important.⁸

High or extremely low leukocyte counts with band cells and toxic granules are suggestive of infection. Hemoconcentration helps assess the hydration status. LFT, KFT, electrolytes, amylase, lactate and arterial blood gases help assess and monitor organ dysfunction. Assessment of coagulation is essential in children with SIRS. The role of

Table 2: Organ dysfunction criteria*Cardiovascular dysfunction*

- Hypotension (systolic BP <70 mm Hg in infant; < 70 + 2 × age after 1 year of age) or
- Need for vasoactive drug to maintain BP above the fifth centile range (dopamine >5 mcg/ kg/ min or dobutamine, epinephrine or norepinephrine at any dose) or
- Signs of hypoperfusion—any three of the following; decreased pulse volume (weak or absent dorsalis pedis pulse), capillary refilling time >3s, tachycardia heart rate, core (rectal/oral) to peripheral (skin-toe) temperature gap >3°C and urine output <1 ml/ kg/ h (<20 ml/h in >20 kg child)
- In early stage, there is an increase in heart rate and poor peripheral perfusion in form of weak pulse and prolonged capillary refill time. Hypotension occurs late, and may lead to precipitous cardiac arrest.

Respiratory dysfunction

- Proven need for supplemental oxygen or >50% FiO₂ to maintain saturation >92% or
- Need for nonelective mechanical ventilation or
- PaO₂/FiO₂ <300 in absence of cyanotic heart disease or pre-existing lung disease or
- PaCO₂ >65 torr or 20 mm Hg over baseline PaCO₂

Neurologic dysfunction

- Glasgow coma scale <11 or
- Acute change in mental status with a decrease in Glasgow coma score >3 points from abnormal baseline

Hematological dysfunction

- Platelet count <80,000/ mm or a decline of 50% in platelet count from highest value recorded over the past 3 days [for chronic hematology/oncology patients] or
- International normalized ratio >2

Renal dysfunction

- Serum creatinine > 1 mg/ dL

Hepatic dysfunction

- Total bilirubin >4 mg/dl (not applicable for newborn) or alanine transaminase 2 × upper limit of normal for age

Acute respiratory distress must include a PaO₂/FiO₂ ratio <200 mm Hg, bilateral infiltrates, acute onset and no evidence of left heart failure. Acute lung injury is defined identically except the PaO₂/FiO₂ ratio must be <300 mm Hg.

acute phase reactants like ESR, CRP, procalcitonin interleukins and TNF- α is debatable.

Imaging studies like chest X-ray chest, ultrasonography of abdomen and other body parts, CT, MRI and echocardiography are helpful to localize infection and evaluation of organ systems.

MANAGEMENT^{9,10}

The management of severe sepsis with evidence of circulatory, respiratory and metabolic abnormalities is best done in a pediatrics ICU by experts and is discussed in detail elsewhere in this book. However, the initial assessment and stabilization should start in any pediatrics clinic or emergency room pending transfer.

The therapeutic strategies are:

- Optimize organ perfusion (Early Goal Directed Therapy EGDT)
 - Fluid resuscitation
 - Oxygen delivery
 - Maintenance of circulatory, respiratory and metabolic alterations.

- Control infection by antibiotics and source control
- Support dysfunctional organ systems
- Modulation of host responses especially the inflammatory response which is full of controversies.
- Adjunctive therapy, e.g. glycemic, hypocalcemia control, sedation/ analgesia, stress ulcer and DVT prophylaxis and nutrition.

The nonavailability of high tech gadgets should not be a deterrent to early recognition and management of severe sepsis as strong evidence exists for dramatic reduction in mortality just by meticulous clinical monitoring of therapeutic endpoints like oxygen saturation, CVP, CRT, urine output, blood pressure and auscultation.

Empirical Antibiotic Therapy

Early antibiotic therapy preferably within one hour of diagnosis after taking the appropriate culture samples is critical for a favorable outcome. To cover the most likely organisms a combination of third generation cephalosporin, e.g. ceftriaxone and an aminoglycoside like amikacin is appropriate for community acquired sepsis. The

nosocomial infections are best treated by drugs based on the local epidemiology and available antibiograms. The source control measures like drainage, debridement and removal of foreign bodies are important if the focus of infection is amenable to such interventions.

Corticosteroids

Hydrocortisone 50 mg/ sqm/dose every 6 hours is recommended for catecholamine resistant septic shock till reversal of shock. Suspected adrenal insufficiency is another indication in pediatric sepsis. The adrenal insufficiency is likely in children with severe septic shock and purpura, history of chronic illness requiring steroids, pituitary or adrenal problems and a documented random cortisol level <18 mcg/dl. The replacement dose is 50 mg/sqm/ 24 hr. There is no recommendation for routine use of steroids in severe sepsis as it was associated with a higher mortality in a large study.¹¹

Activated Protein C

Recombinant activated protein C though has shown some improvement in sepsis induced coagulation abnormalities is not recommended in pediatric sepsis. The product has been withdrawn from the market after the PROWESS-SHOCK study.^{12,13}

Other Modalities

IVIG in severe sepsis has no strong recommendation. Stress ulcer prophylaxis by H2 blockers is widely used without any strong evidence or recommendation. ECMO is reserved for refractory septic shock and respiratory failure. DVT prophylaxis is important for postpubertal children.

The diagnosis and management of pediatric sepsis is a dynamic process and has witnessed tremendous inputs in the last two decades and shall keep evolving over the years with more evidence based recommendations. Recently, the Surviving Sepsis Campaign (SSC) guidelines have been criticized for being more opinion based rather than evidence based.¹⁴ the Australian and New Zealand intensive care society has questioned the validity of SSC guidelines and declined endorsement.^{15,16} However, the crux remains in a high index of suspicion, early diagnosis and prompt intervention with whatever resources available to have a favorable outcome in this potentially life-threatening event.

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CHAPTER 42

Understanding Meningococcal Disease

Arvind Taneja

Meningococcal meningitis was first historically described in 1805 in Geneva, Switzerland. *Neisseria meningitidis* cause endemic and epidemic disease across the world including our country. The last two epidemics we had in our country were in 1986 and again in 2005 caused by serogroup 'A'. There is however a 'multicountry meningitis belt' in Sub Saharan Africa where the disease is hyper endemic due to unknown reasons and the incidence here peaks in the dry months between November and May only to subside with the onset of the Rainy season. The disease in this area is almost exclusively caused by Serogroup 'A'. Other epidemics caused by other serogroups have been described in Norway, Finland, Saudi Arabia, United Kingdom, New Zealand and Brazil. The background incidence in developing countries is 15 to 20 cases per 100,000 population per year. This increases dramatically during epidemics.

MICROORGANISM

The genus *Neisseria* has two important human pathogens *N. meningitidis* and *N. gonorrhoea*. The other species in the genus are mostly commensals like *N. lactamica*, etc. which colonize the nasopharynx but are not pathogenic. The organism is a gram-negative *Diplococcus* but may even exist as a tetrad morphologically. The adjacent sides are flattened giving it a 'kidney bean' appearance and may be encapsulated. The organism grows best on chocolate agar or blood agar in the presence of 10 percent carbon dioxide. The species differentiation is made on the basis of sugar fermentation reactions.

N. meningitidis has the ability to share DNA with other serogroups and species of *Neisseria* colonizing the nasopharynx through transfer of DNA, thus changing its morphologic characteristics such as its capsule or its virulence or its susceptibility to sulfonamides or penicillin.

Meningococci also have pili which are important in some phases of adherence to host cells, colonization and invasion. The genes that code for pili can also be turned on and off so at times the organism may not exhibit pili.

Meningococci may also exhibit phase variation through gene transfer which allows variation of the number of surface antigens including turning 'off or on' polysaccharide capsule synthesis.

Serogrouping

There are 13 serogroups of meningococci but the ones with a pathogenic potentials are A, C, Y, W-135, X and 29-E. The polysaccharide capsule protects the organism from phagocytosis, by not allowing opsonization.

Some outer membrane proteins (OMPs) functions as porins (channels for transfer of nutrients, ions, antibiotics, etc.) from the extracellular to the intracellular compartment and vice versa). Some of the OMP facilitate adhesion and invasion.

Serotyping

The serotyping of organisms is based on outer membrane Proteins (OMP's). All meningococci have either antigenic class 2 or class 3 porin B.

Subtyping

Different subtypes are based on antigenic differences in porin A.

The outer and inner cell membrane layers of *N. meningitidis* are phospholipid bilayers. These layers sandwich a layer of peptidoglycan. Lipooligosaccharide (LOS) which is similar to LOS and Lipopolysaccharide (LPS) seen in other gram-negative bacteria is associated with the outer phospholipid layer.

EPIDEMIOLOGY

Clonal strains of *Meningococcus* can transmigrate transcontinentally. Interestingly serogroup 'A' strains do not cause disease in the North America continent in spite of being episodically introduced there on many occasions.

International outbreaks by serogroup 'A' (1987) and 'W-135' (2000) strains also originated from the pilgrims congregating in Saudi Arabia at the annual Hajj pilgrimage. Some of these pilgrims returned home before falling sick leading to intra familial spread in their home country. Saudi Arabia now mandates meningococcal quadrivalent Vaccination with A, C, Y, W-135 before allowing pilgrims into their country.

Serogroup 'B' generally causes sporadic endemic disease through the epidemic in Brazil in 1974 and the current ongoing epidemic in New Zealand since 2004 are caused by this strain.

The United Kingdom has seen an epidemic of disease caused by serogroup 'C' since the late 1990's. This epidemic has been controlled by widespread vaccination with a meningococcal C conjugate vaccine given in 3 primary doses in infancy starting at age 3 months since 1999. The risk of acquiring meningococcal disease is related inversely to age, with the highest rates occurring in children less than 1 year except in epidemic situations.

Maternal transplacental IgG antibody generally protects infants in the first three months of life. In epidemics an age shift occurs with older children, adolescents and adults more commonly affected.

Nasopharyngeal carriage is the immunizing process antibody production both homologous (to same serogroup) but also heterologous (other cross reactive serogroups) is seen within two weeks of carriage. Bacteria such as *Escherichia coli* and *bacillus* which share some polysaccharide capsular surface antigens with meningococci also contribute to immunity colonization can persist for months.

Invasive disease is favored by crowding, exposure to active or passive smoking, preceding viral and Mycoplasma infections and intimate kissing with multiple partners. These predisposing factors probably explain the spurt of meningococcal disease seen in adolescents entering colleges and living in dormitories and are the reason for classifying these groups as 'high-risk'. Functional or anatomic asplenia, congenital late complement component (C5-C9) deficiencies and properdin (Alternative pathway) deficiency also predispose to invasive meningococcal infections. Acquired complement deficiencies as seen in nephrotic syndrome chronic liver disease and Systemic lupus erythematosus (SLE) also put one in the same bracket of an immune compromised host.

PATHOLOGY AND PATHOGENESIS

Encapsulated typeable meningococci are pathogenic and virulent, whereas non encapsulated strains are relatively

nonpathogenic. Meningococci adhere to non-ciliated columnar epithelial cells in the nasopharynx via pili. Binding induces endocytosis of the organism into the epithelial cell and subsequent invasion of the blood stream if anybody is insufficient.

Occasionally unsuspected bacteremia has been detected on a blood culture in a normal appearing febrile patient and this bacteremia and fever has subsequently cleared on a follow-up blood culture without antibiotics. However in most cases such clearance does not occur and the individual becomes progressively ill. Bacteria in blood may then seed the meninges or other tissues and cause meningitis arthritis, pneumonitis, etc.

Meningococci release blebs from their surface that contain outer membrane proteins laden with LOS. LOS is a potent endotoxin and concentrations of LOS correlate with the severity of disease LOS mediates release of tumor necrosis factor (TNF- α) and other host of proinflammatory and anti inflammatory cytokines.

These cytokines contributes to a procoagulant state resulting in formation of microthrombi, endothelial damage, capillary leakage and vasodilatation as seen in shock and peripheral gangrene and ARDS.

Adrenal hemorrhage is seen in 50 percent of fatal cases and necrotizing myocarditis in 75 percent of the cases.

CLINICAL MANIFESTATIONS AND DIFFERENTIAL DIAGNOSIS

The manifestations of meningococcemia and meningitis are already very well known to Pediatricians and shall not be covered in this review, since they are not really recent advances in the body of knowledge on the subject.

Skin Manifestations

Meningococcal disease cutaneous changes if present, range from diffuse mottling to diffuse extensive purpuric lesions with shock (Purpura fulminans).

Chronic Meningococcemia

Presents as a fever of unknown origin with or without chills lasting more than a week with arthralgia, petechial rashes and headaches. These patients are non toxic and the mean duration of illness before diagnosis is generally 6 to 8 weeks. Bacteremia and symptoms are intermittent and clear rapidly with antibiotic administration.

Pneumonia

Meningococci of serogroup Y are generally responsible for 90 percent of cases. Pathogenesis is thought to be through inhalation of pulmonary droplets. Isolation of organism by sputum culture is not confirmatory, only blood culture or lung fluid aspirate is diagnostic.

Arthritis

It occurs primarily in adults. Rarely it could occur secondary to bacterial seeding into synovium from a bacteremia and more commonly immune mediated arthritis due to antigen-antibody immune complexes could occur 3 to 7 days after initiation of antibiotic treatment for meningococemia since the joint fluid is often sterile.

MYOCARDITIS AND PERICARDITIS

Bacterial pericarditis occurs in less than 5 percent cases. Most symptomatic pericardial effusions develop late in the course of the illness, are serous in nature and are sterile reflecting an immune complex pathogenesis. They may be severe enough to cause cardiac tamponade.

Miscellaneous meningococcal infections include conjunctivitis, mesenteric adenitis, peritonitis and genitourinary infections.

LAB DIAGNOSIS

Meningococci have been demonstrated in a gram stain of CSF in the absence of CSF pleocytosis.

Gold standard for diagnosis is based on recovering the organism from the blood and CSF (culture), and needle aspiration of purpuric lesions (Gram stain and culture).

Latex agglutination for antigen detection on serum or urine is not recommended because of shared antigens with *E. coli*. Latex particle agglutination in CSF is useful.

Polymerase chain reaction (PCR) is one of the newer tests increasingly being used in Europe and is sensitive even in patients who have been treated with antibiotics before collecting the sample. Sensitivity and specificity of PCR is almost 90 percent.

Mortality and Prognosis

Five features are identified with a poor prognosis:

- Shock or seizures on initial evaluation
- Hypothermia
- Total WBC count less than 5000/mm³
- Platelet count less than 100,000/mm³
- Development of purpura fulminans.

Mortality is substantially higher in epidemic than in endemic disease and higher in young adolescents and also in patients who present without clinical or laboratory features suggestive of meningitis and have a rapid progression of disease.

Evidence suggest that genetic component of host cytokine production may be associated with severity of disease. Westendorp and co-workers reported that families with low TNF- α production or high IL-10

(Interleukin-10) production are at increased risk for having fatal outcomes.

TREATMENT WITH ANTIBIOTICS

Ceftriaxone is the drug of choice and the first dose should be administered as soon as possible after a presumptive diagnosis is made. In dire emergent situations it is perfectly justified in giving the 1st dose of IM Ceftriaxone in the Pediatric office even before transporting the patient to the hospital since the doubling time of the bacteria is 20 minutes and bacterial load can build up dramatically affecting ultimate prognosis.

EXPERIMENTAL AND ADJUNCTIVE THERAPIES

Infusion of activated protein C concentrate (Xigris) found favor a few years ago based on initial clinical trials in adults but subsequent data in pediatric trials do not support its use since it does not reduce mortality rates and in fact may increase DIC and bleeding manifestations.

Two antiendotoxin therapies have been evaluated in clinical trials in the year 1999 and 2000. These are HA-IA (human monoclonal antibody) and recombinant bactericidal/permeability increasing protein (rBPI).

The beneficial effect of neither of the therapies achieved statistical significance.

Prophylactic low dose heparin has also been used but it is very difficult to monitor the dosage leading to over dosage and toxic effects. Caudal block has been used to restore lower extremity perfusion in gangrene.

Chemoprophylaxis

Since the secondary attack rate is very high in the 96 hr after detection in the index case, this modality is indicated to reduce nasopharyngeal carriage in intimate contacts at home (living under the same roof), day care centre or crèche or same section of the class at school. Incidental exposure on the playground or in the school bus lasting less than an hour or two does not constitute intimate contact and does not necessitate chemoprophylaxis.

The index patient should also receive chemoprophylaxis before discharge home to eliminate nasopharyngeal carriage, especially if the therapeutic antibiotic chosen was not ceftriaxone/ cefotaxime but penicillin or Sulfonamide or Chloramphenicol.

All contacts given chemoprophylaxis should also receive meningococcal vaccine (with the realization that there is no effective vaccine against serogroup B disease.

The various regimes used for chemoprophylaxis are given in Table 1.

Table 1: Various regimes used for chemoprophylaxis

Drug	Age	Dose/Duration
Rifampin	Adults	P.O. 600 mg twice daily x 4 doses (Max daily dose 600 mg.)
	Children >1 month	P.O 10mg/kg/ dose twice daily x 4 doses (Max daily dose 600 mg)
	Babies <1 month	P.O 5 mg/kg/ dose twice daily x 4 doses
Ceftriaxone	Children >15 yrs	IM 250 mg single dose
	Children <15 Yrs	I/M 125 mg single dose
Ciprofloxacin	Adults	P.O. 500 mg single dose
	Children	P.O. 10mg/kg single dose (Not to exceed 500 mg)
Azithromycin	Adults	P.O 500 mg single dose
	Children	P.O 10 mg/kg single dose

MENINGOCOCCAL VACCINE

Two kinds of vaccines are available. Meningococcal polysaccharide vaccine (MPSV) and meningococcal conjugate vaccine (MCV).

The polysaccharide vaccine is poorly immunogenic in children below 2 years of age and shows the phenomena of immune tolerance i.e. hyporesponsiveness of antibody production when booster doses are administered specially in children below 5 yrs of age. These vaccines do not elicit immunological memory, i.e. are T-cell independent and booster doses are recommended every 3 years. Immunity induced by group A vaccine given below 24 months of age is poor and immunity with group C vaccine in this age group is nonexistent. These vaccines are administered subcutaneously.

In our country routine childhood vaccination schedule till the age 12 yr does not recommend meningococcal vaccine except in exceptional circumstances like an ongoing epidemic, complement or properdin deficiency, functional or anatomic asplenia or travel to a hyperendemic zone such as the meningitis belt of sub saharan Africa. This vaccine is much less expensive than the conjugate vaccine.

The MCV4 quadrivalent conjugate vaccine (Menactra) is to be introduced by aventis this country in the next year and induces immune memory since it is T-cell dependent but is expected to cost around Rs. 5000/- a dose. It utilizes the same technology as the HIB vaccine since it binds the purified capsular polysaccharide to the CRM 197 component of the diphtheria toxoid which acts as its protein carrier. It is administered intramuscularly.

Encouraging trials are ongoing on its effectivity below 2 yr of age and current recommendations recommend a booster dose 3 to 5 years later to maintain ongoing immunity. It is the vaccine of choice to be given to adolescent populations and adults.

In response to an ongoing epidemic of meningococcal serogroup B disease in Northern New Zealand especially among the "Maori" a new vaccine has been formulated by Novartis in 2007 by using the outer membrane vesicle and this vaccine has helped considerably in controlling the epidemic.

Similarly in response to the UK and Irish epidemic a group C-conjugate vaccine has been in use and has effectively controlled the spread of the disease.

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CHAPTER 43

Poliomyelitis

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INTRODUCTION

Poliomyelitis is an acute infectious disease of humans, particularly children caused by any of three serotypes of human poliovirus.

Persons at risk of polio—*Polio mainly affects children under 5 years of age.*

Polio caseload—Polio cases have decreased by over 99 percent since 1998, from estimated more than 35,000 cases to 871 cases in 2007, 559 cases in 2008, 740 cases in 2009, 42 cases in 2010 and only 1 case of wild polio till 21st November 2011. The reduction is the result of the global effort to eradicate the disease.

HISTORY

Poliomyelitis, the first enteroviral disease to be recognized and the most important one, has a long history.¹ The earliest record is an Egyptian stele of the 18th dynasty (1580 to 1350 BC), which shows a young priest with a withered, shortened leg, the characteristic deformity of paralytic poliomyelitis.^{2,3} Michael Underwood,⁴ a London pediatrician, published the first medical description in 1789 in *A Treatise on Diseases of Children*. During the 19th century, many reports appeared in Europe and the United States describing small clusters of cases of “infantile paralysis.” The authors were puzzled about the nature of the affliction; not until the 1860s and 1870s was the spinal cord firmly established as the seat of the pathologic process. The contagious nature of poliomyelitis was not appreciated until the latter part of the 19th century. Medin, a Swedish pediatrician, was the first to describe the epidemic nature of poliomyelitis (1890), and his pupil Wickman worked out the basic principles of the epidemiology.⁵

The virus first was isolated in monkeys by Landsteiner and Popper in 1908.⁶ The availability of a laboratory animal assay system opened up many avenues of research

that in the ensuing 40 years led to the demonstration that an unrecognized intestinal infection was the usual one and the paralytic disease a relatively uncommon event (Figs 1 and 2).

THE VIRUS

Morphology and Classification⁷⁻¹³

The enteroviruses (coxsackie viruses, echoviruses, polioviruses and newer enteroviruses and paraechoviruses) are single-stranded RNA viruses belonging to the family Picornaviridae (pico = small). They are grouped together because they share certain physical, biochemical, and molecular properties. On electron micrographs, the viruses are seen as 30-nm particles that consist of naked protein capsids constituting approximately 70 to 75 percent of the particles and dense central cores (nucleoloid) of RNA. Enterovirus capsids are composed of four structural proteins: VP1, VP2, VP3, and VP4. The shell is formed by VP1, VP2, and VP3; VP4 is on its inner surface.

The coat proteins protect the RNA genome from nucleases and are important determinants of host range and tropism. They determine antigenicity and they deliver the RNA genome into the cytoplasm of new host cells.

The genome of enteroviruses is a single-stranded, positive-sense RNA molecule.¹

Viral components and complete virions are formed in the cytoplasm of infected cells.

Characteristics and Host Systems^{8,15,16}

Enteroviruses are relatively stable viruses in that they retain activity for several days at room temperature and can be stored indefinitely at ordinary freezer temperatures (– 20°C). They are inactivated quickly by heat (>56°C), formaldehyde, chlorination and ultraviolet light.

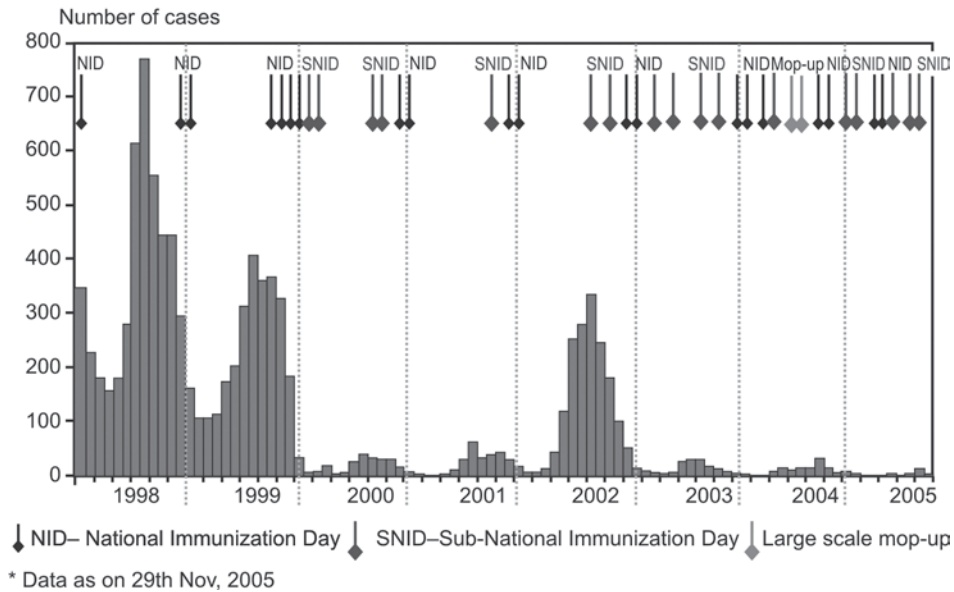


Fig. 1: Monthly incidence of polio in India (January 1998–September 2005) (For color version see plate 4)

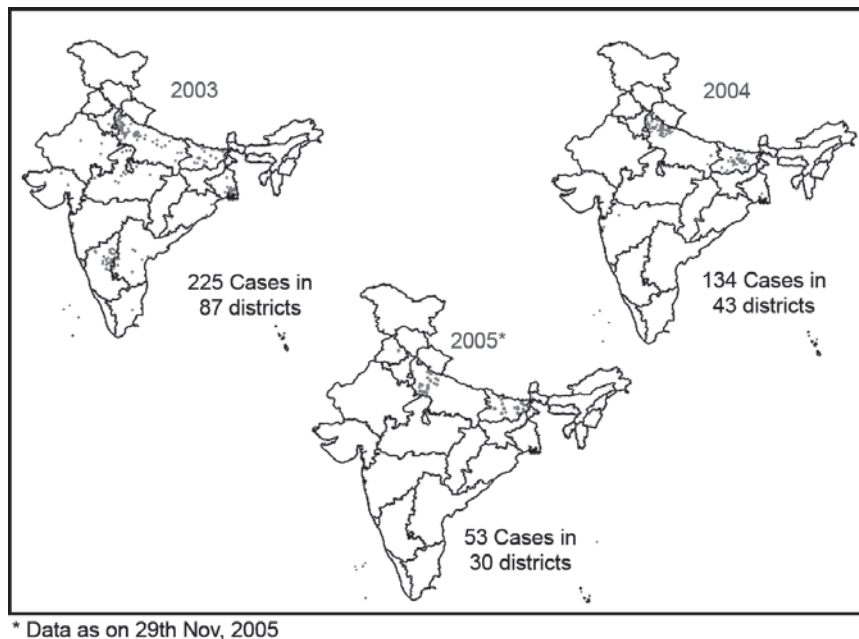


Fig. 2: Location of poliovirus, India 2003–2005 (For color version see plate 4)

Enteroviral strains grow rapidly when adapted to susceptible host systems and cause cytopathology in 2 to 7 days.

Unadapted viral strains frequently require long periods of incubation.

Host Range

Humans are the only natural hosts of polioviruses.

Epidemiology

Transmission

Humans are the only natural hosts of human polioviruses;^{17–24} spread is from person to person by the fecal oral route and possibly the oral-oral (respiratory spread) route. Children are the main susceptible cohort; they are immunologically susceptible, and their unhygienic habits

facilitate spread. Spread is from child to child (via feces to skin to mouth) and then within family groups. Recovery of enteroviruses is related inversely to age, but the prevalence of specific antibodies is related directly to age. The incidence of infection and the prevalence of antibodies do not differ between boys and girls.

Geographic Distribution and Season

Enteroviruses have a worldwide distribution.²⁵⁻²⁷ In any given area, frequent fluctuations occur in predominant types. Epidemics probably depend on newly susceptible individuals in the population rather than reinfection; they may be localized and sporadic and may vary in etiology from place to place in the same year. In temperate climates, enteroviral infections occur primarily in the summer and fall, but in the tropics, they are prevalent all year.^{18,25,27,28}

Pathogenesis and Pathology

Events During Pathogenesis^{8,16,25,29-31}

In Flow chart 1 events of pathogenesis. After initial acquisition of virus by the oral or respiratory route, attachment to the cellular receptor (PVR) takes place. After attachment replication cycle takes 5 to 10 hours and occurs in the cytoplasm, implantation occurs in the pharynx and the lower alimentary tract. Within 1 day, the infection extends to the regional lymph nodes. On approximately the third day, minor viremia occurs and results in the involvement of many secondary infection sites.

Multiplication of virus in secondary infection sites coincides with the onset of clinical symptoms. Illness can vary from minor infections to fatal ones. Major viremia occurs during the period of multiplication of virus in secondary infection sites; this period usually lasts from the third to the seventh day of infection.

Cessation of viremia correlates with the appearance of serum antibody. The viral concentration in secondary infection sites begins to diminish on approximately the seventh day. However, infection continues in the lower intestinal tract for prolonged periods.

In Figure 3, clinical and subclinical events in polioviral infections are presented. By 3 to 5 days after exposure, virus can be recovered from blood, the throat and feces. This finding may be accompanied by symptoms of the “minor illness,” or the infection may be unrecognized clinically. The end of the period of viremia coincides with the appearance of antibodies and the onset of clinical signs of CNS involvement. The available evidence factors blood as the main pathway of CNS invasion in natural disease but experimental infections in monkeys indicate that the virus can travel along the axons of peripheral nerves. Possibly, when tonsillectomy is performed on a child with inapparent poliovirus infection, the virus enters the nerve fibers exposed during surgery and spreads to the cranial nerve nuclei in the brain, thereby resulting in bulbar paralysis.

Flow chart 1: Pathogenesis of enteroviral infections (Modified from Cherry JD: Enteroviruses. In Remington JS, Klein JO (Eds): Infectious Disease of the Fetus and Newborn Infant. Philadelphia: WB Saunders, 1976

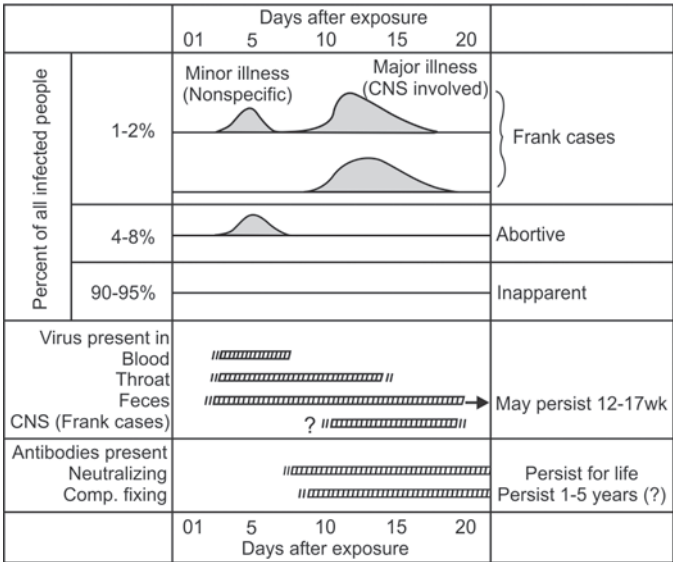
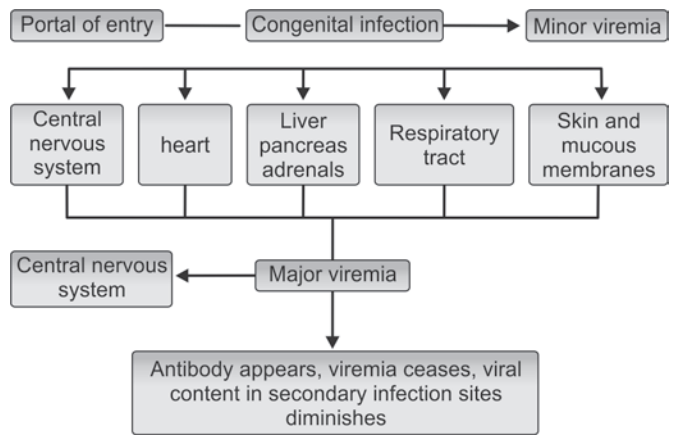


Fig. 3: The course of clinical and subclinical forms of poliovirus infection in relation to the presence of virus and the development of antibodies (From Bodian D and Horstmann D/M Poliomyelitis. In Horsfall FL and TAM I (Eds). Viral and Rickettsial Infections of Man (4th edn.) Philadelphia, JB Lippincott 1965;430-73)

Factors that Affect Pathogenesis

The pathogenesis and pathology of enteroviral infections depend on the virulence, tropism and inoculum concentration of virus, as well as on many specific host factors. Enteroviruses have marked differences in both tropism and virulence. Although some generalizations can be made with regard to tropism, marked differences occur even among strains of specific viral types. Differences in the virulence of specific enteroviral types may be the result of recombination among enteroviruses or point mutations.³²⁻³⁴

Van Eden and Associates³⁵ studied 17 families during an outbreak of poliomyelitis caused by type 1 virus in the Netherlands and their findings suggested that HLA-related genetic factors were important in the occurrence of paralytic disease.

In the past, researchers assumed that specific pathology in various organs and tissues in enteroviral infections was caused by the direct cytopathic effect and tropism of a particular virus. In more recent years, however, a large number of studies using murine model systems have suggested that host immune responses contribute to the pathology. These studies suggest that T cell-mediated processes and virus-induced autoimmunity cause both acute and chronic tissue damage. In contrast, other studies suggest that the primary viral cytopathic effect is responsible for the tissue damage and that the various T cell responses are a reaction to the damage and not the cause of the damage.³⁶

Pathology^{29,37}

The neuropathy of poliomyelitis usually is pathognomonic; only certain cells and areas of the neuraxis are susceptible to the virus. Neuronal damage is caused directly by virus multiplication but not all affected neurons are killed. The injury may be reversible and function may be restored within 3 to 4 weeks after onset. Little histologic evidence of meningeal reaction exists. Perivascular cuffing and some interstitial glial infiltration is present. Histologic sections generally reveal more widespread lesions than would be estimated from the clinical findings. Scattered neurons may undergo considerable destruction without clinical disability.

Regions in which neuronal lesions occur are:

- The spinal cord (anterior horn cells chiefly and to a lesser degree the intermediate and dorsal horn and dorsal root ganglia)
- The medulla (vestibular nuclei, cranial nerve nuclei, and the reticular formation that contains the vital centers)
- The cerebellum (nuclei in the roof and vermis only)
- The midbrain (chiefly the gray matter but also the substantia nigra and occasionally the red nucleus)
- The thalamus and hypothalamus
- The pallidum
- The cerebral cortex (motor cortex). The viruses spare the following areas:
 - The entire cerebral cortex except the motor area,
 - The cerebellum except the vermis and deep midline nuclei
 - The white matter of the spinal cord. This distribution of lesions permits a histological diagnosis of poliomyelitis.

Extraneural pathology usually is a secondary phenomenon. Bronchopulmonary changes such as aspiration

pneumonia, atelectasis and purulent bronchitis may occur because of impaired coughing and decreased thoracic movement. Cardiovascular changes may result in hypertension, cardiac failure and pulmonary edema. Prolonged immobilization leads to negative nitrogen and calcium balance along with urinary lithiasis, renal failure, hypertension with encephalopathy and convulsions. Treatment itself may cause untoward complications, such as urinary tract infection after catheterization, decubitus ulcers and psychotic disturbances. Ulcerations in the alimentary tract may result in serious bleeding and occasional perforation. Respiratory failure culminates in respiratory acidosis and anoxic changes.

Clinical Manifestations^{29,30,37,39,41}

When a susceptible person has had effective contact with a poliovirus, one of several responses may occur in the following order of frequency:

- Inapparent infection
- Minor illness (abortive poliomyelitis)
- Nonparalytic poliomyelitis (aseptic meningitis)
- Paralytic poliomyelitis.

Paralytic poliomyelitis is the most dramatic expression of the infection and the only one clinically recognizable as caused by a poliovirus; it accounts for not more than 1 to 2 percent of infections during epidemics and considerably less under endemic conditions. The aseptic meningitis syndrome is similarly infrequent; nonspecific “minor illness” is estimated to occur in 4 to 8 percent and 90 to 95 percent of those infected have in apparent infections. Factors that determine the type of clinical response are poorly understood but the degree of virulence of the virus and certain host characteristics are important.

Age has a significant effect on patterns of infection; older patients are more likely to have severe paralytic disease and a higher mortality rate. Tonsillectomy in the presence of inapparent infection can precipitate bulbar poliomyelitis; evidence also suggests that tonsillectomy at any time in the past results in enhanced susceptibility to the bulbar form of the disease. Recent diphtheria-tetanus-pertussis vaccination increases the likelihood of development of paralysis; the site of injection and the site of paralysis appear to be correlated. Physical exertion and trauma around the time of onset also increase the risk for severe paralysis.

Minor Illness (Abortive Poliomyelitis)

The minor illness is mild and nonspecific with low-grade fever, malaise, anorexia, and sore throat. Physical examination reveals no significant abnormalities, CSF is normal, and recovery occurs within 24 to 72 hours. The illness often is so mild that it goes unrecognized and patients rarely are seen by a physician.

Nonparalytic Poliomyelitis (Aseptic Meningitis)

The onset of nonparalytic poliomyelitis is associated with vague malaise followed by fever, headache, aching of the muscles and sometimes hyperesthesia and paresthesia. Anorexia, nausea, vomiting, constipation, or diarrhea may also be present. The temperature rises to 37.8° to 39.5°C (101° to 103°F); stiffness of the neck, back, and hamstrings soon appears.

Approximately, two-third of affected children have a short symptom-free interlude between the first phase (minor illness) and the second phase (CNS or major illness). Nuchal and spinal rigidity is necessary for the diagnosis of nonparalytic poliomyelitis during the second phase.

Physical examination reveals nuchal-spinal signs and changes in superficial and deep reflexes. With cooperative patients, the nuchal-spinal signs are sought first by active tests. The child is asked to sit up unassisted. If doing so causes undue effort, if the knees flex upward, and if the patient writhes a bit from side to side while sitting up and uses the hands on the bed for the tripod supporting position, unmistakable spinal rigidity is present. Still sitting, the patient is asked to flex chin to chest and is observed for nuchal rigidity. Alternatively, from the supine position with the knees held down gently, the patient is asked to sit up and kiss the knees. If the knees draw up sharply or if the maneuver cannot be completed adequately, the patient has stiffness of the spine caused by muscle spasm. If the diagnosis still is uncertain, attempts should be made to elicit the Kernig and Brudzinski signs. Gentle forward flexion of the occiput and neck elicits nuchal rigidity, which may precede spinal rigidity. Head drop may be demonstrated by placing the hands under the patient's shoulders and raising the trunk. Normally, the head follows the plane of the trunk but in poliomyelitis, it often falls backward limply. The frequency of the head-drop sign, even in nonparalytic poliomyelitis, with no subsequent residuals indicates that it is not caused by true paresis of the neck flexors. In struggling infants, distinguishing voluntary resistance from clinically important involuntary nuchal rigidity may be difficult. One may place the infant's shoulders flush with the edge of the table, support the weight of the occiput in the hand and then flex the head anteriorly. Nuchal rigidity that persists during this maneuver may be interpreted as involuntary. When not closed, the anterior fontanel also may be tense or bulging.

In the early stages, the reflexes are normally active and remain so unless paralysis supervenes. Changes in reflexes, either increased or depressed may precede weakness by 12 to 24 hours; hence, detecting such changes is important, especially in nonparalytic patients managed at home. The superficial reflexes (i.e. cremasteric and abdominal and the reflexes of the spinal and gluteal muscles) are usually the first to be diminished. The spinal and gluteal reflexes are elicited by tapping segmentally downward on each side

of the spine and buttocks. These reflexes may disappear before the abdominal and cremasteric ones do. Changes in the deep tendon reflexes, whether exaggerated or depressed, generally occur 8 to 24 hours after depression of the superficial reflexes and indicate impending paresis of the extremities. If no further progression of clinical signs occurs, the disease remains nonparalytic, the temperature falls to normal, and signs of meningeal irritation gradually disappear. Recovery ensues in 3 to 10 days, depending on the severity of the illness.

Paralytic Poliomyelitis

The manifestations of paralytic poliomyelitis are those enumerated earlier for nonparalytic poliomyelitis plus weakness in one or more muscle groups, either skeletal or cranial. Patients in whom paralysis is destined to develop often wear an anxious expression; they are extremely alert, restless, and flushed and appear acutely ill. The fever is higher than that in abortive disease, and the patient may have intense muscle pain. Shortly, before actual muscle weakness is detected, the superficial and deep reflexes often diminish or disappear on the affected side. Frequently, a symptom-free interlude of several days occurs between the initial illness phase and the recurrence of symptoms that culminate in paralysis.

The onset of paralysis may be extraordinarily sudden and progress in a few hours to complete loss of motion in one or more extremities. Asymmetric involvement is typical in milder cases. More gradual spread of weakness also occurs and may continue over a period of 3 to 5 days. Bladder paralysis of 1 to 3 days' duration develops in approximately 20 percent of patients and bowel atony is noted commonly, occasionally to the point of paralytic ileus. In general, when the fever subsides, no further paralysis is likely to occur. The lower limbs are affected more commonly than are the upper, but in severe cases, quadriplegia and loss of function of the intercostals, abdominal, and trunk muscles with resultant respiratory difficulty may ensue. The superficial and deep reflexes in the affected limbs are lost; twitching of the muscles and diffuse fasciculation may be seen transiently. Sensory abnormalities are rare occurrences.

Flaccid paralysis is the most obvious clinical expression of the neuronal changes. The ensuing muscular atrophy is caused by denervation plus the atrophy of disuse. The pain, plasticity, nuchal and spinal rigidity, and hyper-tonia early in the illness probably are caused by lesions in the brainstem, spinal ganglia, and posterior columns. Respiratory and cardiac arrhythmias, blood pressure and vasomotor changes, and the like reflect damage to vital centers in the medulla.

On physical examination, the distribution of paralysis characteristically is spotty. To detect mild muscular weakness, one often must apply gentle resistance in opposition to the muscle group being tested. The spinal form has

weakness of some of the muscles of the abdomen, trunk, diaphragm, thorax, or extremities. The bulbar form is characterized by weakness in the motor distribution of one or more cranial nerves, with or without dysfunction of the vital centers of respiration and circulation. Patients with bulbar disease often are extremely agitated, even delirious, or they may become stuporous. The 10th cranial nerve nuclei are involved most commonly and result in paralysis of the pharynx, soft palate, and vocal cords. Facial paralysis occurs less commonly; it is usually asymmetric and involves only selected muscle groups. Ocular palsies are unusual findings.

Components of both the bulbar and spinal forms occur together in bulbospinal poliomyelitis. In the encephalitic form of the disease, irritability, disorientation, drowsiness, and coarse tremors not explained by inadequate ventilation are noted. Even during poliomyelitis epidemics, this form can be recognized only if some peripheral or cranial nerve paralysis coexists or ensues. Hypoxia and hypercapnia caused by inadequate ventilation from respiratory insufficiency may produce disorientation without true encephalitis.

Numerous components acting together may result in insufficiency in ventilation. The most serious consequences are hypoxia and hypercapnia, which may produce profound effects on many other systems. Respiratory insufficiency should be detected early to diminish its widespread effects, and because the situation may shift rapidly, continued clinical evaluation is essential. Despite weakness of the respiratory muscles, the patient may respond with so much respiratory effort that normal alveolar ventilation is maintained. In fact, the increased effort (associated with anxiety and fear) actually may produce over ventilation at the outset and result in respiratory alkalosis. Such effort is fatiguing and soon leads to respiratory failure.

Diagnosis

Clinical Diagnosis

As with all infectious illnesses, knowledge of exposure, incubation time and clinical features is important. Vaccine associated paralytic poliomyelitis (VAPP) should be considered in any child with paralytic disease occurring 7 to 14 days after receiving OPV (and at later times in countries where wild poliovirus has been eradicated and OPV has been administered to the child or a contact.)

Laboratory Diagnosis

CSF is normal in minor illness.

In non-paralytic poliomyelitis (aseptic meningitis), laboratory findings consist of a normal or slightly elevated white blood cell count and the characteristic CSF changes of aseptic meningitis: Approximately 20 to 300 cells, predominantly lymphocytes, a normal glucose level and normal or slightly elevated protein. If a spinal tap is

performed in the first few hours after onset, a predominance of polymorphonuclear leukocytes may be seen but it shifts in 6 to 12 hours to more than 90 percent lymphocytes.

Virus Isolation and Detection Techniques

Most viral diagnostic laboratories have facilities for the recovery of most enteroviruses that cause illness. WHO currently recommends that the laboratory diagnosis of poliomyelitis be confirmed by isolation and identification of wild type and vaccine type strains in the stool. Polioviruses can be separated from other enteroviruses and poliovirus vaccine strains can be identified rapidly by PCR,⁴² along with the wild poliovirus as well.

Treatment

Specific Therapy

No specific therapy for any enteroviral infection presently is approved for use. The antiviral drug pleconaril offers promise for the treatment of enteroviral infections.⁴³⁻⁴⁶ This drug is a novel compound that integrates into the capsid of enteroviruses. It prevents the virus from attachment and subsequent release of viral RNA into the host cell. In a double-blinded, placebo-controlled study of 39 patients with enteroviral meningitis, a statistically significant shortening of disease duration was noted: From 9.5 days in controls to 4.0 days in drug recipients.⁴⁵ Pleconaril also has been used on a compassionate-release basis for the treatment of patients with life-threatening infection.⁴⁶ The following categories of enteroviral illnesses have been treated; chronic meningoencephalitis in patients with agammaglobulinemia or hypogammaglobulinemia, neonatal sepsis, myocarditis, poliomyelitis (wild type or vaccine associated), encephalitis and bone marrow transplant patients. Although these treatments have not had control arms, favorable clinical responses have been observed in 22 of 36 treated patients, including 12 of 18 patients with chronic meningoencephalitis.

Nonspecific Therapy (Mild, Nonspecific Febrile Illness)

In patients in whom fever is the only symptom, careful observation is important. Many patients who eventually become severely ill initially have 2 to 3 days of fever without other localized findings. Care should be taken to administer adequate fluids to febrile infants, and excessive elevation of temperature should be prevented if possible.

Meningoencephalitis

In patients with meningoencephalitis, convulsions, cerebral edema and disturbances in fluid and electrolyte balance, all occur frequently and respond to treatment. Seizures are treated best with phenobarbital, phenytoin, or Lorazepam. Cerebral edema can be treated with urea,

mannitol. Fluids should be monitored closely, and serum electrolyte levels should be determined frequently because inappropriate antidiuretic hormone secretion is a common occurrence.

Management of Poliomyelitis

The broad principles of management are to allay fear, minimize the ensuing skeletal deformities, anticipate and meet complications in addition to the neuromusculoskeletal ones, and prepare the child and family for the prolonged treatment that may be required and for permanent disability when it seems likely. Patients with the nonparalytic and mildly paralytic forms may be treated at home.

Worldwide Cases of Poliomyelitis.

Most patients with paralytic poliomyelitis require hospitalization. A calm atmosphere is desired. Suitable body alignment is necessary to avoid excessive skeletal deformity. A neutral position with the feet at a right angle, knees slightly flexed and hips and spine straight is achieved by the use of boards, sandbags and occasionally, light splint shells. Active and passive motion is indicated as soon as the pain has disappeared. The orthopedist and physiatrist should see these patients as early in the illness as possible and assume responsibility before fixed deformities develop.

Management of pure bulbar poliomyelitis consists essentially of maintaining the airway and avoiding all risks of inhalation of saliva, food, or vomitus. Gravity drainage of accumulated secretions is favored by the head-low (foot of the bed elevated 20 to 25 degrees) prone position with the face to one side. Aspirators with rigid or semirigid tips are preferred for direct oral and pharyngeal use and soft flexible catheters may be used for nasopharyngeal aspiration. Fluid and electrolyte balance is maintained best by intravenous infusion because tube or oral feeding in the first few days may incite vomiting. After the initial few days, sips of sterile water may be given from a spoon, with increments as indicated by the ability to swallow. In addition to close observation for respiratory insufficiency, blood pressure should be recorded at least twice daily. Hypertension is not an uncommon occurrence and occasionally leads to hypertensive encephalopathy. Patients with pure bulbar poliomyelitis may require tracheostomy because of vocal cord paralysis or constriction of the hypopharynx. Most patients with pure bulbar poliomyelitis who recover have little residual impairment; some patients exhibit mild dysphasia and occasional vocal fatigue with slurring of speech.

Impaired ventilation must be recognized early; mounting anxiety, restlessness, and fatigue are early indications for prompt intervention. Tracheostomy is indicated for some patients with pure bulbar poliomyelitis, spinal respiratory muscle paralysis, and bulbospinal paralysis. Unlike other patients on whom tracheostomy is performed, these patients generally are unable to cough, sometimes for many months. Frequent and swift endotracheal aspiration

under aseptic conditions is necessary. Mechanical ventilation often is needed. Patients are fully conscious and aware; terrifying procedures are performed best with an outward atmosphere of calm. Explaining the procedure and having the parents on hand may be helpful. A reduction in thoracic compliance occurs early, and higher than expected pressure gradients may be required to achieve adequate ventilation. Weaning a patient from dependency on respiratory assistance is a torturous process, as is total musculoskeletal rehabilitation. Motivation of the patient and the team of personnel are paramount.

Prognosis: The prognosis for poliomyelitis varies with the degree of muscle involvement. In patients with mild muscle weakness, complete recovery is the rule. If paralysis is present, recovery of muscle function continues for a period of approximately 18 months to 2 years. By 3 months, about 60 percent of the ultimate improvement has been achieved, and by 6 months, 80 percent. The final result depends on the extent and localization of nerve cell damage.

Respiratory failure is responsible for most of the deaths in paralytic poliomyelitis. With the many recent improvements in techniques for handling this complication, the overall mortality rate has been reduced to approximately 4 percent.

Occasionally, new neuromuscular symptoms develop later in life in patients who have had paralytic poliomyelitis.⁴⁷⁻⁵⁴ Although the cause of this late-onset weakness and muscle atrophy (post-polio syndrome) is not understood completely, it is most likely the result of routine attrition of anterior horn cells associated with aging rather than persistent neural infection with polioviruses. However, specific immunopathologic mechanisms possibly play a role in some instances.⁵⁵

Leparc-Goffart and associates,⁵⁶ presented data suggesting the presence of poliovirus-specific genomic sequences in the CSF of patients with post-polio syndrome. However, Muir and colleagues,⁵⁷ who performed similar studies, found no association of chronic neurologic disease with the presence of enteroviral RNA in CSF.

Prevention: There is no cure for polio, it can only be prevented. Polio vaccine, given multiple times, can protect a child for life.

THE GLOBAL POLIO ERADICATION INITIATIVE

The Global Polio Eradication Initiative is spearheaded by WHO, Rotary International, the US Center for Disease Control and Prevention (CDC) and UNICEF. This is the largest public health initiative the world has ever known. Since 1988, some two billion children around the world have been immunized against polio, thanks to the unprecedented cooperation of more than 200 countries and 20 million volunteers, backed by an international investment of US\$3 billion (Figs 4 and 5).

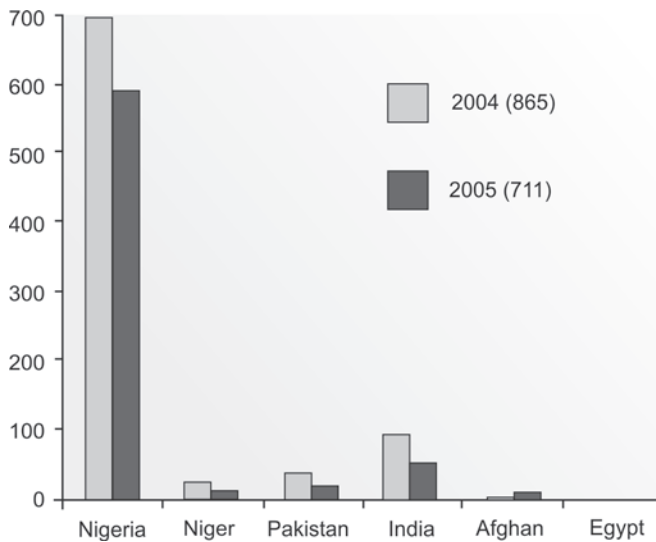
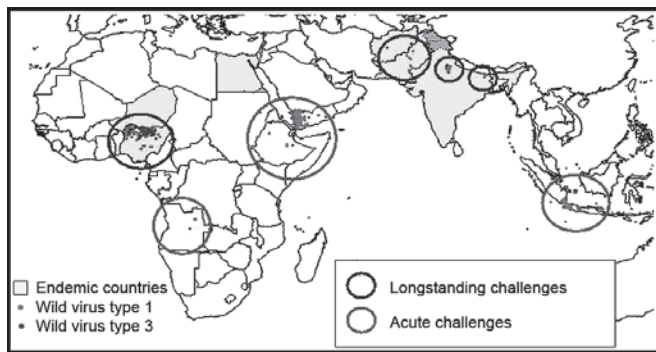


Fig. 4: Worldwide cases of poliomyelitis



Data in WHO HQ, Oct. 2005

Fig. 5: Wild Poliovirus since 1 June 2005
(For color version see plate 4)

The Progress Made

From approximately more than 3.5 lacs cases of wild polio virus from 125 countries across five continents in 1988 to only 1352 cases in 2010 and 520 cases in 2011 till 15th November. They are confined to only five key hot spots in six endemic countries representing a greater than 99 per cent reduction in number of wild poliovirus- the progress made by the eradication initiative is indeed awesome.

The Milestones

- 1991—Last case of polio in America (Peru)
- 1997—Last case of polio in Western Pacific (Cambodia)
- 1998—Last case of polio in Europe (Turkey)

The America, Europe and western pacific regions of the World Health Organization were certified polio-free in 1994, 2000 and 2002 respectively. More than three billion people now live in 134 countries and territories certified polio-free.



Fig. 6: Location of poliovirus, as on 21st November 2011*
(1 case)

Current Status

Poliovirus is more geographically restricted than ever before in history. In 2010, only six countries remained polio-endemic. More than 75 percent of all polio cases worldwide linked to just five key polio hot spots within these countries: Kano (Nigeria), Uttar Pradesh and Bihar (India) and Sindh and North west frontier province (Pakistan).

Importations of poliovirus from endemic to polio-free areas threaten to derail efforts to contain the virus. In the 2002 to 2003 period, for the first time in history, more countries suffered polio cases due to importations than were themselves endemic for the disease.

Indian Scenario

Within India, the greatest risk was in western Uttar Pradesh and Bihar, the only area of India that had never stopped wild poliovirus transmission till 2010 (Fig. 6).

India presents the greatest opportunity for success or failure in stopping polio transmission in 2011. In last two years, India dramatically increased the quantity and quality of its large-scale immunization campaigns. As a result, India now has the lowest-ever levels of poliovirus transmission in the country including two key polio hot spots of Uttar Pradesh and Bihar.

CURRENT SITUATION OF POLIO ERADICATION IN INDIA

Key Findings

- In 2010, total of 42 cases of WPV were reported from total of 4 states all over the country out of which 2 states had imported cases.

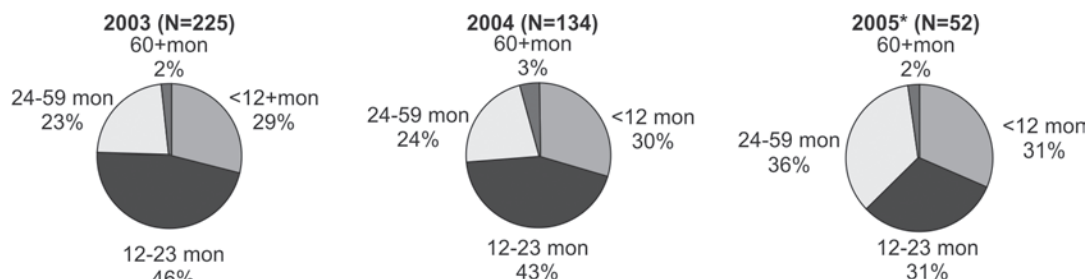


Fig. 7: Wild polio cases by age, 2003-2005*

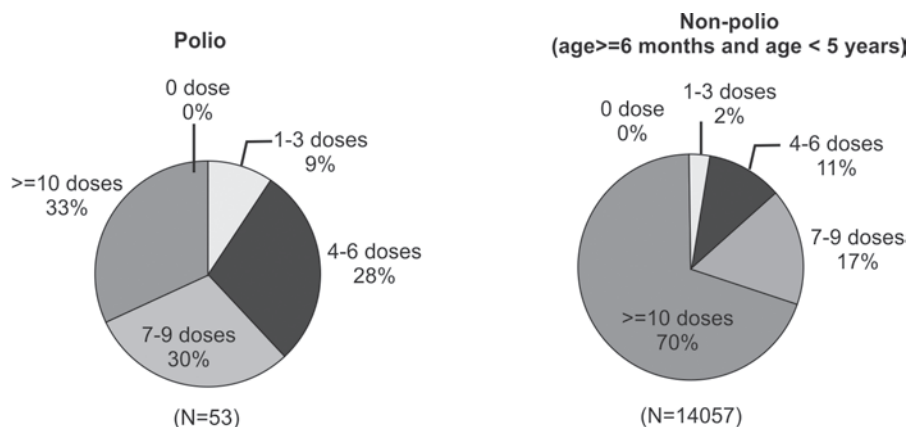


Fig. 8: OPV status of AFP cases, India, 2005*

- Paralytic polio cases were due to P-3 WPV (24 cases) and P-1 WPV (18 cases).
- In the year 2011 till 21st November not a single case of WPV from both the hot states - UP and Bihar.
- P2 WPV is no more in India (last case in Oct 1999).
- In year 2005
 - Majority of the cases (62%) were below 24 months of age (Fig. 7).
 - Community wise break up of WPV Cases: All India cases–52 percent Muslims–48 percent Hindu; (In UP: 58% Muslims, 42% Hindu, in Bihar: 46% Muslims, 54% Hindu).
 - OPV status of WPV cases: Only 9 percent of WPV cases had received 3 or less than 3 doses (Fig. 8).
 - The OPV3 immunization status of children with AFP aged <5 years had substantially improved nationally (98% more than 3 doses), also in most of the North Indian states, particularly in UP and Bihar.

Typical Polio Cases in 2005

- Less than 2 years of age
- Had received >3-4 doses of OPV
- Religious difference narrowed down.

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Vaccines Against Poliomyelitis

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INTRODUCTION

There are two types of polio vaccine.

The Salk vaccine (inactivated polio vaccine, IPV) was developed by Dr Jonas Salk in 1955. It consists of injections of dead (inactivated) polio virus.

The Sabin vaccine oral polio vaccine OPV was developed more recently. This vaccine contains weakened, live virus. It is a liquid that is given by mouth. The trivalent form (TOPV) is effective against all known forms of polio; the monovalent form (MOPV) is effective against one type of polio. Oral polio vaccine is no longer used routinely in the United States.

Oral polio vaccine (OPV) is a suspension of over 1 million particles of poliovirus types 1, 2 and 3. It is supplied with a stabilizing agent, magnesium chloride. It is quite stable under refrigeration.

IPV is formaldehyde-killed poliovirus grown in monkey kidney cells/ human diploid cells containing 20, 8 and 32 antigen units of types 1, 2 and 3 respectively. Enhanced potency IPV (eIPV) that is now available contains 40, 8 and 32 antigen units.

Available Forms

OPV is available as vial containing multi doses, usually 25 doses in ready to use liquid forms. It is a live vaccine. The dose is 2 drops per dose. IPV is available as a single dose vial containing 0.5 ml of vaccine. It is also available as combination vaccines containing IPV + DPT or IPV + DPT + Hepatitis B or IPV + DPT + Hib or IPV + DPT + Hepatitis B + Hib or in combination with DPaT. IPV is now available in India.

Storage

Both OPV and IPV are to be stored in a refrigerator. OPV stocks can be stored frozen; working vials should be stored

at 2 to 8°C in the chiller tray. Once thawed it should not be frozen again as repeated freezing and thawing decreases the potency. Being a live and thermolabile vaccine strict cold chain should be maintained while transporting the vaccine. In the field, the OPV vial in use should be kept on ice. Once a vial is opened, the balance should be discarded and not used again. Nowadays vaccine vial monitors (VVM) are available which change color when subjected to a fixed hours of cumulative exposure to more than 8°C.

OPV is a pink colored solution. It may turn yellow due to changes in pH of vaccine. Such discolored vaccine or presence of visible turbidity in the vaccine is suggestive of growth of bacteria or fungi. Such vaccines should be discarded.

Schedule

OPV is given as 2 drops per orally. The first dose is given at birth – 15 days as zero does OPV. Next 3 primary doses are given at 4 weeks interval starting at 6 to 8 weeks of age. It is given along with 3 primary doses of DPT. Indian Academy of Pediatrics recommends a 5th primary dose at 9 months along with measles vaccine.

Routine Immunization of Infants

All infants should receive a minimum of four doses of oral polio vaccine OPV during their first year of life. Routine immunization provides a basic level of immunity against polio. High routine immunization coverage also reduces the amount of circulating wild poliovirus, thus facilitating eradication.

Supplementary Immunization

National immunization day is a mass campaign that aims to deliver two doses of OPV to all children aged less than five years in an entire country, on a subnational immunization

day (SNID) the same approach is used in a large area of a country. All children are immunized regardless of their prior immunization status. The two rounds are approximately a month apart and are normally conducted during the cool dry season in order to facilitate the logistics and improve the immune response to vaccination. NID's rapidly increase population immunity, particularly intestinal secretory IgA, to high levels that interrupt the circulation of wild polioviruses.

When is the Booster Dose of OPV Given?

Additional dose of OPV popularly known as booster dose of OPV is recommended by Govt. of India under EPI at 15 to 18 months of age along with the 1st booster dose of DPT. Indian Academy of Pediatrics recommends one more dose of OPV at 4 to 6 years of age along with 2nd booster dose of DPT. Govt. of India under EPI does not recommend any more dose of OPV and 2nd booster dose of DPT at 5 years and recommends only DT as 2nd booster at 4 to 6 years of age.

Initially EPI recommended only 3 primary doses in first year of life and one more dose of OPV at 18 to 24 months. The seroconversion and protection with only 3 primary doses was shown to be as less as 60 percent in some studies. This was also proved by the fact that poliomyelitis did occur even in a fully immunized child. Hence, Indian Academy of pediatrics and most of the pediatricians recommend 5 primary doses in first year of life to have better efficacy (80-90% protection) and lesser chances of mishap. Now the EPI recommends an extra OPV during primary schedule as zero dose at birth. As the immunity can wear off and lead to risk of polio by 5 years IAP also recommends one more dose at 4 to 6 years of age.

Efficacy/Seroconversion

The efficacy of 3 doses of OPV in West is around 80 to 90 percent while that in temperate countries like India is only 60 to 70 percent.

The reasons behind poor efficacy in temperate climate are multifocal:

- Poor cold chain maintenance
- Interference by other GI viral infections
- Genetic reasons

The efficacy goes up to 90 percent with 5 doses of OPV in India. Theoretically, one may require 10 to 15 doses of OPV to reach near 100 percent efficacy. This is achieved by pulsing for 3 to 5 years with 2 pulse polio doses every year as has been proved in some countries.

With IPV, sero conversion rates are 90 to 95 percent after 2 doses and 99 percent after 3 doses. It produces excellent humoral immunity as well as local pharyngeal and, possible intestinal immunity.

These antibodies persist for several years after primary immunization with IPV. Study in Tamil Nadu (India)

comparing efficacy of OPV and IPV has shown higher efficacy with latter (66% vs 92%). There were initial concerns that IPV induces lower level of mucosal immunity than OPV and it doesn't get excreted in the stools of vaccines so it may be less efficacious in preventing wild virus circulation. But now studies have shown that enhanced IPV (eIPV) induces adequate amount of IgA formation in nasopharyngeal and intestinal secretions almost equivalent to that induced by oral polio vaccine.

Mechanism of Action

When OPV is given by mouth, the vaccine viruses reach the intensities where they must establish infection (vaccine virus 'take') before an immune response may occur. A high level of gut immunity ensures that vaccinated children would not participate in the chain of transmission of wild (pathogenic) polioviruses.

Poliovirus has been widely studied for many decades, and many significant scientific discoveries have been made during this time. However, research on specific mucosal and cellular immune responses has not been performed until very recently in the history of polio vaccines. The cellular immunity necessary for poliovirus clearance and its role in the development of the disease poliomyelitis are still not well defined. The immunological background of individuals predisposed to contract poliomyelitis is still undefined and further investigations are required to gain a comprehensive picture of the host immune status and susceptibility to polio disease.

Mucosal Responses

Mucosal immunity is the first line of defense for protection against poliovirus infection. IgA was found to be the predominant immunoglobulin class in external secretions and exhibited structural differences compared to IgA found in serum. On mucosal surfaces, IgA exists mainly as a dimeric molecule that possesses a unique secretory component (s.c.) secretory IgA also contains one J chain per four light chains. The structure of S-IgA is thought to help the molecule survive in the harsh environment of low pH and proteases of the intestinal mucosa. The majority of S-IgA is synthesized locally in plasma cells found predominantly beneath the epithelium of secretory surfaces. Another component of S-IgA, the s.c., is found primarily in the mucosal epithelium. The dimer of S-IgA is produced in the plasma cells below the site where s.c. is made. As dimeric IgA passes through the epithelium, it combines with the s.c. portion. The joining of the two molecules completes the S-IgA molecule. Many studies have been performed to establish the concept of a common mucosal immune system where IgA precursor cells emigrate to different mucosal sites such as mesenteric lymph nodes, lamina propria of the small intestine and bronchi, gestational mammary glands, salivary glands, genital

areas, and ocular area to provide protection at these portals of entry into the body.

Salk IPV induces the production of IgM, IgG and IgA antibodies in serum. IPV Salk, however, was found not to induce a significant neutralizing secretory antibody (S-IgA) response in the alimentary tract or nasopharynx. IPV may not induce a good secretory immune response due to the limited amount of antigen that presents itself to the gut associated lymphoid tissue (GALT). A booster effect has been seen in individuals previously primed with IPV Salk upon revaccination with IPV Salk as well as a modest secretory antibody response. Oral poliovirus vaccine induces secretory immune and neutralizing antibody responses in the mucosal sites that are superior to those elicited by IPV. Mucosal immunization (intranasal) with IPV induces a secretory antibody response that is superior to immunization by the parental route. Parenteral administration of IPV – Salk induces much less mucosal immune response, although eIPV has been found to induce more of a mucosal response compared to IPV Salk. Boosting with OPV after immunization with IPV leads to an enhanced S-IgA response. Table 1 summarizes the features of the immune responses induced by conventional inactivated and live vaccines administered by parenteral and mucosal routes, and correlates to responses to vaccination with Salk and OPV, respectively.

Immune responses have been measured in children receiving IX enhanced potency IPV, double strength eIPV, or quadruple strength eIPV and compared to OPV immune responses. Responses to types 1 and 3 poliovirus in eIPV vaccines were compared to those of infants receiving three

doses of OPV at 6, 12 and 18 weeks of age. Secretory IgA responses measured in salivary samples were greater in OPV vaccines compared to any of the IPV groups. Secretory IgA appears to have a role in inhibiting the application of poliovirus at mucosal surfaces. This is exemplified by a study where IgA deficient individuals were found to shed poliovirus for prolonged periods of time after oral vaccination. Even though an enhanced potency formulation of IPV induced better secretory responses compared to earlier IPV formulations, the responses still do not meet or exceed the response elicited by OPV. These data are important for illustrating the difference in immune response elicited by a live-replicating vaccine virus versus a parenterally administered vaccine. To gain the benefit of both vaccines, combination schedules have been investigated. Combination of IPV immunization first with OPV to follow may help prevent vaccine associated disease while still inducing superior local immunity found with OPV vaccination.

T-Cell Responses

Firstly evidence that T-cell responses were important for polio clearance came from individuals with severe T- cell deficiency, these individuals became chronically infected with poliovirus; one individual described in these studies came down with paralytic poliomyelitis.

Polio specific cellular immune responses have recently been studied. The aim of these studies was to begin to understand the participation of cell mediated immune responses in clearance of virus and in the

Table 1: Features of immune responses

<i>Features of response</i>	<i>Response to immunization by indicate route and type of vaccine</i>	
	<i>Parenteral inactivated</i>	<i>Mucosal live</i>
Immunologic response similar to natural infection	–	+
Development of systemic immune response	+	+
Persistence of systemic immune response	±	+
Detection of viral antigen in mucosal surfaces	–	+
Development of secretory immune response	±	+
Persistence of secretory immune response	–	+
Development of secretory immunity in other mucosal sites and milk	–	+
Protection against mucosal natural reinfection	–	+
Protection against systemic disease after natural reinfection	+	+
Development of herd immunity via spread of vaccine virus to contacts	–	+

potential destruction of nervous tissue infected with poliovirus. First step in answering these questions have been to define T- and B cell epitopes on the poliovirus cased. The mouse model has been used to study T-cell responses to polio. T helper and CTL epitopes have been localized in capsid protein VP1 in areas of the protein that were identified as neutralizing antibody recognition sites. Both virus and VP1 capsid protein induced a major histocompatibility complex class I restricted T-lymphocyte response. Vaccine recombinants expressing different portions of the polio capsid proteins VP1, VP2, VP3 and VP4 were used to define regions of the capsid proteins recognized by bulk virus specific CTL population. The CTL population was found to recognize target cells carrying VP1 sequences but not sequences of VP2, VP3 or VP4. In contrast, peripheral blood mononuclear cells of Sabin immunized human donors proliferated to all four capsid proteins. This indicated the presence of T-cell epitopes located in all four capsid proteins. The contribution of CTL response to virus clearance or damage of nervous tissue remains unknown but the studies described have provided a basis to investigate these questions.

Nature of immunologic reactivity after parental or mucosal immunization with Conventional Live or Inactivated Vaccine.

Advantages and Disadvantages

OPV is cheaper and being given orally is more acceptable. It is safe with virtually no side effects. It includes both local gut as well as systems immunity. It leads to excellent herd immunity. Mass vaccination is easier with oral vaccine. IPV is available in injection form and is costlier. It can precipitate paralytic polio in a child who is in incubation

period of wild polio especially during epidemics. Hence OPV is preferred over IPV for routine and mass vaccination (Table 2).

But on the other hand, OPV is less efficacious in tropical climate. It has the potential of vaccine-associated paralysis (VAP) and worldwide experience has proved that polio eradication is not possible just by high coverage of universal immunization with OPV. It also needs strict cold chain maintenance. Whereas IPV is more efficacious, less thermolabile and has no chances of vaccine induced paralysis. Of late even IPV is shown to lead to local gut immunity as well as herd immunity. Good routine coverage of 5 primary doses of IPV can eradicate polio from a country. However, pulsing is easier with OPV than with IPV.

The second major problem with use of OPV is the emergence of circulating Vaccine Derived Polio Viruses (cVDPVs), which are mutants that re-acquire wild virus-like properties and have been in communities with low population immunity especially when polio vaccine coverage rates decline but OPV use continues. The duration and extent of spread of cVDPVs are dependent on the magnitude of the immunity gap. As long as OPV is in use it is mandatory that very high immunization coverage must be maintained so as to decrease the risk of emergence of cVDPV. Whereas VAPP occurs in individual cases, cVDPV can result in large outbreaks.

It has been suggested that mass OPV campaigns should be synchronized with the cessation of OPV use once eradication of wild poliovirus has been achieved, so as to eliminate the risk of VAPP and the emergence of cVDPVs. At the same time, a gradual transition to IPV should be encouraged.

Table 2: Comparison of OPV vs IPV

	<i>OPV</i>	<i>IPV</i>
Type	Live	Killed
Route	Oral	IM
Cost	Cheap	Costly
Storage	2-8° can be frozen	2-8°C (Strictly)
Doses (primary)	5	3
Side effects	Mild	Mild
Vaccine induced paralysis	+	-
(VAP) Injection induced PPT of paralysis	-	+
Efficacy	++	+++
Pulsing	Possible	Difficult
Gut immunity	++	-
Herd immunity	++	-
Use in immune compromised host	No	Yes
Interference with virus isolation	+	-

There are few limitations of IPV as well:

- Virus content is 10,000 times more than OPV hence it is costlier.
- Requires trained personnel to administer.
- No excretion of virus, hence contacts are not benefited.
- Not useful in controlling epidemics.
- Injection is to be avoided in epidemic times, as there is risk to paralysis.
- Lack of feasibility for mass administration.

Herd Immunity

The protection extended to even the unvaccinated by mass vaccination is called as herd immunity. For a disease to occur one needs the infecting organism, the susceptible host and the cycle of transmission. In an endemic area, the cycle of transmission continues from one infected person to another susceptible and so on. Herd immunity in polio is possible in two ways. One is the excretion of vaccine poliovirus, which can infect the unvaccinated susceptible contacts and leads to indirect vaccination. However, as the vaccine virus is an attenuated strain, this may not be very efficacious. The second way of herd immunity is blocking the transmission of poliovirus. When many hosts are vaccinated, especially simultaneously the transmission of wild virus is blocked, as it cannot find a suitable susceptible host. The virus cannot survive in environment for more than 48 to 72 hours. This appears to be a major way of herd immunity and the mechanisms behind the pulse strategy. When 80 to 90 percent of susceptible hosts are vaccinated, the herd effect will protect remaining 10 to 15 percent unvaccinated hosts.

Side Effects

OPV has minimum side effects. It can lead to GI upset like diarrhea, vomiting. It does not lead to fever. The most important but extremely rare side effect with OPV is vaccine-associated paralysis (VAP). It occurs in 1 in million doses. Massive benefits of OPV far outweigh the rare risk of paralysis. In west, though, it can become a medico-legal problem. Hence in west, people use first IPV to induce systemic antibodies and then use OPV, which will lead to local gut immunity without the risk of vaccine induced paralysis due to the partial immunity conferred by prior IPV.

IPV can lead to local side effects like pain, swelling, redness and tiredness in 10 to 20 percent of vaccines. It can lead to fever, which is mild and lasts for 24 to 48 hours. If not given at proper site it can damage important nerves like sciatic nerves if given in gluteal region. Like any other IM injection it can precipitate paralysis in a patient who is already in incubation period of polio, as can occur during polio epidemics. Hence, IPV or any other IM injection should be avoided in an unimmunized sick child with fever especially during seasons of polio epidemics. Lastly, like any other injection, an abscess may form if aseptic precautions are not followed while giving IM injection.

Polio Eradication

Defined as no case of paralytic poliomyelitis by wild poliovirus in last three calendar years along with absence of wild poliovirus in the community, when excellent clinical and virological surveillance exists and the coverage of routine OPV is more than 80 percent. Polio elimination is defined as no case of paralytic poliomyelitis by the wild poliovirus in one calendar year with other criteria being the same as in eradication. Adequate immunization, clinical surveillance and appropriate virological investigations in all children with acute flaccid paralysis (AFP) are the cornerstones of polio eradication.

Pulse Polio Immunization

It is a strategy of mass immunization by which one can eradicate poliomyelitis. Extra doses (pulses) of OPV are given to all children below 5 years of age in an area (like country, state, city) at a time on a given day (or few days). Such pulses are repeated every year. The aim is to achieve 100 percent coverage.

Who Should be Given Pulse Polio Doses?

The aim is to flood the intestines of susceptible hosts by OPV. Hence, all children <5 years of age should receive pulse OPV and this is given even if they have completed their routine OPV, even if they have taken a vaccine in recent past, they are going to receive a vaccine in the recent future, even if they are hospitalized, even if they may have taken or not taken prior pulse doses of OPV. Only very sick children especially in hospital intensive care units, preterm babies, leukemia children or severely immunocompromised children should not be given pulse OPV. Even those who are traveling should receive the pulse dose wherever they are on the day of pulse immunization. Even if a baby is born after the last date of registration or even if the name is not found at a center, pulse OPV must be given at any nearby center.

How does Pulse Immunization Work?

Wild poliovirus can survive either in the intestines of a susceptible host (usually children <5 years of age) or in the sewage water. In the sewage water it can survive only for 48 to 72 hr. And, hence, it has to find shelter into another susceptible host for it to survive and to continue cycle of transmission. When pulse OPV is given to all the children of <5 years of age, the intestines of these children are flooded by vaccine virus and hence wild poliovirus cannot get entry into it. As wild poliovirus cannot survive for more than 48 to 72 hr in environment, its circulation will drastically fall when such pulse is repeated after 6 weeks it still further reduces transmission. Such pulses done every year will ultimately eradicate the wild poliovirus from nature.

How Many Pulses are usually Required?

Strategy of 2-pulses/year as NID and 2 to 4 SNIDs per year takes about 5 years or so of such pulsing in developing countries to eradicate polio. Unfortunately multiple problems of administration and complacency at all levels have delayed eradication in India. Year 2011 has brought some cheer and hope among all the workers who are toiling hard since last 15 years. We may achieve '0' polio status by mid 2012.

Precautions and Contraindications

People who have had severe allergic (anaphylactic) reactions after a previous dose of IPV, or to streptomycin, polymyxin B, or neomycin should not be administered IPV. They should receive OPV. There have been no adverse effects in women who have received IPV during pregnancy; however, in theory it should be avoided. If a pregnant woman is at an increased risk for infection and requires immediate protection, IPV should be administered in accordance with the recommended schedules for adults.

For persons with a disorder or condition that make it hard for the body to fight infection or are immune deficient, the IPV is the only type of vaccine recommended. This includes persons with AIDS, HIV infection, and other immunodeficiency diseases (cancer, leukemia, lymphoma, and so on). It also includes people who are receiving radiation treatments, medications to treat cancer, corticosteroids (such as prednisone), or other immunosuppressive medications.

IPV can be given during breastfeeding and to a child who has diarrhea. Persons who have minor upper respiratory illnesses with or without fever, mild to moderate local reactions to a previous dose of vaccine, current antimicrobial therapy or are in the improvement stage of an acute illness may all still receive the vaccine. Those who are moderately or severely ill should usually wait until they have recovered before receiving the vaccine.

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HIV in Children: Clinical Features and Diagnosis

Triptei Pensi

BACKGROUND

HIV is a preventable infection. The incidence of new HIV infections has leveled off but is not in rapid decline. Approximately 90 percent of all HIV positive people in the world live in developing countries. Many societal factors are driving the spread of the epidemic, including people on the move, complex emergencies, cultural factors, (e.g. the status of women), poverty, stigma, and denial. HIV is most commonly transmitted during high-risk events such as unprotected sex with an infected person; blood-to-blood contact with an infected person; and pregnancy, childbirth, and breastfeeding by HIV positive women.

Globally, the number of children younger than 15 years living with HIV has increased from 1.6 million in 2001 to 2.5 million in 2009. However, the number of newly infected children has been declining since 2003 due to increasing access to prevention of parent-to-child transmission (PPTCT) services. In 2009 alone, globally, 370,000 children under the age of 15 years were newly infected, i.e. around 1,000 a day; and 260,000 died, the majority under the age of five.¹

In India, with 27 million pregnancies annually, and an estimated overall HIV prevalence of 0.48 percent in antenatal women, it is estimated that there are 1,29,600 HIV-infected pregnant women annually.² If no intervention is done, this would mean adding 38,880 infants with HIV infection, using a conservative vertical transmission rate of 30 percent, however, with the present national PPTCT program, this figure should be estimated at approximately 19,440 infants with HIV infection through vertical transmission. HIV disease progresses very rapidly in young children, especially in the first few months of life, often leading to death. HIV infected infants frequently present with clinical symptoms in the first year of life. Without care and treatment, about one third of infants living with HIV will die in their first year of life and almost 50 percent of children by the second year of life.

ROLE OF HIV EPIDEMIOLOGY IN HIV DIAGNOSIS

HIV Types 1 and 2

There are two primary types of HIV that cause AIDS—HIV type 1 (HIV-1) and HIV-2 (Fig. 1). HIV-2 is limited largely to western Africa, whereas the more contagious HIV-1 continues to drive the current pandemic. For this reason, most diagnostic laboratory tests focus on HIV-1; however, most standard ELISA technology will detect antibodies to both HIV-1 and -2. The particular tests needed to identify HIV-2 are sometimes different from those used for HIV-1, and providers must exercise caution when using HIV-1 lab tests in areas with higher rates of HIV-2 infection.

The subtypes of HIV-1 also differ by continent and region. Although most new infections are subtype C, the geographic distribution of HIV-1 subtypes is complex. Africa, for example, has most subtypes but little subtype B, whereas the United States has a higher prevalence of subtype B. Type C is prevalent in India in majority of the region. HIV diagnostic tests detect specific proteins and/or genetic material (i.e. HIV DNA and RNA PCR), and many are designed and engineered for the subtype(s) of HIV in a particular population. Health care workers must be familiar with the distribution of certain subtypes in their region and to understand the potential limitations of diagnostic tests depending on local prevalence

DIAGNOSIS OF HIV INFECTION

Several types of HIV diagnostic tests have been developed. The affordability and availability of these tests vary by country. Diagnostic tests fall into two main categories; antibody tests (HIV rapid tests, HIV enzyme-linked immunosorbent assay [ELISA; also called EIA {enzyme immunoassay}], and Western blot) and virologic tests (HIV DNA polymerase chain reaction [PCR] assays, RNA assays, p24 antigen assays, and viral culture).

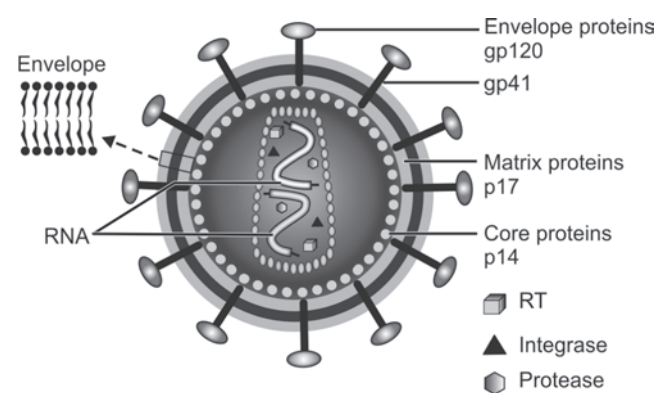


Fig. 1: HIV structure

- Subtype A:** Central Africa sub-Saharan Africa
- Subtype B:** South America, Brazil, United states, Thailand, Europe, Caribbean, India, Japan
- Subtype C:** Brazil, India, South Africa
- Subtype D:** Central Africa, sub-Saharan Africa
- Subtype E:** Thailand, Central African Republic, Southeast Asia
- Subtype F:** Brazil, romania, democratic republic of congo (zaire)
- Subtype G:** Democratic Republic of Congo (Zaire), Gabon, Thailand, Russia, Central
- Subtype H:** Democratic Republic of Congo (Zaire), Gabon, Russia, Central Africa
- Subtype I:** Cyprus
- Subtype O:** Cameroon, Gabon

Type of tests	
Antibody	Virologic
HIV rapid test	HIV-1 DNA PCR
HIV ELISA (also called EIA)	HIV-1 RNA PCR (viral load)
Western blot	Ultrasensitive <i>p24</i> antigen assay test
	HIV culture

COMMON DIAGNOSTIC TEST

Once HIV infection is diagnosed, the stage of infection can be established clinically and immunologically. Staging the severity of the patient’s disease allows health care professionals to determine the best time to initiate treatment with antiretroviral (ARV) therapy.

Antibody Tests

One type of laboratory test used to diagnose HIV is the antibody test. This category of test includes HIV rapid tests, ELISA, and western blot. Antibody tests, as the name suggests, detect the antibodies that are produced during the immune response to HIV.

Because antibody tests are inexpensive and relatively easy to perform, they are the most widely available. Antibody tests have both advantages and disadvantages. Like most lab tests, they can yield false-negative and false-positive results.

False-negative tests occur when HIV-infected individuals do not produce detectable antibodies, such as during the early, acute phase of the infection (“window” period) and the very late stages of infection (when immune suppression is severe and antibodies are no longer being produced in response to HIV infection). Usually, individuals produce antibodies within 6 weeks of infection, and almost all infected individuals have detectable antibodies by 12 weeks postinfection. However, some may take as long as 6 months to make detectible antibodies. For this reason, the World Health Organization (WHO) and NACO^{3,2}

recommends using the antibody test 6 weeks after exposure to HIV because almost all infected individuals will have detectable antibodies (also called seroconversion) by then.

Regardless of exposure history, a negative antibody test should be interpreted with the window period in mind. Also, a negative test does not exclude HIV in an individual with continual or recent exposure to HIV (e.g. breastfeeding infants or persons engaging in high-risk behavior).

The other primary cause of false-negative antibody tests is severe immunosuppression. During the very late stages of HIV-infection, antibody levels can fall so far as to become undetectable. When a false-negative is suspected in the presence of severe clinical symptoms, further testing is required.

One of the most important diagnostic limitations of antibody tests occurs in infants younger than 18 months. During pregnancy, HIV-infected mothers passively transfer immunoglobulin G HIV antibody to the infant through the placenta. The presence of these antibodies means that the infant is exposed and might be infected.

Rapid Test (Fig. 2)

The development of HIV rapid tests in the 1990’s increased access to testing and care, especially in resource-limited settings. These simple antibody tests can be performed at the point of care and have a fast turnaround time, with results available within 15-30 min. These tests are inexpensive (US\$1-\$2 per test) and are ideal for situations in which an immediate result is necessary (e.g. a pregnant woman in labor). Also, they can be done with a simple heel, toe, or finger prick. Rapid tests are highly sensitive (99.3-100%) and specific (98.6-100%). (A sensitivity of 99.3 percent means that the test is falsely negative only 0.7 percent of the time, and a specificity of 98.6 percent means that the rapid test is falsely positive only 1.4 percent of the time.). Like all diagnostic tests, rapid tests need to be interpreted within the context of the clinical situation. The window period needs to be considered any

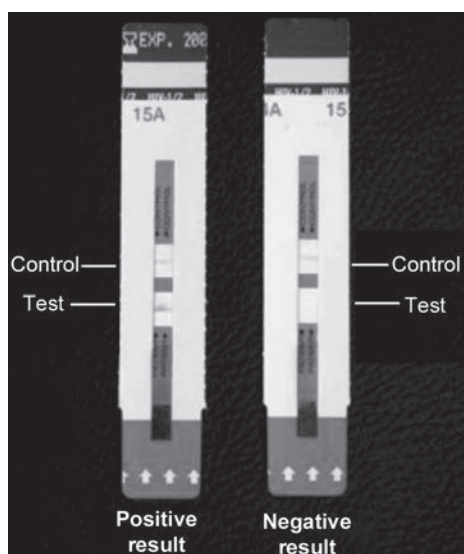


Fig. 2: Rapid slide test

time that there is a negative rapid test, and positive rapid tests need to be interpreted with care in infants.

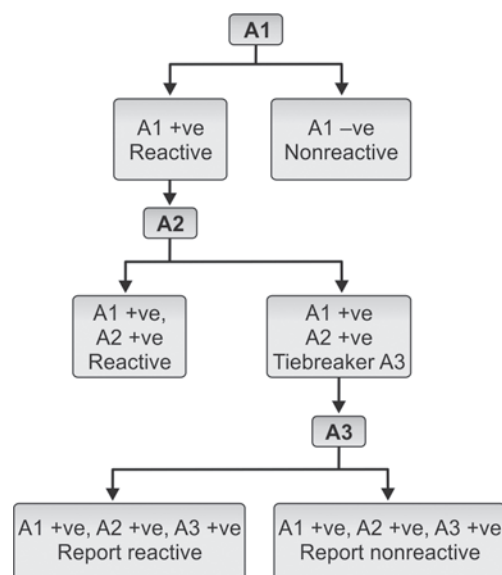
Rapid Antibody Test

ELISA: Like the rapid test, ELISAs (also called EIAs) are inexpensive and highly sensitive in identifying antibodies to HIV (meaning rarely falsely negative). Though several conditions can cause an ELISA to be falsely positive—autoimmune disease, certain viral infections, syphilis, hematologic malignancies, pregnancy, and recent blood transfusions—the test is also specific (rarely falsely positive). Compared to the HIV rapid test, however, ELISA has several disadvantages, including the need to perform a venous blood draw (rather than a simple skin prick), the need for laboratory facilities, and the longer turnaround time for results.

Because of the low levels of antibodies during the window period, the first generation of ELISAs were frequently falsely negative for a long time after initial infection. Fourth generation have been developed to capture existing antibodies at lower levels. With each successive generation of ELISA's, the window period has decreased significantly and the test has become more useful.

ELISAs usually require serum samples for processing, but tests that use urine or oral fluid have also been developed. ELISA is usually a qualitative (i.e., positive-negative type) test, but semiquantitative ELISAs have also been developed. These tests can estimate the amount of antibody present and detect trends in the quantity of antibody over time. Although these tests are potentially useful in monitoring the decrease in an infant's maternal antibodies during late infancy, they are less useful in the

Flow chart 1: HIV testing strategy IIB (blood/plasma/serum)
Adapted from NACO (2007) antiretroviral therapy guidelines



first months of life and are not included in most current guidelines.

A negative ELISA does not require confirmatory testing, provided that the patient was not tested during the window period. A positive ELISA, however, should be confirmed with a Western blot assay to further minimize the possibility of a false result (Flow chart 1).

But Western Blot is rarely used nowadays, except for research purpose.

National testing guidelines for children above five years:

The guidelines are same as adults that for symptomatic person the sample should be reactive with two different kits (Flow chart 1). For asymptomatic case the sample should be positive with three different kits (Flow chart 2) i.e., with different principals. The blood sample collected is tested with first kit, if it is reactive then it is retested sequentially with second and third kits.²

Western Blot

Western blot is another category of antibody test that detects the presence of antibodies against specific HIV proteins. Western blots are typically used to confirm a reactive ELISA result. The Western blot test is a polyacrylamide gel electrophoresis that detects several proteins that are specific to HIV antibodies (*p24*, *gp41*, *gp120*, *gp160*). If these proteins are not seen, the Western blot is negative. If most or all of the proteins are seen, the Western blot is positive. A negative Western blot indicates that the positive ELISA or rapid test was a false-positive. A positive Western blot confirms the presence of HIV-1 antibodies. An indeterminate Western blot could mean early infection or, in an uninfected, exposed infant, the partial loss

However, p24 lab equipment is not yet commercially available on a scale that would allow national coverage, and the recent decrease in the price of other virologic tests (e.g. DNA and RNA PCR) has decreased p24's price advantage.

HIV Culture

HIV culture is a virologic test that requires incubating peripheral blood cells from a patient to determine the presence of HIV in the blood sample. The sensitivity of HIV culture is the same as that of DNA PCR. However, HIV culture is expensive and time consuming, taking up to 6 weeks to obtain results, it is therefore used for research only. HIV culture is also unavailable in most settings and is no longer the test of choice for diagnosis of HIV in infants, children, or adults.

DBS AND HIV TESTING

Until recently, HIV testing required a phlebotomist, a centrifuge, and quick transport of the serum sample between the health clinic and the lab. The development of the DBS collection method has eliminated many of these logistical barriers and has provided increased access to HIV testing.

DBS simplifies blood sample collection and, owing to its high stability, allows for convenient sample handling and transport. Only a few drops of blood are required from a finger, toe, or heel stick, which are collected on special filter paper. The DBS cards are then dried; specially packaged; stored in a plastic, zip-locked bag; and transported to the lab at room temperature. See the "How to collect DBS" text box for more information on this collection technique (Fig. 3).

DBS collection has been used successfully to perform virologic and antibody tests, including DNA PCR, RNA PCR, p24 antigen detection, and ELISA. Both DNA and RNA DBS samples are stable for more than a year when properly collected and stored. DNA PCR using DBS technology is as accurate as DNA PCR testing on whole blood (sensitivity of 100% and specificity of 99.6%). Testing programs using DBS are currently being implemented in various countries, and they have greatly facilitated the early infant diagnosis of HIV.

Antibody Testing in Infants

Early diagnosis and treatment of HIV can greatly affect child survival. The high mortality rates of infected infants underscore the importance of early diagnosis. Without interventions, up to 30 percent of infants born to HIV-positive mothers are infected during pregnancy, delivery, and breast-feeding. Median infant survival time after HIV infection in infancy is just over a year. Without treatment, one in five HIV-infected infants dies before 6 months, more than a third die by 1 year, and more than half die before 2 years.

Diagnostic testing for HIV-1 in infants younger than 18 months differs from that for older children, adolescents, and adults because of the presence of maternal antibodies. HIV-specific immunoglobulins such as immunoglobulin G HIV antibodies are passively transferred to the infant across the placenta. The mean age for clearing maternal antibody is just over 10 months, but maternal antibodies may persist in the infant until 18 months of age.

Because antibodies are transferred to the fetus during pregnancy, antibody tests such as rapid tests and ELISA are positive in all newborns of HIV-infected mothers, including infants who are not infected. Even if an infant becomes infected and begins making his or her own antibodies, antibody tests cannot differentiate between antibodies from the mother and those from the infant. Therefore, a positive antibody test in infancy indicates that an infant has been exposed and may or may not be infected.

Despite these factors, HIV antibody testing is still a useful screening tool later in infancy. Up to 93 percent of 9-month-old HIV-uninfected infants and 95 percent of 12-month-old HIV-uninfected infants will have lost their maternal antibodies. For this reason, a positive test later in infancy is more likely to indicate HIV infection. Many national guidelines recommend first doing a rapid test in infants aged 9 months to see if they are still antibody positive and then doing the more expensive virologic testing on those that still have circulating antibodies. This approach provides health care providers with a simple and relatively inexpensive strategy to exclude HIV infection in many infants aged 9 months because uninfected infants are likely to be antibody negative at that time.

Virologic Testing in Infants

During early infancy, when maternal HIV antibodies can complicate the interpretation of antibody tests, virologic tests can be used to determine whether the infant is HIV infected. Virologic testing is becoming increasingly available worldwide and has an increasing role in guiding early clinical decisions related to feeding choices, cotrimoxazole prophylaxis, and early HIV care and treatment.

In countries in which pediatric ARV therapy and infant formula are readily available and resources permit multiple tests, infants of HIV positive mothers are tested at 14 to 21 days, 1 to 2 months, and 4-6 months. Some experts also recommend testing at birth to capture those infected during pregnancy. However, this approach is not practical in resource-limited settings, where often only one virologic test is available per child.

In these settings, the DNA PCR test is often performed at 6 weeks of age or at the earliest clinical encounter thereafter. Testing at 6 weeks allows the provider to detect prenatal and perinatal infections and ensures that exposed infants begin to integrate into the child health care system (e.g. for immunizations and cotrimoxazole prophylaxis).

1. Fill out appropriate paperwork: DBS card lab order form, clinic logbook.

2. Choose the puncture site

Small infants (<4 mos, <5 kg)

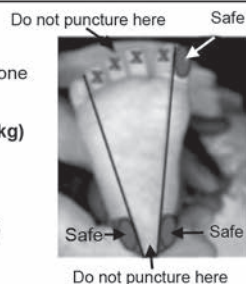
- Puncture the **heel**
- Not finger, since risk of hitting bone

Medium infants (4-10 mos, 5-10 kg)

- Puncture the **toe**
- If malnourished, still use heel

Larger infants (>10 mos, >10 kg)

- Puncture 4th finger
- Slightly lateral side



3. Warm the puncture site



4. Wash hands, put on gloves



5. Position baby with foot down

6. Clean the site with an alcohol swab and allow to dry for 30 seconds



7. Press lancet on to site, prick skin

8. Wipe away first drop



9. Allow large drop to collect

10. Touch blood drop to card

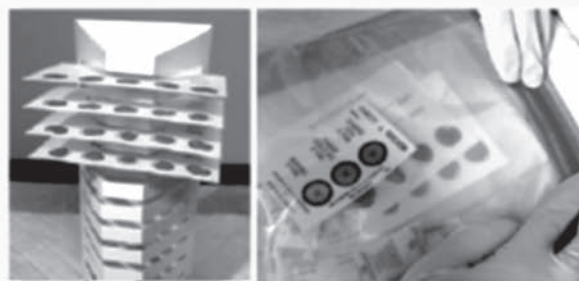
11. Fill entire circle with drop

12. Fill all 5 circles (at least 3)

13. Apply mild pressure and clean the puncture site



14. Dry and package the DBS samples for storage and transport to the laboratory



Job well done!



Fig. 3: Method of collection of DBS sample (Photos courtesy of Julian Kim, MD: Baylor Initiative for Paediatric AIDS 2010)⁴
(For color version see plate 5)

In our National program NACO facilitates a second testing for reactive infants again at 6 months of age. However the gold standard for HIV infection conformation still remains antibody testing at 18 months. When HIV DNA

is used for diagnosis, the use of HIV drugs for PPTCT in mother or infant does not affect the test results.

If resources permit, a second DNA PCR test can be done 6 weeks after breastfeeding has stopped. Because

HIV exposure ends when a child is weaned from breast milk, this second DNA PCR allows for a definitive diagnosis in these children. DNA PCR tests are useful in other clinical scenarios as well, such as when an exposed infant older than 9 months with an unknown HIV status has a positive rapid test. Most HIV negative infants are antibody negative by 9 months, and DNA PCR testing can offer a definitive diagnosis in this case. Finally, even if an infant has an initial DNA PCR test that is negative, the test should be repeated if the infant later develops signs and symptoms of HIV infection

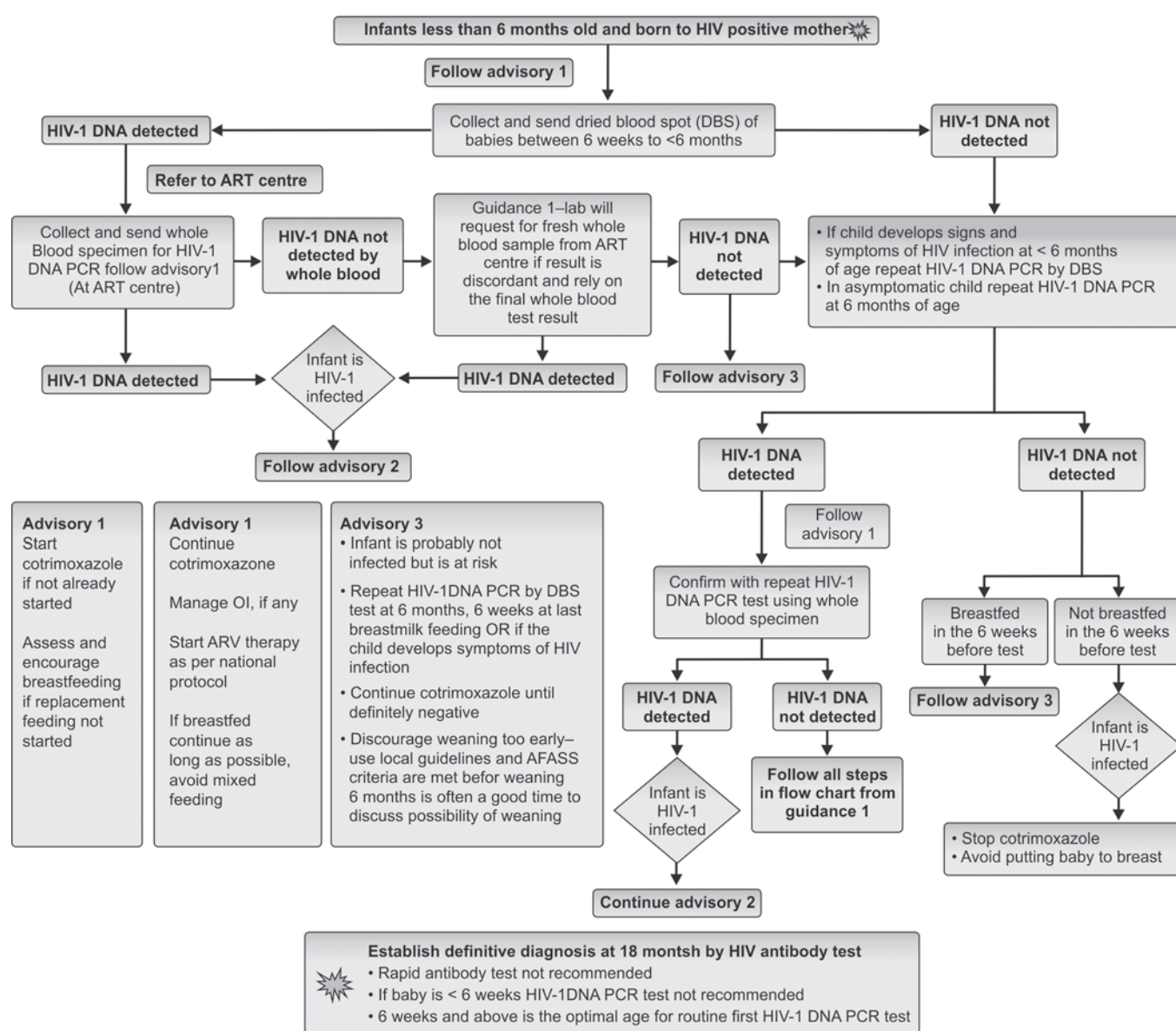
The Pediatric Technical Resource Group at NACO has provided testing algorithms for infants up to six months (Flow chart 3) and 6 to 18 months for confirmation of HIV infection in exposed infants (Flow chart 4).⁵

Additional algorithms used in other guidelines are given in annexure (I, II, III)

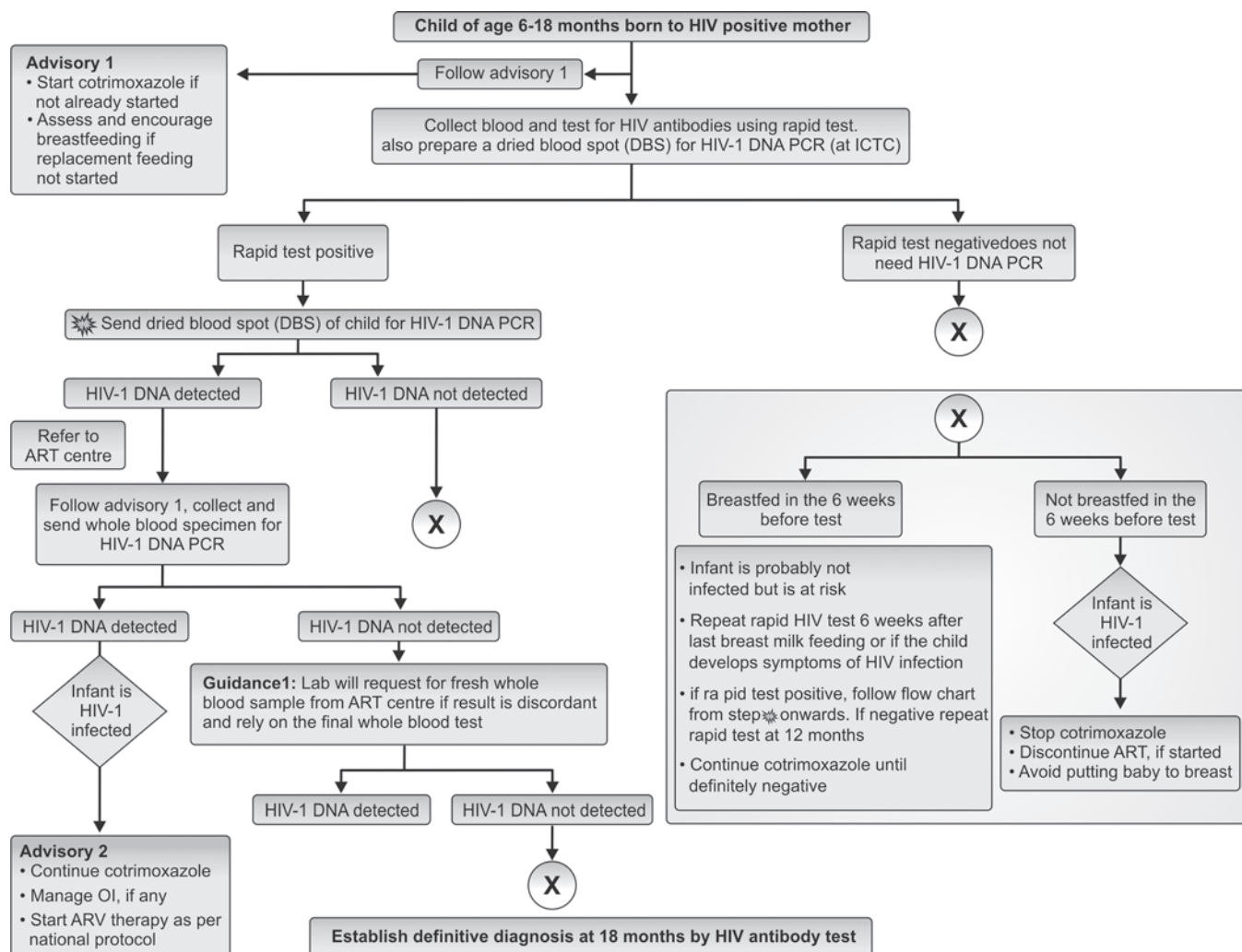
Presumptive diagnosis where there is no virologic testing available
If the child is less than eighteen months of age and has symptoms and signs that are suggestive of HIV infection and there is no virologic testing available, it is possible to make a presumptive diagnosis by addressing the following situation and by the help of the given table the child can be presumed positive the HAART is to be started in order to reduce the mortality in infants born to HIV positive mothers in resource limited settings (Flow chart 5).

- Does the child meet the clinical criteria for presumptive diagnosis of severe HIV infection?
- Is there evidence of HIV exposure—mother or baby's serology shows HIV antibody positive?

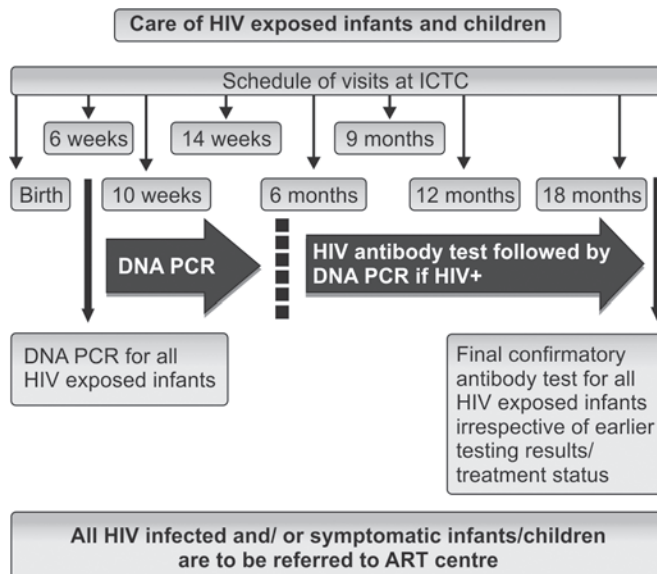
Flow chart 3: Management of a child <6 months born to an HIV positive mother



Flow chart 4: Management of a child 6-18 months born to a HIV positive mother



Flow chart 5: Care of a child born to a HIV positive mother



- Is there evidence of immune suppression (low CD4 count/%) and/or symptoms or illnesses consistent with HIV infection?

Clinical criteria for presumptive diagnosis of severe HIV disease in infants and children less than 18 months of age requiring ART in situations where virological testing is not available

A presumptive diagnosis of severe HIV disease should be made if:
The infant is confirmed HIV antibody positive; and
Diagnosis of any AIDS-indicator condition (s) can be made; or
The infant is symptomatic with two or more of the following:

- Oral thrush;
- Severe pneumonia;
- Severe sepsis.

Other factors that support the diagnosis of severe HIV disease in an HIV seropositive infant include:

Recent HIV-related maternal death; or advanced HIV disease in the mother;
CD4 <20%.

Confirmation of the diagnosis of HIV infection should be sought as soon as possible.

Notes: As per IMCI definition:

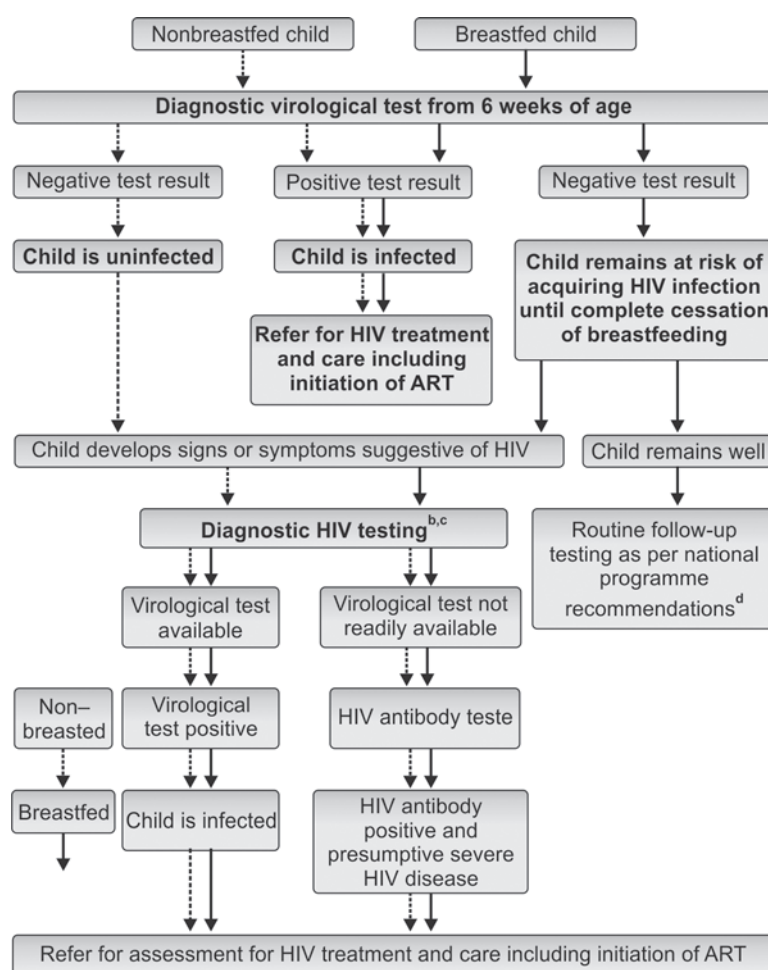
1. *Oral thrush*: Creamy white to yellow soft small plaques on red or normally colored mucosa which can often be scraped off (pseudo membranous), or red patches on tongue, palate or lining of mouth, usually painful or tender.
2. *Severe pneumonia*: Cough or difficult breathing in a child with chest indrawing, stridor or any of the IMCI general danger signs, i.e. lethargic or unconscious, not able to drink or breast-feed, vomiting, and presence or history of convulsions during current illness; responding to antibiotics.
3. *Severe sepsis*: Fever or low body temperature in a young infant with any severe sign such as fast breathing, chest indrawing, bulging fontanelle, lethargy, reduced movement, not feeding or sucking breast milk, convulsions, etc.

Virologic Testing and Infant Feeding (Flow chart 6)

Appropriate infant feeding is crucial to a child's well-being and survival. Infant feeding counseling in the context of HIV should aim to provide the best possible nutrition to optimize growth, development, and survival while also preventing HIV transmission as much as possible. Nutritional counseling needs to balance the risk of HIV transmission through breast milk with the risks of replacement feeding—improper infant replacement feeding itself can lead to severe malnutrition and death.

For each patient, one must assess the acceptability, feasibility, affordability, sustainability, and safety (AEASS) criteria of replacement feeding to ensure that it

Flow chart 6: Evaluation of breast and nonbreast fed child



- a. The risk of HIV transmission remains if breastfeeding continues beyond 18 months of age.
- b. Infants over 9 months of age can be tested initially with HIV antibody test, as those who are HIV AB negative are not usually HIV infected, although still at risk of acquiring infection if still breastfeeding.
- c. In children older than 18 months antibody testing is definitive.
- d. Usually HIV antibody testing from 9 to 18 months of age
- e. Where virological testing is not readily available HIV antibody testing should be performed, it may be necessary to make a presumptive clinical diagnosis of severe HIV disease in HIV seropositive children (see box 1) confirmation of diagnosis should be sought as soon as possible.

is appropriate. Replacement feeding is possible only with access to clean water, a steady income to purchase formula and other supplies, fuel for safe preparation, HIV disclosure in the household, safe storage, and an understanding of the importance of proper preparation and delivery of formula.

In settings where replacement feeding with formula does not fulfil AFASS criteria, the WHO recommends exclusive breastfeeding for the first 6 months of life unless AFASS criteria can be fulfilled before then. Because HIV-positive mothers in many resource-limited areas cannot fulfil AFASS criteria, they are counseled to exclusively breastfeed. In these cases, the infant's need for adequate nutrition requires continued HIV exposure.

Clinical Staging of HIV Infection

Children infected with HIV often have severe disease when first evaluated, or they may develop AIDS over time, much like adults. Immunologic and clinical categories are used to evaluate the HIV disease status in children and to make treatment decisions.

Primary Infection or Acute Retroviral Syndrome

Primary infection refers to the time when HIV first enters the body. At the time of primary infection with HIV, a person's blood carries a high viral load, meaning that there are many individual viruses in the blood. The number of copies of virus per milliliter of plasma or blood can exceed 1 million. An acute retroviral syndrome is mainly encountered in adults and occasionally in older children and adolescents. Signs and symptoms of acute retroviral syndrome include fever, myalgia (muscle pain), headache, nausea, vomiting, diarrhea, night sweats, weight loss, and rash. These signs and symptoms usually occur 2–4 weeks after infection, subside after a few days, and often are misdiagnosed as influenza or infectious mononucleosis.

During primary infection, the CD4+ count in the blood decreases remarkably but rarely drops to less than 200 cells/ μ L. The virus targets CD4+ cells in the lymph nodes and the thymus during this time, making the HIV-infected person vulnerable to opportunistic infections and limiting the thymus's ability to produce T lymphocytes. HIV antibody testing using an enzyme-linked immunosorbent assay (ELISA) or enzyme immunoassay may yield positive or negative results depending on the time of seroconversion. DNA PCR and RNA PCR will be positive, but confirmation with Western blot analysis may yield an indeterminate result because seroconversion can take up to 2–8 weeks to occur. The average time to seroconversion is 25 days. This stage is not much appreciated in young children and in children who are infected by parents.

Clinical Latency/Asymptomatic Disease (Clinical Stage 1)

Although patients recently infected with HIV usually experience a “clinically latent” period of years between HIV infection and clinical signs and symptoms of AIDS, evidence of HIV replication and host immune system destruction exists from the onset of infection. Early during this time, referred to as Clinical Stage 1, the immune system produces antibodies in an attempt to protect itself from HIV. This is when the “viral set point” is established. The viral load of the set point can be used to predict how quickly disease progression will occur. People with higher viral load set points tend to exhibit more rapid disease progression than those with lower viral load set points.

During latency, HIV-infected patients may or may not have signs and symptoms of HIV infection though persistent lymphadenopathy is common. In HIV-infected adults, this phase may last 8–10 years and is very short 20–40 weeks in children less than 12 years. The HIV enzyme-linked immunosorbent assay and Western blot or immunofluorescence assay will be positive. The CD4+ count is greater than 500 cells/ μ L in children over 5 years of age.

Mild Signs and Symptoms of HIV (Clinical Stage 2)

HIV-infected people may appear to be healthy for years, and then minor signs and symptoms of HIV infection begin to appear. They may develop candidiasis, lymphadenopathy, molluscum contagiosum, persistent hepatosplenomegaly, papular pruritic eruptions, herpes zoster, and/or peripheral neuropathy. The viral load increases, and the CD4+ count falls to between 350–499/ μ L in children older than 5 years. Once patients are in this stage they remain in stage 2. They can be reassigned stage 3 or 4 if a condition from one of those occurs, but they cannot be reassigned to Clinical Stage 1 or 2 if they become asymptomatic.

Advanced Signs and Symptoms of HIV (Clinical Stage 3)

HIV-infected patients with weakened immune systems can develop life-threatening infections. The development of cryptosporidiosis, pulmonary and lymph node tuberculosis, wasting, persistent fever (longer than one month), persistent candidiasis, recurrent bacterial pneumonia, and other opportunistic infections is common. These patients may be wasting, or losing weight. Their viral load continues to increase, and the CD4+ count falls to less than 200–349 cells/ μ L in children older than 5 years.

Clinical Stage 4

Patients with advanced HIV disease, or AIDS, can continue to develop new opportunistic infections, such as

Pneumocystis jirovecii pneumonia (formerly *Pneumocystis carinii* pneumonia), cytomegalovirus infection, toxoplasmosis, *Mycobacterium avium* complex, cryptococcal meningitis, progressive multifocal leukoencephalopathy, Kaposi sarcoma and other infections that commonly occur with a severely depressed immune system. The viral load is very high, and the CD4+ count is less than 200 cells/ μ L in children older than 5 years. At this point in the disease course death can be imminent.

Who Clinical Classification

WHO Clinical Classification (Table 1)³

Table 1: WHO clinical classification

Clinical stage 1

Asymptomatic

Persistent generalized lymphadenopathy

Clinical stage 2⁽ⁱ⁾

Unexplained persistent herpatosplenomegaly

Papular pruritic eruptions

Fungal nail infections

Angular cheilitis

Lineal gingival erythema

Extensive molluscum contagiosum

Recurrent oral ulceration

Unexplained persistent parotid enlargement

Herpes zoster

Recurrent or chronic upper respiratory tract infections (otitis media, otorrhea, sinusitis, tonsillitis)

Clinical stage 3⁽ⁱ⁾

Unexplained moderate malnutrition or wasting not adequately responding to standard therapy

Unexplained persistent diarrhea (14 days or more)

Unexplained persistent fever (above 37.5°C, intermittent or constant, for longer than one month)

Persistent oral candidiasis (after first 6-8 weeks of life)

Oral hairy leukoplakia

Acute necrotizing ulcerative gingivitis or periodontitis

Lymph node tuberculosis

Pulmonary tuberculosis

Severe recurrent bacterial pneumonia

Symptomatic lymphoid interstitial pneumonitis

Chronic HIV-associated lung disease including bronchiectasis

Unexplained anemia (<8.0 g/dl), neutropenia ($< 0.5 \times 10^9/L^3$) and or chronic thrombocytopenia ($< 50 \times 10^9/L^3$)

Clinical stage 4^{(i) (ii)}

Unexplained severe wasting, stunting or severe malnutrition not responding to standard therapy

Pneumocystis pneumonia

Recurrent severe bacterial infections (e.g. empyema, pyomyositis, bone or joint infection, meningitis, but excluding pneumonia)

Chronic herpes simplex infection; (orolabial or cutaneous of more than one month's duration, or visceral at any site)

Extrapulmonary tuberculosis

Kaposi sarcoma

Esophageal candidiasis (or Candida of trachea, bronchi or lungs)

Cytomegalovirus (CMV) infection; retinitis or CMV infection affecting another organ, with onset at age over 1 month

Cental nervous system toxoplasmosis (after the neonatal period)

Extrapulmonary cryptococcosis (including meningitis)

HIV encephalopathy

Disseminated endemic mycosis (extrapulmonary histoplasmosis, coccidiomycosis)

Chronic cryptosporidiosis (with diarrhea)

Chronic isosporiasis

Disseminated non-tuberculous mycobacteria infection

Cerebral or B cell non-Hodgkin's lymphoma

Progressive multifocal leukoencephalopathy

HIV-associated cardiomyopathy or nephropathy

(i) Unexplained refers to where the condition is not explained by other causes.

(ii) Some additional specific conditions can be included in regional classifications (e.g. disseminated Penicilliosis in Asia, HIV associated rectovaginal fistula in Africa), and reactivation of American trypano somiasis.

Pictorial of Clinical Staging (Adapted from Bpai)⁴

Figure 4 shows the common manifestation of WHO clinical staging diseases.

Immune Staging of HIV Infection

CD4 counts and percentage values in healthy infants who are not infected with HIV are considerably higher than values than observed in uninfected adults and slowly decline to the adult values by five years. Clinicians interpreting CD4 must consider age as a variable. In children younger than age five years, the absolute CD4 count tends to vary more with age than does CD4 percentage. Therefore, HIV exposed infants and children younger than age 5 years, CD4 percentage is preferred for clinical assessment of degree of immune suppression and monitoring immune recovery, whereas absolute CD4 count can be used in older children (Table 2).

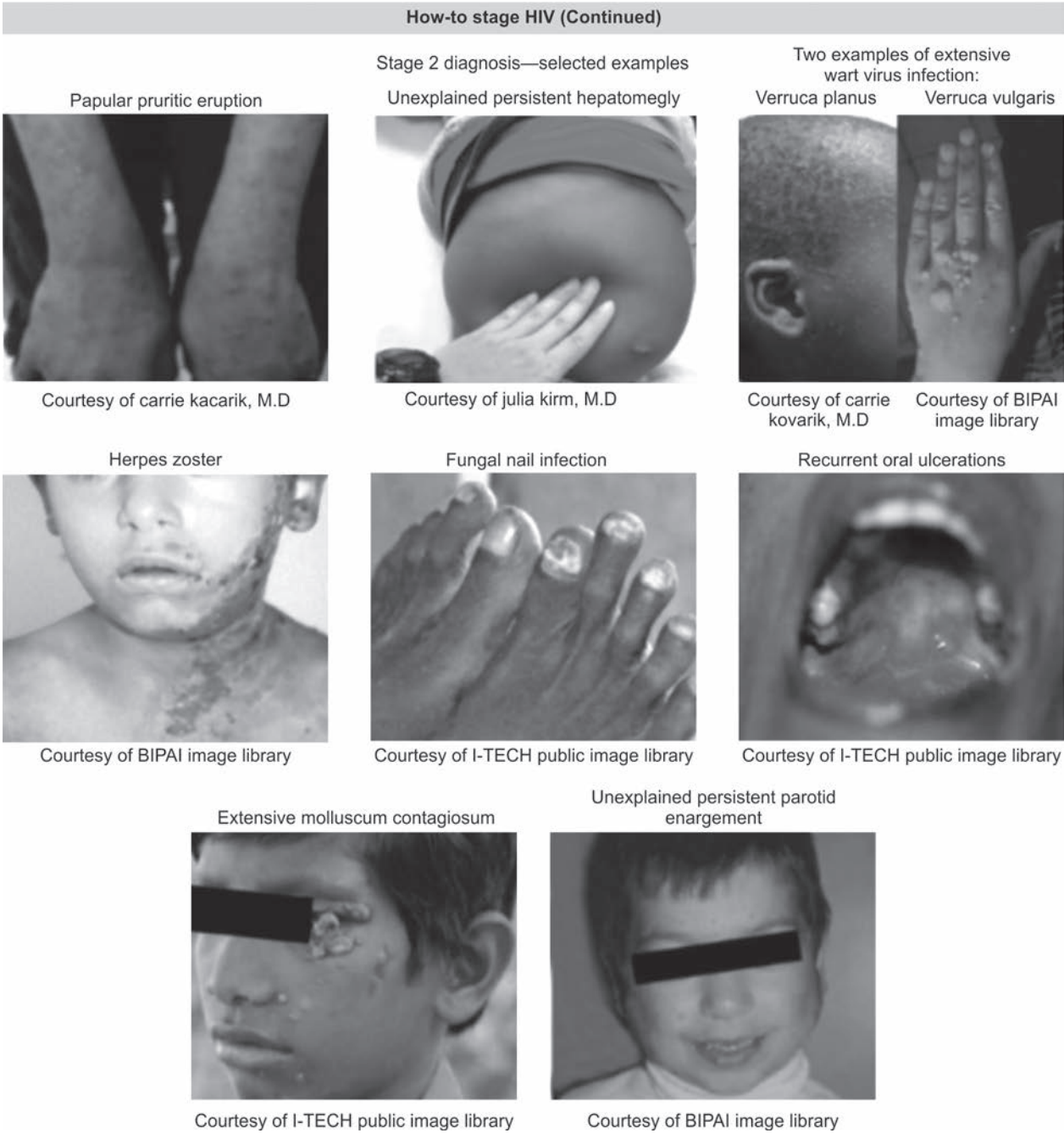


Fig. 4: Common manifestations of WHO clinical estaging diseases (For color version see plate 6)

Table 2: Classification of HIV associated immunodeficiency				
Classification of HIV-associated immunodeficiency	Age-related CD4 values			
	≤ 11 months (%)	12-35 months (%)	36-59 months (%)	≥ 5 years (cells/mm ³)
Not significant	> 35	> 30	> 25	> 500
Mild	30-35	25-30	20-25	350-499
Advanced	25-29	20-24	15-19	200-349
Severe	<25	<20	<15	<200 or <15%

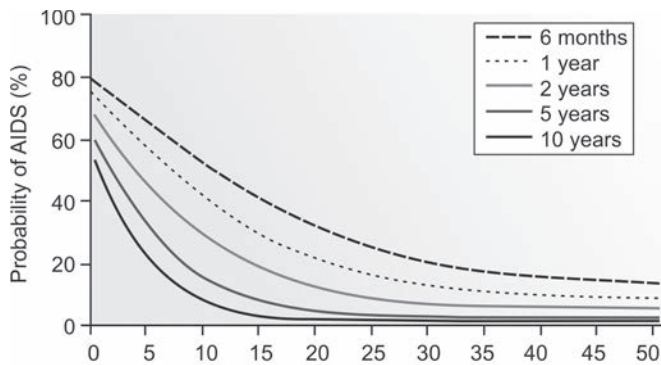


Fig. 5: Estimated probability of AIDS within 12 months by age and CD4 percentage in HIV-infected children receiving no. Theory or zidovudine monotherapy [Modified from *Lancet* 2003;363; 1605-1611]

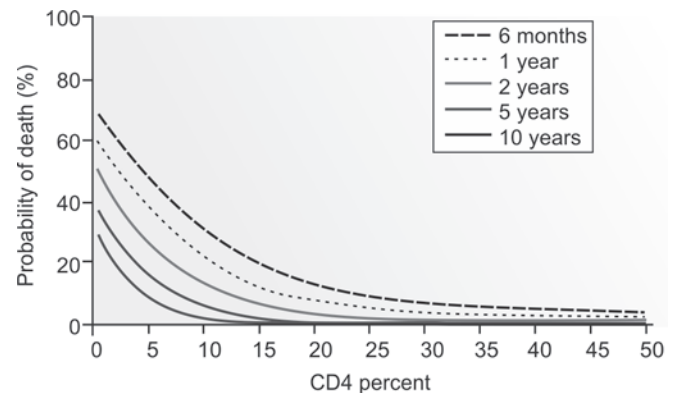


Fig. 6: Estimated probability of death within 12 months by age and CD4 percentage in HIV-infected children receiving no therapy or zidovudine monotherapy [Modified from *Lancet* 2003; 362; 1605-1611]

In HIV exposed children, as in infected adults, the CD4 count and percentage decline as HIV infection progresses, and patients with lower CD4 values have a poor prognosis than patients with higher values as shown by the study below.

The risk of disease progression associated with a specific CD4 percentage or count varies with age of the child. Infants in the first year of life experience higher risk of progression or death than older children for any given CD4 stratum. For example, comparing a one year old child with a CD4 percentage of 25 percent to a child of five years with same CD4 percentage, there is an approximately four fold increase in the risk of AIDS and a six fold increase in the risk of death in the one year old child (Figs 5 and 6).

KEY POINTS

- HIV disease is diagnosed using clinical signs and symptoms as well as specific laboratory tests.
- The HIV rapid test and HIV enzyme-linked immunosorbent assay are the screening tests used to detect HIV antibodies. These tests determine HIV exposure in infants younger than 18 months and diagnose HIV infection in children older than 18 months and in adults.
- Antibody tests cannot be used to definitively diagnose HIV in infants younger than 18 months because of passive placental transfer of maternal HIV immunoglobulin G antibody during pregnancy.

- Virologic testing (e.g., DNA polymerase chain reaction [PCR]) can be used to definitively diagnose HIV infection in infants younger than 18 months.
- Early diagnosis of HIV infection in infants on the basis of clinical signs and symptoms, rapid testing, and virologic testing is important to ensure timely enrolment of HIV-exposed infants into care, initiation of cotrimoxazole prophylaxis, and appropriate infant feeding counseling.
- Dried blood spot collection is highly stable and increases access to DNA PCR testing because of convenient sample handling and transport.
- If virologic testing is not readily available for infants younger than 18 months and an infant has a positive antibody test plus certain signs and symptoms of HIV, a presumptive diagnosis of HIV may be made and ARV therapy initiated as a potentially life-saving measure.

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2. NACO—Antiretroviral Therapy Guidelines for HIV infected Adults and Adolescents including Post-exposure (Date Uploaded: 29/08/2007).
3. World Health Organization: Antiretroviral Therapy for HIV Infection in Adults and Adolescents in Resource-Limited Settings: Towards Universal Access—Recommendations for a Public Health Approach, 2010 <http://www.who.int/hiv/paediatric/en/index.html>.
4. HIV Curriculum for Health professionals. Baylor International Paediatric AIDS Initiative (BIPAI) 2010.
5. NACO—Guidelines for HIV Care and Treatment in Infants and Children 2007.

Annexure I

1994 Revised human immunodeficiency virus pediatric classification system: clinical categories**Category N: Not symptomatic*

Children who have no signs or symptoms considered to be the result of HIV infection or who have only one of the conditions listed in category A.

Category A: Mildly symptomatic

Children with two or more of the following conditions but none of the conditions listed in Categories B and C:

- Lymphadenopathy (≥ 0.5 cm at more than two sites; bilateral = one site)
- Hepatomegaly
- Splenomegaly
- Dermatitis
- Parotitis
- Recurrent or persistent upper respiratory infection, sinusitis, or otitis media

Category B: Moderately symptomatic

Children who have symptomatic conditions, other than those listed for Category A or Category C, that are attributed to HIV infection. Examples of conditions in Clinical Category B include but are not limited to, the following:

- Anemia (< 8 gm/dl), neutropenia ($< 1,000$ cells/mm³) or thrombocytopenia ($< 100,000$ cells/mm³) persisting ≥ 30 days
- Bacterial meningitis, pneumonia or sepsis (single episode)
- Candidiasis, oropharyngeal (i.e. thrush) persisting for > 2 months in children age > 6 months
- Cardiomyopathy
- Cytomegalovirus infection with onset before age 1 month
- Diarrhea, recurrent or chronic
- Hepatitis
- Herpes simplex virus (HSV) stomatitis, recurrent (i.e. more than two episodes within 1 year)
- HSV bronchitis pneumonitis, or esophagitis with onset before age 1 month
- Herpes zoster (i.e. shingles) involving at least two distinct episodes or more than one dermatome
- Leiomyosarcoma
- Lymphoid interstitial pneumonia (LIP) or pulmonary lymphoid hyperplasia complex
- Nephropathy
- Nocardiosis
- Fever lasting > 1 month
- Toxoplasmosis with onset before age 1 month
- Varicella, disseminated (i.e. complicated chickenpox)

Category C: Severely symptomatic

Children who have any condition listed in the 1987 surveillance case definition for acquired immunodeficiency syndrome (below), with the exception of LIP (which is a Category B condition):

- Serious bacterial infections, multiple or recurrent (i.e. any combination of at least two culture-confirmed infections within a 2-year period), of the following types: septicemia, pneumonia, meningitis, bone or joint infection, or abscess of an internal organ or body cavity (excluding otitis media, superficial skin or mucosal abscesses, and indwelling catheter-related infections)
- Candidiasis, esophageal or pulmonary (bronchi, trachea, lungs)
- Coccidioidomycosis, disseminated (at site other than or in addition to lungs or cervical or hilar lymph nodes)

Contd...

- Cryptococcosis, extrapulmonary
- Cryptosporidiosis or isosporiasis with diarrhea persisting > 1 month
- Cytomegalovirus disease with onset of symptoms at age > 1 month (at a site other than liver, spleen, or lymph nodes)
- Encephalopathy (at least one of the following progressive findings present for at least 2 months in the absence of a concurrent illness other than HIV infection that could explain the findings): (a) failure to attain or loss of developmental milestones or loss of intellectual ability, verified by standard developmental scale or neuropsychological tests; (b) impaired brain growth or acquired microcephaly demonstrated by head circumference measurements or brain atrophy demonstrated by computerized tomography or magnetic resonance imaging (serial imaging is required for children <2 years of age); (c) acquired symmetric motor deficit manifested by two or more of the following: paresis, pathologic reflexes, ataxia, or gait disturbance
- Herpes simplex virus infection causing a mucocutaneous ulcer that persists for > 1 month or bronchitis, pneumonitis, or esophagitis for any duration affecting a child > 1 month of age
- Histoplasmosis, disseminated (at a site other than or in addition to lungs or cervical or hilar lymph nodes)
- Kaposi's sarcoma
- Lymphoma, primary, in brain
- Lymphoma, small, noncleaved cell (Burkitt's), or immunoblastic or large cell lymphoma of B-cell or unknown immunologic phenotype
- *Mycobacterium tuberculosis*, disseminated or extrapulmonary
- *Mycobacterium*, other species or unidentified species, disseminated (at a site other than or in addition to lungs, skin, or cervical or hilar lymph nodes)
- *Mycobacterium avium* complex or *Mycobacterium kansasii*, disseminated (at site other than or in addition to lungs, skin, or cervical or hilar lymph nodes)
- *Pneumocystis jiroveci* pneumonia
- Progressive multifocal leukoencephalopathy
- *Salmonella* (nontyphoid) septicemia, recurrent
- Toxoplasmosis of the brain with onset at > 1 month of age
- Wasting syndrome in the absence of a concurrent illness other than HIV infection that could explain the following findings: (a) persistent weight loss > 10% of baseline; OR (b) downward crossing of at least two of the following percentile lines on the weight-for-age chart (e.g. 95th, 75th, 50th, 25th, 5th) in a child ≥1 year of age; OR (c) <5th percentile on weight-for-height chart on two consecutive measurements, ≥30 days apart PLUS (1) chronic diarrhea (i.e. ≥ two loose stools per day for ≥30 days), OR (2) documented fever (for >30 days, intermittent or constant)

* Centers for Disease Control and Prevention. 1994 Revised classification system for human immunodeficiency virus infection in children less than 13 years of age. MMWR. 1994. 43 (No. RR-12): D. 1-10.

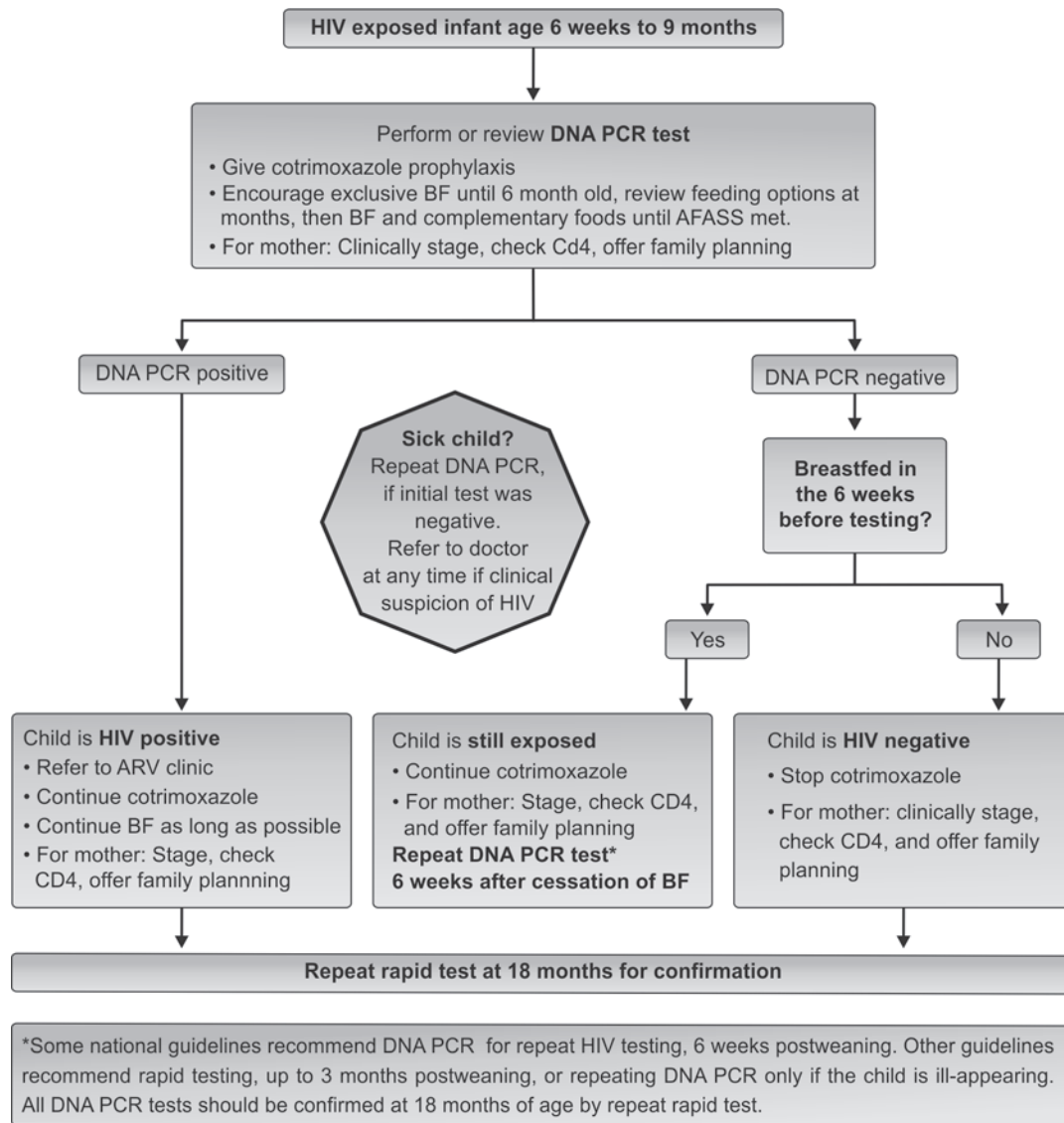
1994 Revised Human Immunodeficiency Virus Pediatric Classification System: Immune Categories Based on Age-Specific: CD4+ T-Lymphocyte Count and Percentage*

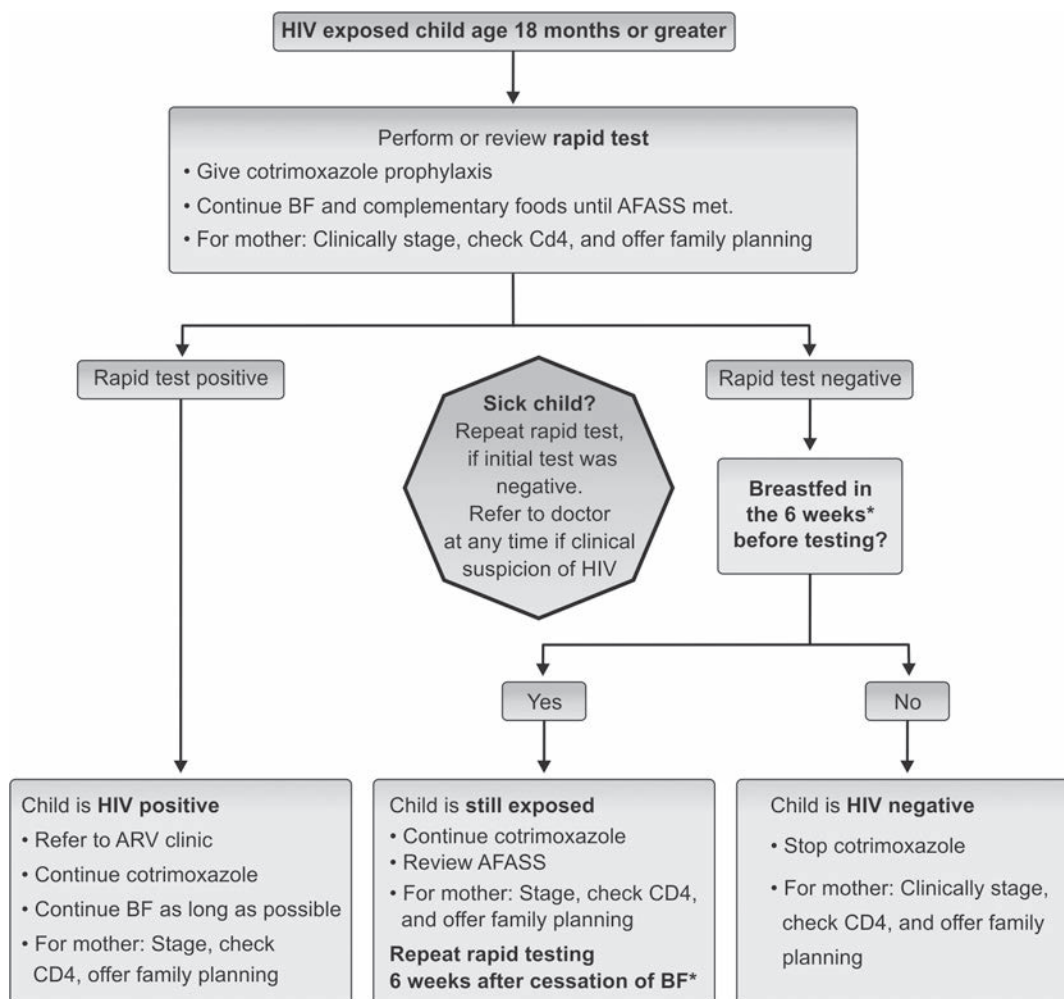
Immune Category	<12 months		1-5 years		6-12 years	
	No./uL	(%)	No./uL	(%)	No/uL	(%)
1: No suppression	>1500	(>25%)	>1000	(>25%)	>500	(>25%)
2: Moderate suppression	750-1499	(15-24%)	500-999	(15-24%)	200-499	(15-24%)
3: Severe suppression	<750	(<15%)	<500	(<15%)	<200	(<15%)

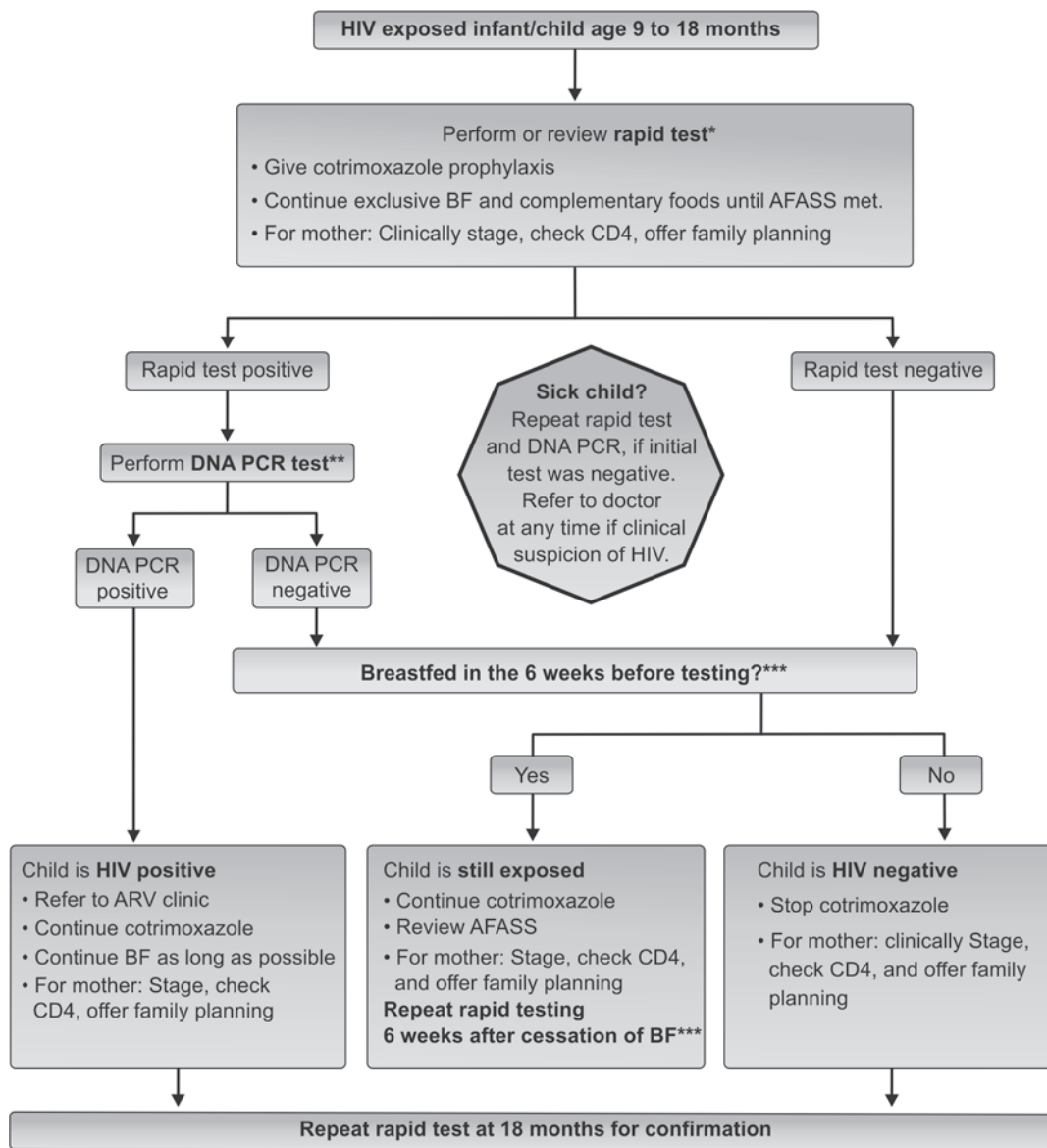
* Modified for CDC, 1994. Revised classification system for human immunodeficiency virus infection in children less than 13 years of age. MMWR 1994;43 (no. RR-12):1-10.

Annexure II

HIV Diagnosis in exposed infants and young children







*WHO recommends that, from 9 months of age, antibody tests are performed first to ensure that virologic testing is only done on children who still have HIV antibodies. The use of a rapid tests in the 9-18 month age group varies by country.

** While awaiting DNA PCR results, CD4 evaluation is recommended in most settings due to a high likelihood of true infection. Clinical judgement should be used to determine if a patient should be referred to an ARV clinic at this time

*** WHO recommends using a 6 weeks window period for rapid testing after 9 months of age. Several national guidelines use a 3 months window period for rapid testing. All DNA PCR tests should be confirmed at 18 months of age by repeat rapid test

Integrated Management of Childhood Illness (IMCI) HIV Clinical Diagnosis Algorithm			
CHECK FOR HIV INFECTION	Signs	Classify	Identify Treatments
<ul style="list-style-type: none"> Does the mother or child have a HIV test done? Does the child have one or more of the following conditions: <ul style="list-style-type: none"> Pneumonia* Persistent diarrhea* Ear discharge (acute or chronic) Very low Weight for age" <p><i>*Note that the severe forms such as severe pneumonia, severe persistent diarrhea and severe malnutrition can be used to enter the box. Complete assessment quickly and refer child.</i></p> <p>If yes, enter the box below and look for the following conditions suggesting HIV infection:</p>	<ul style="list-style-type: none"> Positive HIV antibody test in child 18 months and above <p>OR</p> <ul style="list-style-type: none"> Positive HIV virological test <p>AND</p> <ul style="list-style-type: none"> 2 or more conditions 	<p><i>Confirmed Symptomatic HIV Infection</i></p> <ul style="list-style-type: none"> Treat, counsel and follow-up existing infection. Give cotrimoxazole prophylaxis Check immunization status Give Vitamin A supplements from 6 months of age every 6 months Assess the child's feeding and provide appropriate counselling to the mother Refer for further assessment including HIV care/ART Advise mother on home care Follow-up in 14 days, then monthly for 3 months and then every 3 months or as per immunization schedule 	<ul style="list-style-type: none"> Treat, counsel and follow-up existing infection. Give cotrimoxazole prophylaxis Check immunization status Give Vitamin A supplements from 6 months of age every 6 months Assess the child's feeding and provide appropriate counselling to the mother Test to confirm HIV infections Refer for further assessment including HIV care/ART Advise mother on home care Follow-up in 14 days, then monthly for 3 months and then every 3 months or as per immunization schedule
<p>Note or Ask:</p> <ul style="list-style-type: none"> Pneumonia? Persistent diarrhea? Ear discharge? Very low Weight? <p>Look and Feel:</p> <ul style="list-style-type: none"> Oral thrush Parotid enlargement Generalized persistent infection Lymphadenopathy <p><i>Classify for HIV infection</i></p>	<ul style="list-style-type: none"> Positive HIV antibody test in child is months and above <p>OR</p> <ul style="list-style-type: none"> Positive HIV virological test <p>AND</p> <ul style="list-style-type: none"> Less than 2 conditions 	<p><i>Confirmed HIV Infection</i></p> <ul style="list-style-type: none"> Treat, counsel and follow-up existing infection Give cotrimoxazole prophylaxis Give Vitamin A supplements from 6 months of age every 6 months Assess the child's feeding and provide appropriate counselling to the mother Test to confirm HIV infections Refer for further assessment including HIV care/ART Advise mother on home care Follow-up in 14 days, then monthly for 3 months and then every 3 months or as per immunization schedule 	

CHECK FOR HIV INFECTION

<i>Signs</i>	<i>Classify</i>	<i>Identify Treatments</i>
<ul style="list-style-type: none"> No test results in child of positive antibody test in child <18 months 		<ul style="list-style-type: none"> Treat, counsel and follow-up existing infection
AND		<ul style="list-style-type: none"> Give cotrimoxazole prophylaxis
<ul style="list-style-type: none"> 2 or more conditions 	<i>Suspected Symptomatic HIV Infection</i>	<ul style="list-style-type: none"> Give Vitamin A supplements from 6 months of age every 6 months Assess the child's feeding and provide appropriate counselling to the mother Confirm HIV infection status of child as soon as possible with best available test Follow-up in 14 days, then monthly for 3 months and then every 3 months or as per immunization schedule
<ul style="list-style-type: none"> Treat, counsel and follow-up existing infection 		<ul style="list-style-type: none"> Treat, counsel and follow-up existing infection
<ul style="list-style-type: none"> Give cotrimoxazole prophylaxis 		<ul style="list-style-type: none"> Give cotrimoxazole prophylaxis
<ul style="list-style-type: none"> Give Vitamin A supplements from 6 months of age every 6 months 		<ul style="list-style-type: none"> Give Vitamin A supplements from 6 months of age every 6 months
<ul style="list-style-type: none"> Assess the child's feeding and provide appropriate counselling to the mother 	<i>Possible HIV/ HIV Exposed</i>	<ul style="list-style-type: none"> Assess the child's feeding and provide appropriate counselling to the mother
<ul style="list-style-type: none"> Follow-up in 14 days, then monthly for 3 months and then every 3 months or as per immunization schedule** 		<ul style="list-style-type: none"> Follow-up in 14 days, then monthly for 3 months and then every 3 months or as per immunization schedule**
AND		<ul style="list-style-type: none"> Treat, counsel and follow-up existing infections
<ul style="list-style-type: none"> No test result in child or mother 	<i>Symptomatic HIV Infection Unlikely</i>	<ul style="list-style-type: none"> Advise the mother about feeding and about her own health
Less than 2 conditions		<ul style="list-style-type: none"> Encourage HIV testing
<ul style="list-style-type: none"> Negative HIV test in mother or child AND not enough signs to classify as suspected symptomatic HIV infection 	<i>HIV infection Unlikely</i>	<ul style="list-style-type: none"> Treat, counsel and follow-up existing infections Advise the mother about feeding and about her own health

Integrated Management of Childhood illness (IMCI) is a WHO/UNICEF strategy; aimed at reducing mortality in children under five years by improving health care at a primary level. IMCI was introduced in 1995 and has been implemented in over 100 countries worldwide. IMCI provides a series of guidelines, often in the form of screening questions and symptom checklists, for assessing and treating common causes of childhood morbidity and mortality on the primary (Me level). IMCI has been adapted to include an algorithm to identify children with symptomatic HIV infection at the primary care level. Though this algorithm is useful where laboratory testing is not available, it fails to identify large portion of infected children and should not be used alone for HIV diagnosis.

Source: Adapted from "Integrated Management of Childhood Illness for High HIV Settings", WHO 2006

WHO case definitions for HIV-related disease (continued.)

<i>Clinical event</i>	<i>Clinical appearance</i>	<i>Clinical stage 3 (continued)</i>	<i>How to diagnose</i>
Oral candidiasis (after the first 6-8 weeks of life)	Persistent or recurring creamy white to yellow soft small plaques which can be scraped off (pseudomembranous), or red patches on tongue, palate or lining of mouth, usually painful or tender (erythematous form)		Microscopy or culture
Oral hairy leukoplakia	Fine small linear patches on lateral borders of tongue, generally bilateral that do not scrape off		Clinical diagnosis
Acute necrotizing ulcerative gingivitis or stomatitis, or periodontitis	Severe pain, ulcerated gingival papillae, loosening of teeth, spontaneous bleeding, bad odor, and rapid loss of bone and/or soft tissue.		Clinical diagnosis
Lymph node tuberculosis	Nonacute, painless "cold" enlargement of peripheral lymph nodes, localized to one region. Response to standard anti-TB treatment in one month.		Histology or fine needle aspirate positive for Ziehl-Nielsen stain or culture.
Pulmonary TB	Nonspecific symptoms, such as chronic cough, fever, night sweats, anorexia and wt loss. In the older child, also productive cough and hemoptysis. History of contact with adults with smear-positive pulmonary TB. No response to standard broad-spectrum antibiotic treatment.		One or more sputum smear-positive for acid-fast bacilli and/or radiographic abnormalities c/w active TB and/or culture-positive for <i>Mycobacterium</i> .
Severe recurrent bacterial pneumonia	Cough with fast breathing, chest indrawing, nasal flaring, wheezing and grunting. Crackles or con solidation on auscultation. Responds to course of antibiotics. Current episode plus one or more in previous 6 months.		Isolation of bacteria from appropriate clinical specimens (included sputum, bronchoalveolar lavage and lung aspirate)
Symptomatic lymphocytic interstitial pneumonia	No presumptive clinical diagnosis		CXR: bilateral reticulonodular interstitial pulmonary infiltrates present for more than 2 months with no response to antibiotic treatment and no other pathogen found. O ₂ saturations: <90%, persistently. Cor pulmonale and increased exercise-induced fatigue. Characteristic histology.
Chronic HIV-associated lung disease (including bronchiectasis)	History of cough productive of copious amounts of purulent sputum (bronchiectasis only), with or without clubbing, halitosis, and crepitations and/or wheezes on auscultation		CXR may show honeycomb appearance (small cysts) and/or persistent area of opacification and/or widespread lung destruction, with fibrosis and loss of volume.
Unexplained anemia (<8 g/dl), neutropenia (<0.5 × 10 ⁹ /L and or chronic thrombocytopenia (<50 × 10 ⁹ /L)	No presumptive clinical diagnosis		Lab testing, not explained by other non-HIV conditions, not responding to standard therapy with hematinics, antimalarial, or antihelminthic agents as outlined in WHO IMCI guidelines.
CLINICAL STAGE 4			
Unexplained severe wasting, stunting, or severe malnutrition not adequately responding to standard therapy	Persistent wt loss not explained by poor or inadequate feeding; other infections, and not adequately responding in 2 wks to standard therapy. Visible severe wasting of muscles with or without edema of both feet, and/or wt-for-ht of -3 SD from the mean, as defined by WHO IMCI guidelines		Documented loss of over more than - 3 SD from the mean with or without edema.
Pneumocystis pneumonia	Dry cough, progressive difficulty in breathing, cyanosis, tachypnea and fever; chest indrawing or stridor. (Severe or very severe pneumonia as in WHO IMCI guidelines). Rapid onset especially in infants younger than 6 months of age. Response to high-dose cotrimoxazole with or without prednisolone. CXR shows typical bilateral perihilar diffuse infiltrates.		Cytology or immunofluorescent microscopy of induced sputum or bronchoalveolar lavage (BAL) or histology of lung tissue

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Clinical event	Clinical appearance	How to diagnose
<i>Clinical State 4</i>		
Recurrent severe bacterial infection, i.e. empyema, pyomyositis, bone/joint infection, meningitis, but excluding pneumonia	Fever accompanied by specific symptoms or signs that localize infection. Responds to antibiotics. Current episode plus 1 or more in previous 6 months.	Culture of appropriate clinical specimen.
Chronic herpes simplex infection; (orolabial/cutaneous of more than 1 month's, duration or visceral at any site)	Severe and progressive painful orolabial, genital, or anorectal lesions caused by herpes simplex virus infection present for more than 1 month.	Culture and/or histology
Esophageal candidiasis (or candidiasis of trachea, bronchi, lungs)	Difficulty in swallowing, or pain on swallowing (food and fluids). In young children, suspect particularly if oral Candida observed and food refusal occurs and or difficulty or crying when feeding.	Macroscopic appearance at endoscopy, microscopy of specimen from tissue or macroscopic appearance at bronchoscopy or histology
Extrapulmonary or disseminated TB	Systemic illness usually with prolonged fever, night sweats and wt loss. Clinical features of organs involved, such as sterile pyuria pericarditis, ascites, pleural effusion, meningitis, arthritis, or orchitis, pericardial or abdominal	Positive microscopy showing acid-fast bacilli or culture of <i>Mycobacterium tuberculosis</i> from blood or other relevant specimen except sputum of BAL. Biopsy and histology.
Kaposi sarcoma	Typical appearance in skin or oropharynx of persistent, initially flat, patches with a pink or blood-ruise color, skin lesions that usually develop into nodules.	Not required but may be confirmed by: (1) typical red-purple lesions seen on bronchoscopy/endoscopy; (2) dense masses in lymph nodes, viscera, or lungs by palpation or radiology and (3) histology.
CMV retinitis or CMV infection affecting another organ, with onset older than 1 month of age	CMV retinitis may be diagnosed by experienced clinicians: typical eye lesions on serial fundoscopic exam: discrete patches of retinal whitening with distinct borders, spreading centrifugally, often following blood vessels, associated with retinal vasculitis, hemorrhage necrosis.	Definitive diagnosis required for other sites. Histology. CSF PCR.
CNS toxoplasmosis, onset after 1 month of age	Fever, headache, focal nervous system signs and convulsions. Usually responds within 10 days to specific therapy.	Computed tomography scan (or other neuroimaging) showing single or multiple lesions with mass effect or enhancing with contrast.
Extrapulmonary cryptococcosis, (including meningitis)	Meningitis: Usually subacute, fever with increasing severe headache, meningism, confusion behavioral changes that respond to cryptococcal therapy	CSF microscopy (India ink or Gram stain), serum or CSF cryptococcal antigen test or culture

Source: WHO case definitions of HIV for surveillance and revised clinical staging and immunological classification of HIV-related disease in adults and children, 2007. Available at: <http://www.who.int/hiv/pub/guidelines/en/>.

CHAPTER 46

Postexposure Prophylaxis and Prevention of Parent to Child Transmission

Ajay Arora, SP Yadav, Anupam Sachdeva, Nivedita Dhingra

ABBREVIATIONS AND ACRONYMS

AEB: accidental exposure to blood
ART: antiretroviral therapy
ARV: antiretroviral (drug)
AZT: zidovudine (also known as zdv)
d4T: stavudine
ddI: didanosine
EFV: efavirenz
HBV: hepatitis B virus
HCP: health care professional
HCV: hepatitis C virus
NNRTI: nonnucleoside reverse transcriptase inhibitor
NRTI: nucleoside analog reverse transcriptase inhibitor
PLHA: people living with HIV/AIDS
SQV: saquinavir

OCCUPATIONAL EXPOSURE

Occupational exposure refers to exposure to potential blood-borne infections (HIV, HBV and HCV) that may occur in health care settings during performance of job duties. Postexposure prophylaxis (PEP) refers to comprehensive medical management to minimize the risk of infection among health care personnel (HCP) following potential exposure to blood-borne pathogens (HIV, HBV, HCV). This includes counseling, risk assessment, relevant laboratory investigations based on informed consent of the source and exposed person, first aid and depending on the risk assessment, the provision of short-term (four weeks) of antiretroviral drugs, with follow-up and support.

What is the Risk?

Health care personnel are at risk of blood-borne infection transmission through exposure of a percutaneous injury (e.g. needle-stick or cut with a sharp instrument), contact

with the mucous membranes of the eye or mouth of an infected person, contact with nonintact skin (particularly when the exposed skin is chapped, abraded, or afflicted with dermatitis) or contact with blood or other potentially infectious body fluids.

Any direct contact (i.e. contact without barrier protection) with concentrated virus in a research laboratory or production facility requires clinical evaluation. Transmission of HIV infection from human bites is rarely reported.

The average risk of acquiring HIV infection from different types of occupational exposure is low compared to risk of infection with HBV or HCV. In terms of occupational exposure the important routes are needle-stick exposure (0.3% risk for HIV, 9-30% for HBV and 1-10% for HCV) and mucous membrane exposure (0.09% for HIV).

What is infectious and what is not?

Exposure to blood, semen, vaginal secretions, cerebrospinal fluid, synovial, pleural, peritoneal, pericardial fluid, amniotic fluid and other body fluids contaminated with visible blood can lead to infection. Exposure to tears, sweat, saliva, urine and feces is noninfectious unless these secretions contain visible blood.

FIRST AID IN MANAGEMENT OF EXPOSURE

For skin — if the skin is broken after a needle-stick or sharp instrument:

- Immediately wash the wound and surrounding skin with water and soap, and rinse. Do not scrub.
- Do not use antiseptics or skin washes (bleach, chlorine, alcohol, betadine)
- *After a splash of blood or body fluids on unbroken skin:*
- Wash the area immediately
- Do not use antiseptics

For the eye:

- Irrigate exposed eye immediately with water or normal saline. Sit in a chair, tilt head back and ask a colleague to gently pour water or normal saline over the eye.
- If wearing contact lens, leave them in place while irrigating, as they form a barrier over the eye and will help protect it. Once the eye is cleaned, remove the contact lens and clean them in the normal manner. This will make them safe to wear again
- Do not use soap or disinfectant on the eye.

For mouth:

- Spit fluid out immediately
- Rinse the mouth thoroughly, using water or saline and spit again. Repeat this process several times
- Do not use soap or disinfectant in the mouth
- Consult the designated physician of the institution for management of the exposure immediately.

Don'ts

- Do not panic
- Do not put pricked finger in mouth
- Do not squeeze wound to bleed it
- Do not use bleach, chlorine, alcohol, betadine, iodine or any antiseptic or detergent

Establish Eligibility for PEP

The HIV seroconversion rate of 0.3 percent after an AEB (for percutaneous exposure) is an average rate. The risk of infection transmission is proportional to the amount of HIV transmitted, which depends on the nature of exposure and the status of the source patient. A baseline rapid HIV testing of exposed and source person must be done for PEP. However, initiation of PEP should not be delayed while waiting for the results of HIV testing of the source of exposure. Informed consent should be obtained before testing of the source as per national HIV testing guidelines.

First PEP dose within 72 hours

A designated person/trained doctor must assess the risk of HIV and HBV transmission following an AEB. This evaluation must be quick so as to start treatment without any delay, ideally within two hours but certainly within 72 hours; PEP is not effective when given more than 72 hours after exposure. The first dose of PEP should be administered within the first 72 hours of exposure. If the risk is insignificant, PEP could be discontinued, if already commenced.

ASSESSING RISK OF TRANSMISSION

Exposure is defined under three categories based on the amount of blood/ fluid involved and the entry port. These categories are intended to help in assessing the severity of the exposure but may not cover all possibilities (Table 1).

Table 1: Categories of exposure

Mild exposure	Mucous membrane/nonintact skin with small volumes For example, a superficial wound (erosion of the epidermis) with a plain or low caliber needle, or contact with the eyes or mucous membranes, subcutaneous injections following small-bore needles.
Moderate exposure	Mucous membrane/nonintact skin with large volumes or percutaneous superficial exposure with solid needle For example, a cut or needlestick injury penetrating gloves
Severe exposure	Percutaneous with large volume e.g. an accident with a high caliber needle (>18 G) visibly contaminated with blood; a deep wound (hemorrhagic wound and/or very painful); transmission of a significant volume of blood; an accident with material that has previously been used intravenously or intra-arterially.

The wearing of gloves during any of these accidents constitutes a protective factor.

Note: In case of an AEB with material such as discarded sharps/needles, contaminated for over 48 hours, the risk of infection is negligible for HIV, but still remains significant for HBV. HBV survives longer than HIV outside the body.

Counseling for PEP

Exposed persons should receive appropriate information about what PEP is about and the risk and benefits of PEP in order to provide informed consent for taking PEP. It should be clear that PEP is not mandatory.

Psychological Support

Many people feel anxious after exposure. Every exposed person needs to be informed about the risks, and the measures that can be taken. This will help to relieve part of the anxiety. Some clients may require further specialised psychological support.

Document Exposure

Documentation of exposure is essential. Special leave from work should be considered initially for a period of two weeks. Subsequently, it can be extended based on the assessment of the exposed person's mental state, side effects and requirements.

Deciding on PEP Regimen

There are two types of regimens:

Basic regimen: Two-drug combination

Expanded regimen: Three-drug combination

Table 2: HIV PEP evaluation

Exposure	Status of source		
	HIV+ and Asymptomatic	HIV+ and Clinically symptomatic	HIV status unknown
Mild	Consider 2-drug PEP	Start 2-drug PEP	Usually no PEP or consider 2-drug PEP
Moderate	Start 2-drug PEP	Start 3-drug PEP	Usually no PEP or consider 2-drug PEP
Severe	Start 3-drug PEP	Start 3-drug PEP	Usually no PEP or consider 2-drug PEP

The decision to initiate the type of regimen depends on the type of exposure and HIV serostatus of the source person (Table 2).

In the case of a high risk exposure from a source patient who has been exposed to or is taking antiretroviral medications, consult an expert to choose the PEP regimen, as the risk of drug resistance is high. Refer/consult expert physician. Start 2-drug regimen first.

Seek expert opinion in case of:

- Delay in reporting exposure (>72 hours)
- Unknown source
- Known or suspected pregnancy, but initiate PEP
- Breastfeeding mothers, but initiate PEP
- Source patient is on ART
- Major toxicity of PEP regimen

HIV CHEMOPROPHYLAXIS

Because postexposure prophylaxis (PEP) has its greatest effect if begun within two hours of exposure, it is essential to act immediately. The prophylaxis needs to be continued for four weeks. Exposure must be immediately reported to designated authority and therapy administered. Never delay start of therapy due to debate over regimen. Begin

with basic 2-drug regimen, and once expert advice is obtained, change as required (Tables 3 and 4).

Selection of PEP regimen when the source patient is on ART:

The physician should consider the comparative risk represented by the exposure taking in view exposure source's history of and response to antiretroviral therapy based on clinical response, CD4 cell counts, viral load measurements (if available), and current disease stage (WHO clinical staging and history). If the source person's virus is known or suspected to be resistant to one or more drugs considered for the PEP regimen, exposed person needs to be given alternate PEP drug regimen, and referred for expert opinion.

Changes in the PEP regimen can be made after PEP has been started. Re-evaluation of the exposed person should be considered within 72 hours postexposure, especially as additional information about the exposure or source person becomes available.

ARV DRUGS DURING PREGNANCY

Data regarding the potential effects of antiretroviral drugs on the developing fetus or neonate are limited. There is

Table 3: Dosage of drugs for PEP

Medication	2-drug regimen	3-drug regimen
Zidovudine (AZT)	300 mg twice a day	300 mg twice a day
Stavudine (d4T)	30 mg twice a day	30 mg twice a day
Lamivudine (3TC)	150 mg twice a day	150 mg twice a day
Protease inhibitors		<p><i>1st choice</i></p> <p>Lopinavir/ritonavir (LPV/ r) 400/ 100 mg twice a day or 800/ 200 mg once daily with meals</p> <p><i>2nd choice</i></p> <p>Nelfinavir (NLF)</p> <p>1250 mg twice a day or 750 mg three times a day with empty stomach</p> <p><i>3rd choice</i></p> <p>Indinavir (IND)</p> <p>800 mg every 8 hours and drink 8-10 glasses (1.5 liters) of water daily</p>

Note: If protease inhibitor is not available and the 3rd drug is indicated, one can consider using Efavirenz (EFV 600 mg once daily).

Monitoring should be instituted for side effects of this drug, e.g. CNS toxicity such as nightmares, insomnia, etc.

* Fixed dose combination (FDC) are preferred, if available. Ritonavir requires refrigeration.

Table 4: PEP regimens to be prescribed by health centers

	<i>Preferred</i>	<i>Alternative</i>
<i>2-drug regimen (basic PEP regimen)</i>	Zidovudine (AZT) + Lamivudine (3TC)	Stavudine (d4T) + Lamivudine (3TC)
<i>3-drug regimen (consult expert opinion for starting 3-drug, e.g. LPV/r, NLF or IND regimen)</i>		
<i>Not recommended</i>	ddI + d4T combination NNRTI such as Nevirapine should not be used in PEP	

a clear contraindication for Efavirenz (first 3 months of pregnancy) and Indinavir (prenatal).

For a female HCP considering PEP, a pregnancy test is recommended in case of a doubt. Pregnant HCP are recommended to begin the basic 2-drug regimen, and if a third drug is needed, Nelfinavir is the drug of choice.

SIDE EFFECTS AND ADHERENCE TO PEP

Studies have indicated more side effects, most commonly nausea and fatigue, among HCP taking PEP than PLHAs taking ART. These side effects occur mainly at the beginning of the treatment and include nausea, diarrhea, muscular pain and headache. The person taking the treatment should be informed that these may occur and should be dissuaded from stopping the treatment as most side-effects are mild and transient, though possibly uncomfortable. Anemia and/or leukopenia and/ or thrombocytopenia may occur during the month of treatment.

Adherence information and psychological support are essential. More than 95 percent adherence is important in order to maximize the efficacy of the medication in PEP. Side effects can be reduced through medications. A complete blood count and liver function tests (transaminases) may be performed at the beginning of treatment (as baseline) and after 4 weeks.

FOLLOW-UP OF AN EXPOSED PERSON

Whether or not postexposure prophylaxis is started, a follow up is needed to monitor for possible infections and to provide psychological support.

Clinical Follow-up

In the weeks following an AEB, the exposed person must be monitored for the eventual appearance of signs indicating an HIV seroconversion: acute fever, generalized lymphadenopathy, cutaneous eruption, pharyngitis, non-specific flu symptoms and ulcers of the mouth or genital area. These symptoms appear in 50 to 70 percent of individuals with an HIV primary (acute) infection and almost always within 3 to 6 weeks after exposure. When a primary (acute) infection is suspected, referral to an ART center or for expert opinion should be arranged rapidly.

An exposed person should be advised to use precautions (e.g. avoid blood or tissue donations, breastfeeding, unprotected sexual relations or pregnancy) to prevent secondary transmission, especially during the first 6 to 12 weeks following exposure. Condom use is essential.

Drug adherence and side effect counseling should be provided and reinforced at every follow-up visit. Psychological support and mental health counseling is often required.

Laboratory Follow-up

Exposed persons should have post-PEP HIV tests. HIV-test at 3 months and again at 6 months is recommended. If the test at 6 months is negative, no further testing is recommended.

PREVENTION OF PARENT TO CHILD TRANSMISSION (FLOW CHART 1)

Mother to child transmission (MTCT) is by far the most significant route of transmission of HIV infection in children below the age of 15 years. HIV can be transmitted during pregnancy, during childbirth, or breastfeeding. Without intervention, the risk of transmission from an infected mother to her child ranges from 15 to 25 percent in developed countries and from 25 to 45 percent in developing countries. This difference is largely attributed to breast-feeding practices (Table 5).

The prevention of parent to child transmission (PPTCT) of HIV/AIDS programme was started in the country in the year 2002 following a feasibility study in 11 major hospitals in the five high HIV prevalence states. Currently, there are more than 4000 Integrated Counseling

Table 5: Estimated risk and timing of MTCT in the absence of interventions

During pregnancy	5-10%
During labor and delivery	10-15%
During breastfeeding	5-20%
Overall without breastfeeding	15-25%
Overall with breastfeeding to 6 months	20-35%
Overall with breastfeeding to 18 to 24 months	30-45%

and Testing Centers (ICTCs) in the country, most of these in government hospitals, which offer PPTCT services to pregnant women. Of these ICTCs, 502 are located in obstetrics and gynecology departments and in maternity homes where the client load is predominantly comprised of pregnant women.

The Joint Technical Mission on PPTCT (2006) estimated that out of 27 million annual pregnancies in India, 189,000 occur in HIV positive pregnant women. In the absence of any intervention, an estimated cohort of 56,700 infected babies will be born annually. *The PPTCT programme aims to prevent the perinatal transmission of HIV from an HIV infected pregnant mother to her newborn baby.* The program entails counseling and testing of pregnant women in the ICTCs. Pregnant women who are found to be HIV positive are given a single dose of Nevirapine at the time of labor; their newborn babies also get a single dose of Nevirapine immediately after birth so as to prevent transmission of HIV from mother-to-child.

Significant progress is being made in the global scale-up of prevention of mother-to-child transmission of HIV (PMTCT), including in high burden and resource-limited settings. For the first time, the elimination of mother-to-child transmission of HIV (MTCT) is now considered a realistic public health goal and an important part of the campaign to achieve the millennium development goals.

CARE OF THE MOTHER

Pregnancy is a special situation which provides a unique opportunity for the prevention of vertical transmission of HIV using various interventions. The risk of transmission of HIV from an infected mother is 14 to 32 percent if the child is not breastfed, and 25 to 48 percent if the child is breastfed. More than two-thirds of such transmission occurs during labor, when the baby is exposed to maternal genital fluids, and a significant proportion occurs through breastfeeding. Women who are HIV positive are at increased risk of opportunistic infections such as tuberculosis, herpes simplex, cytomegalovirus and invasive bacterial infections such as *Streptococcus pneumoniae* and salmonellosis.

The goals of management of HIV in pregnancy are dual: managing the mother's HIV status and prevention of mother-to-child transmission (PMTCT). The indications for ART and drug selection in pregnancy are similar to those in nonpregnant women. However, in the selection of a drug regimen, the following points should be remembered:

- AZT should be included as one of the components of the regimen unless there are absolute contraindications for using it.
- EFV should be avoided in the first-trimester of pregnancy (because of the risk of teratogenicity)
- When NVP is used and the mother's CD4 count is $>250/\text{mm}^3$, close monitoring of liver function is required.

When women who are already on ART become pregnant, the benefits and risks of ART in the first-trimester need to be considered. The benefits are a reduction in the risk of developing resistance and a decrease in the risk to the mother. The risk of continuing ART consists of the potential for ARV fetal toxicity, particularly during the first trimester of pregnancy. Good clinical management of HIV in pregnant women requires the support of a multidisciplinary team, including antenatal specialists, pediatricians, counselors, members of the ART center and community-based organizations (NGOs, positive network, etc.)

The criteria for initiating ART in pregnant women are the same as for other adults:

- WHO clinical stage 3 or 4 disease
- WHO clinical stage 1 or 2 disease and $\text{CD4} < 200 \text{ cells}/\text{mm}^3$
- WHO stage 3 disease and $\text{CD4} < 350 \text{ cells}/\text{mm}^3$

The initiation of ART helps prevent transmission of HIV to the newborn and also benefits the mother's own health. Once initiated, it should be continued postpartum.

The preferred NRTIs for use in pregnant women are AZT and 3TC. The combination of ddI and d4T should not be used because of associated increased toxicities in pregnant women. Studies have shown that TDF is associated with decreased fetal growth and bone demineralization. The preferred NNRTI is NVP, with which there has been extensive clinical experience globally. Its efficacy in reducing mother-to-child transmission has been proven. SQV/ r and Nelfinavir (NLF) are the preferred PI's if the woman needs to take PIs. EFV may be considered after the first-trimester.

The consistent use of condoms is recommended for all HIV infected women who are on ART. This is for the prevention of secondary transmission of HIV from/to the partner, as well as the prevention of unplanned pregnancy. *Antiretroviral treatment options recommended for HIV infected pregnant women who are eligible for treatment:*

Maternal ART + infant ARV prophylaxis

Mother

Maternal antepartum daily ART, starting as soon as possible irrespective of gestational age, and continued during pregnancy, delivery and thereafter. Recommended regimens include:

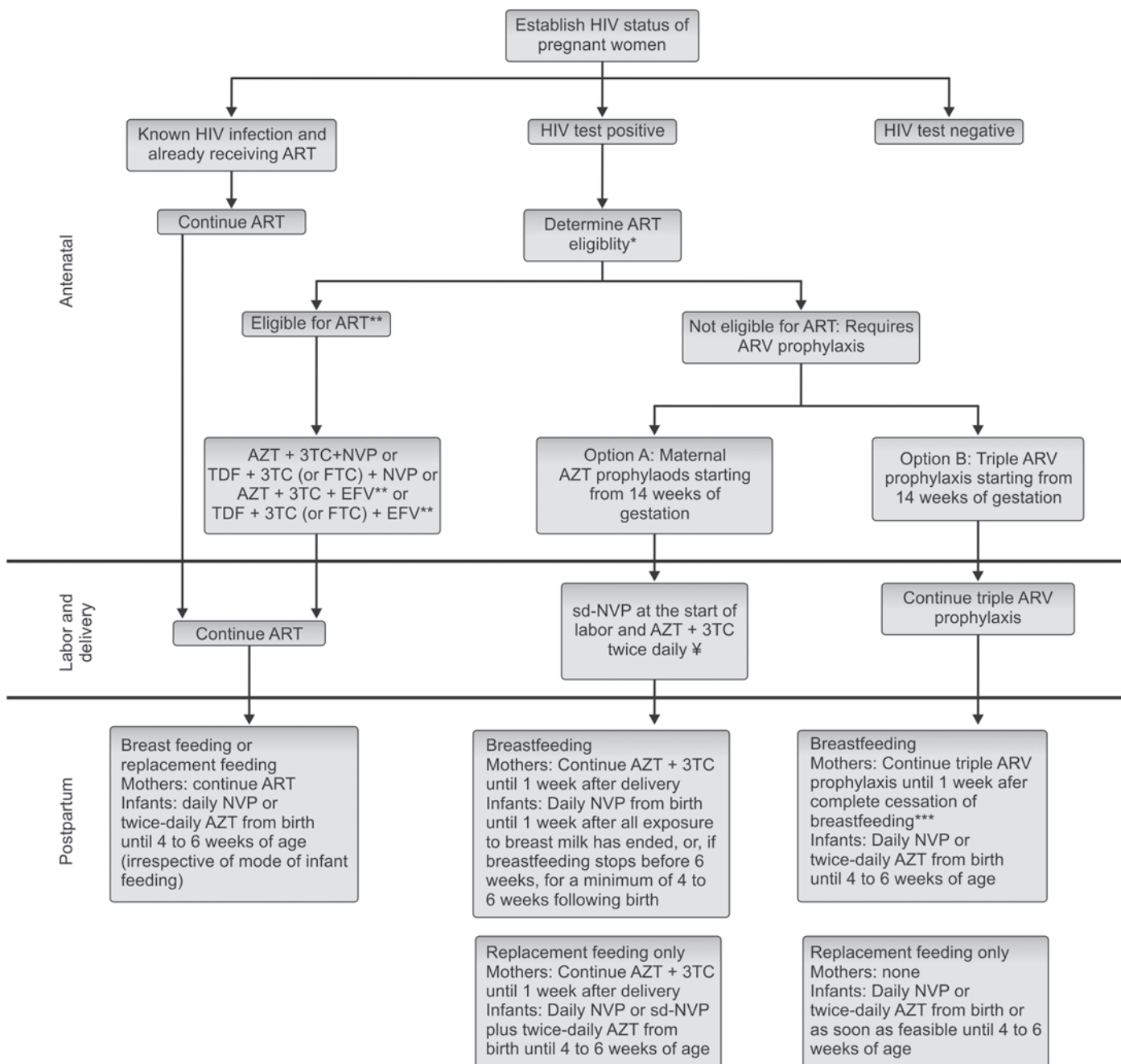
AZT + 3TC + NVP or
AZT + 3TC + EFV* or
TDF + 3TC (or FTC) + NVP or
TDF + 3TC (or FTC) + EFV*

Infant

Daily NVP or twice-daily AZT from birth until 4 to 6 weeks of age (irrespective of the mode of infant feeding)

* Avoid use of EFV in the first-trimester and use NVP instead.

ARV-prophylaxis options recommended for HIV infected pregnant women who do not need treatment for their own health (Table 6).

Flow Chart 1: Algorithm for the 2010 PMTCT recommendations

*Start ARV prophylaxis while waiting to determine ART eligibility

** Avoid use of EFV in first-trimester use NVP instead

*** When stopping any NNRTI-based regimen, stop the NNRTI first and continue the two NRTIs for 7 days and then stop them to reduce the chance of NNRTI resistance.

¥ FAZT was taken for at least the last 4 weeks before delivery, omission of the maternal sd-NVP and accompanying tail (AZT-3TC) can be considered. In this case, continue maternal AZT twice daily during labor and stop at delivery.

Care of the Infant at Birth

HIV infection is difficult to diagnose in infants, as most infected babies appear healthy and exhibit no signs and symptoms at birth. Maternal predictors of infant disease

progression include maternal viral load, maternal CD4 count (<200), rapidly progressing maternal disease, maternal death. Care of the neonate and infants will need to include adequate referral linkages between the maternal and child units and adult care facilities.

Table 6: ARV prophylaxis options for HIV infected pregnant women

<i>Maternal AZT + infant ARV prophylaxis (Option A)</i>	<i>Maternal triple ARV prophylaxis (Option B)</i>
<i>Mother</i>	<i>Mother</i>
Antepartum twice-daily AZT starting from as early as 14 weeks of gestation and continued during pregnancy. At onset of labor, sd-NVP and initiation of twice daily AZT + 3TC for 7 days postpartum. (Note: If maternal AZT was provided for more than 4 weeks antenatally, omission of the sd-NVP and AZT + 3TC tail can be considered; in this case, continue maternal AZT during labor and stop at delivery).	Triple ARV prophylaxis starting from as early as 14 weeks of gestation and continued until delivery, or, if breastfeeding, continued until 1 week after all infant exposure to breast milk has ended. Recommended regimens include: AZT + 3TC + LPV/r or AZT + 3TC + ABC or AZT + 3TC + EFV or TDF + 3TC (or FTC) + EFV
<i>Infant</i>	<i>Infant</i>
<i>For breastfeeding infants</i> Daily NVP from birth for a minimum of 4 to 6 weeks, and until 1 week after all exposure to breast milk has ended. <i>Infants receiving replacement feeding only</i> Daily NVP or sd-NVP + twice-daily AZT from birth until 4 to 6 weeks of age.	<i>Irrespective of mode of infant feeding</i> Daily NVP or twice daily AZT from birth until 4 to 6 weeks of age

Definition of HIV-exposure: Infants and children born to mothers living with HIV, until HIV infection in the infant or child is reliably excluded and the infant or child is no longer exposed through breastfeeding. Care of HIV-exposed infants should follow standard neonatal care according to safe motherhood guidelines including the following:

- The baby's mouth and nostrils should be wiped as soon as the head is delivered
- Infants should be handled with gloves until all blood and maternal secretions have been washed off (early baby bathing)
- The cord should be clamped soon after birth, but milking should be avoided. Cover the cord with gloved hand and gauze before cutting to avoid blood splattering.
- Initiate feeding within the first hour of birth according to the mother's preferred and informed choices.

Infant Feeding Choices

Breastfeeding provides the infant with all required nutrients and immunological factors that help to protect against common infections. This protection is reduced when the child is given water or any other substance during exclusive breastfeeding. Mixed feeding, i.e. breast milk and formula feeds combined is the most hazardous form of infant feeding. Exclusive replacement feeding is the ideal option but it may not be affordable and feasible, where safe drinking water, fuel or clean utensils are scarce. In such scenario HIV infected women should be counseled during the antenatal period about infant feeding choices and to make an informed decision.

Where exclusive replacement feeding is AFASS—acceptable, feasible, affordable, sustainable and safe, avoidance of all breastfeeding is recommended. The mother who has chosen not to breastfeed must be able to prepare feeds hygienically and should be advised to use cup feeding and not bottle feeding. In case replacement feeding is not possible, exclusive breastfeeding for the first-six months of life with early cessation is recommended. The risks of HIV transmission especially if combined with ART may be less than 0.5 percent, if exclusive breastfeeding is done. If family support is not present, exclusive breast feeding may be difficult and the parent(s) may need consistent psychosocial support.

When the child reaches the age of six months or earlier, breastfeeding should be stopped within two weeks while ensuring the comfort level of both mother and infant. At the same time, good quality complimentary foods should be introduced, ensuring adequate amounts of energy proteins and micronutrients.

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BACKGROUND

The burden of HIV infection in India is huge with estimated adult HIV prevalence of 0.31 percent. According to 2009 data, approximately 23.9 lakh people are living with HIV/AIDS (PLHA) in India. The National AIDS Control Program Phase III (2007-2012) aims to halt and reverse the epidemic of HIV in India over next five years. The strategies to achieve this goal involve preventive measures as well as measures to improve care, support and treatment of people living with HIV/AIDS (PLHA). As the mortality rate is high in children living with HIV/AIDS (CLHA), hence their management is challenging.

Management of Children with HIV Infection

The management of CLHA involves a multidisciplinary approach with appropriate attention to growth, nutrition and immunization of child. It also includes treatment and prevention of opportunistic infections as well as antiretroviral therapy (ART).

PROPHYLACTIC THERAPY**Cotrimoxazole Prophylactic Therapy**

WHO recommends the use of Cotrimoxazole for prevention of *Pneumocystis jiroveci* infection in CLHA. Apart from *P. jiroveci*, CPT also provides protection against toxoplasma, malaria and other common bacterial infections. Cotrimoxazole prophylactic therapy (CPT) should be started in all infants born to HIV infected mothers starting at 4 to 6 weeks age or at first visit to the health care facility. It should be continued till HIV infection has been ruled out and the child is no longer exposed to HIV via breast milk.

In CLHA of 1 to 5 years age, CPT should be started if

- WHO clinical stage 2, 3 or 4 regardless of CD4 counts or

- If CD4 count <25 percent irrespective of WHO clinical stage.

For CLHA >5 years age, CPT should be started if

- WHO clinical stage 2, 3 or 4 if CD 4 count not available or
- WHO stage 3 or 4 irrespective of CD 4 count or
- CD 4 count <350/mm³ irrespective of WHO staging.

Dose

5 mg/kg/day.

Duration

Once started, CPT should be continued till 5 years age. After 5 years age, consider stopping, if CD 4 count >350 cells/mm³ on two occasions at least 3 months apart.

CPT should also be discontinued in HIV exposed infants when HIV infection has been excluded and the child is no longer exposed to HIV via breast milk.

Side Effects

Side effects are mild and include rash, myalgia, pruritus and GI upset. Severe side effects warranting discontinuation are uncommon and include severe anemia, pancytopenia, severe cutaneous reactions like Stevens-Johnson syndrome, hepatotoxicity or nephrotoxicity.

Contraindications

CPT should not be used in children with glucose 6-phosphate dehydrogenase deficiency or hypersensitivity to sulpha drugs.

Alternative Drug

Dapsone can be used in case of intolerance or severe side effects of CPT at 2 mg/kg/day.

Isoniazid Prophylactic Therapy (IPT)

Screening for TB is strongly recommended for all CLHA. WHO recommends three i's for decreasing morbidity and mortality of TB in CLHA.

- Establish *Intensified* TB case finding.
- Introduce *Isoniazid* preventive therapy
- Ensure TB *Infection* control in health care settings.

Regimen

WHO strongly recommends 6 months IPT for CLHA >1 year age who have no contact with a TB case and are unlikely to have active TB on symptom based screening. For infants with HIV, IPT is recommended for only those who have a contact with TB case and who are unlikely to have active TB.

Apart from above recommendations, 6 months IPT should also be given in CLHA after successful completion of treatment for TB.

Dose

INH is given at a dose of 10 mg/kg/day.

Side Effects

rash, nausea, vomiting and hepatotoxicity.

Other Prophylaxis

Antifungal prophylaxis with azoles has been recommended for adults with HIV living in cryptococcal endemic areas but no such recommendations have been made for children.

ANTIRETROVIRAL THERAPY

Antiretroviral therapy (ART) decreases the mortality in CLHA. Therefore early effective ART is recommended by WHO and NACO. It is important to realize that ART is not a cure for HIV infection, however it improves the long term outcome of CLHA.

Pre Art Work Up

The following work up is needed before a child is started on ART.

Clinical

- Weight, height, head circumference and other measures of growth
- Nutritional status, including assessment of dietary intake
- Developmental assessment
- Concomitant medical conditions (e.g. hepatitis B or C infection, TB, other coinfections or OIs)
- WHO clinical staging
- Details of drugs the child may be receiving, including co-trimoxazole therapy.

Laboratory

- Hemoglobin and complete blood counts
- Biochemical tests: Liver function tests (LFTs), kidney function tests (KFTs), blood glucose, serum electrolytes and if available serum lipids, amylase and lipase levels
- Pregnancy test in adolescent girls (especially those who are going to start on EFV based regimen).
- CD 4 counts and percentage
- Viral load if available.

PRE ART COUNSELING

Once started ART has to be continued lifelong. Hence, identification of primary care giver who understands the implications of ART (lifelong treatment, importance of adherence, side effects) is required. Identifying a secondary care giver who will take care of the child in the absence of primary care giver is also advised. Adequate counseling of caregiver regarding dose, duration, timing and side effects of drugs is mandatory before initiating ART. A 90 percent adherence is recommended for optimum outcome.

TIME OF INITIATION OF ART

NACO recommends ART in

- All infected children <24 months age.
- In children <18 months of age with presumptive clinical diagnosis of HIV.
- In 24 to 59 months age:
 - If WHO clinical stage 3 and 4 disease or
 - CD4 <25 percent or CD 4 count <750 cells/mm³ whichever is lower.
- For >60 months age:
 - If WHO clinical stage 3 and 4 disease or
 - CD4 count <350/mm³.

For CLHA with clinical stages 1 or 2 disease, ART should be started when CD 4 counts falls close to threshold value for initiation of ART for each age group as a drop below the threshold value is associated with higher mortality.

ART in Children with Tuberculosis Infection

- All infants with a diagnosis of TB (PTB or EPTB) should be started on ART
- All children with a diagnosis of EPTB except tubercular lymphadenopathy (TBLN) should be started on ART irrespective of CD4 counts.
- All children with a diagnosis of PTB or TBLN should be considered for ART as follows:
 - On the basis of CD4 counts
 - If CD4 measurements are not available, then children should be started on.

Presumptive Diagnosis of HIV

In HIV antibody positive cases <18 months age, where a confirmation of HIV infection is not possible because of

non-availability of virological testing, presumptive diagnosis of severe HIV infection can be made if he/she has positive HIV antibody test and has two of the following: severe pneumonia, severe sepsis or thrush. Other factors that support the diagnosis of severe HIV disease in an HIV seropositive infant include: recent HIV—related maternal death; or advanced HIV disease in the mother or if the patient has CD4 <20 percent. Such cases should be started on ART with family being informed about possibility of HIV infection. However, the confirmation of HIV infection should be done as soon as possible using age appropriate testing methods. ART should be stopped only when the diagnosis of HIV infection has been ruled out and the child is no longer exposed to infection via breastfeeding from an HIV infected mother. Presumptive diagnosis of HIV disease should not be used in children >18 months age as antibody testing establishes their HIV infection status.

Note

For resource poor settings where CD4 counts are not available, total leukocyte count should not be used as a substitute for CD4 counts. Determination of viral load is not considered a prerequisite to start ART. Defer ART until all acute infections have been treated.

ART DRUGS

ART drugs belong to one of the following categories:

- Entry inhibitors:
 - Chemokine coreceptor (CCR/CXCR) antagonist: Maraviroc
 - Fusion inhibitor: Enfuvirtide (T-20)
- Reverse transcriptase inhibitors:
 - Nucleoside reverse transcriptase inhibitors (NRTI/ NRTI): Zidovudine* (AZT), Stavudine* (d4T), Lamivudine* (3TC), Emtricitabine (FTC), Didanosine (ddl), Abacavir (ABC)
 - Nucleotide reverse transcriptase inhibitors (NtRTI): Tenofovir* (TDF)
- Non-nucleoside reverse transcriptase inhibitors (NNRTI): Nevirepine* (NVP), Efavirenz* (EFV)
- Integrase inhibitors: Raltegravir
- Protease inhibitors: Atazanavir (ATV), Ritonavir* (RTV), Lopinavir* (LPV), Saquinavir (SQV), Indinavir (IDV), Nelfinavir (NFV), Amprenavir (APV), Fosamprenavir (FPV), Tipranavir (TPV), Darunavir (DRV) (*Drugs available at NACO ART programmes for use in children).

MECHANISM OF ACTION

Life Cycle of HIV

After attachment to the glycoprotein receptors of cell, the virion enters the cell by fusing with the cell membrane. After entry into the cell, the viral RNA forms viral DNA

by the enzyme reverse transcriptase. The viral DNA integrates with host DNA with the help of enzyme integrase and the viral protein is formed by translation. The final step involves enzyme protease which helps in cleaving the protein, budding and maturation of the virion leading to lysis of cell and infection of a new cell with the released virion. Figure 1 depicts the life cycle of HIV and mechanism of action of ART drugs.

INDIVIDUAL DRUGS

NNRTI

Zidovudine (AZT)

AZT, a thymidine analog is the prototype NRTI. It is effective against HIV 1 and HIV 2. After phosphorylation in

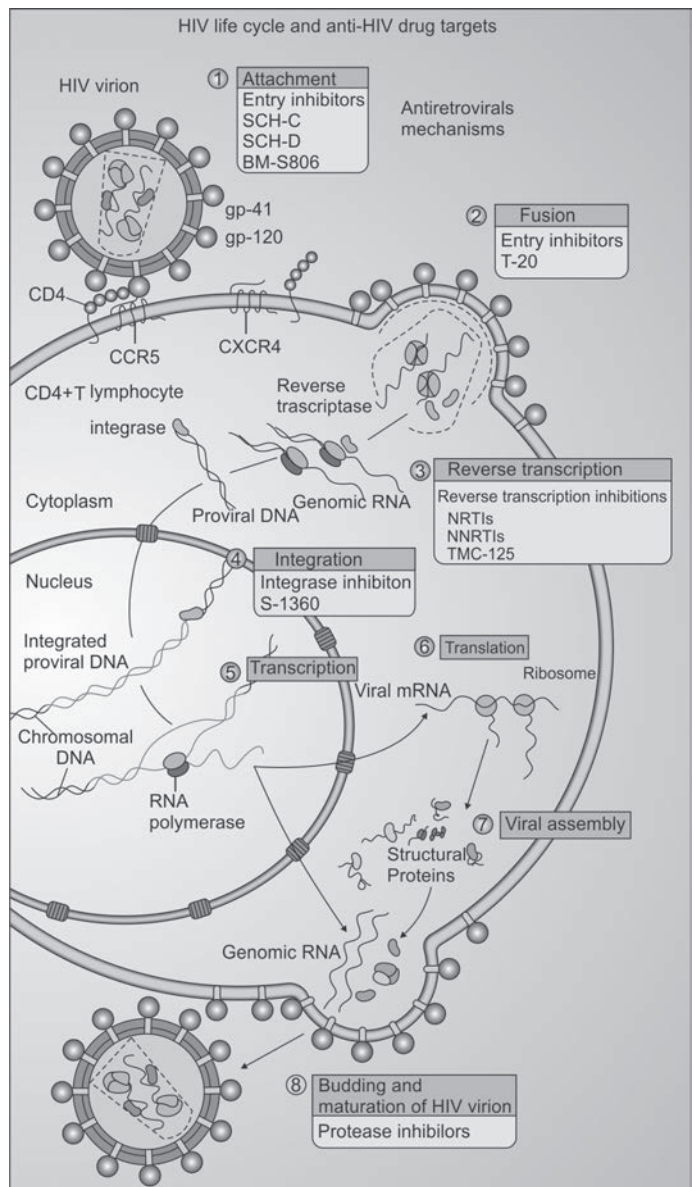


Fig. 1: Mechanism of antiretroviral drug action

the host cell, AZT selectively inhibits viral reverse transcriptase. Hence it prevents infection of new cells by HIV but has no effect on virus directed DNA that has already been integrated into the host chromosome. It also reduces the rate of vertical transmission from mother to child. It is orally absorbed with 65 percent bioavailability and is metabolized in liver. It can cross placenta and is also secreted in breast milk. Hence, it is used for PMTCT.

Side Effects

It is well tolerated by children. The toxicity is due to partial inhibition of cellular DNA polymerase. AZT can lead to anemia and neutropenia by causing bone marrow suppression. Hence hematological monitoring and close follow-up for Hb is advised for children on AZT based regimens (Hb tests to be done at 15 days, 1 month, 2 months, 3 months and six months). Although initial side effects are more common with AZT, it is preferred over other NRTI for long term use. In case of intolerance to AZT, it is substituted with either d4T or ABC, except in cases of lactic acidosis where ABC is preferred.

Dose

180- 240 mg/m²/dose twice daily with a maximum dose 300 mg twice daily.

Stavudine (d4T)

d4T is also a thymidine analog and is effective against both HIV 1 and HIV 2. It is well absorbed orally and is rapidly metabolized. It is used as an alternative to AZT in cases of anemia and neutropenia as it does not have hematological side effects and does not need hematological monitoring. d4T accumulates intracellularly and affects mitochondrial metabolism leading to mitochondrial toxicity, thereby causing side effects like lactic acidosis, peripheral neuropathy, hepatotoxicity and pancreatitis. As the toxicity occurs because of intracellular accumulation of drug and its metabolites, hence the toxicity is gradual and frequently irreversible. The incidence of side effects is less in children as they have higher clearance rate as compared to adults.

Dose

For children with weight <30 kg, the dose is 1 mg/kg/dose twice daily and for children with weight >30 kg, the dose is 30 mg/dose twice daily.

Lamivudine (3TC)

3TC is a deoxycytidine analogue and is a potent NRTI. It is the core component of dual NRTI backbone. It is effective against HIV 1, HIV 2 and Hep B. Point mutation in HIV reverse transcriptase and HBV DNA polymerase gives rise to rapid resistance to 3TC. Some 3TC resistant

mutants also become slow growing. It is absorbed orally and is mostly excreted unchanged in urine. The side effects associated with the use of 3TC are nausea, vomiting, rash and rarely hepatotoxicity.

Dose

2 mg/kg/dose twice daily for infants <30 days old. For >30 days old: 4 mg/kg/dose twice daily. For children with weight >50 kg the dose is 150 mg twice daily.

Abacavir (ABC)

Is an alternative NRTI in first line therapy. It is absorbed orally and it can be taken with food. Of all NRTI, ABC has the least effect on mitochondria and is the preferred substitute for AZT or d4T in children developing lactic acidosis. ABC is associated with fatal hypersensitivity reaction in 3 percent children. Hence, caregivers should be informed about this side effect prior to starting ABC. In children suspected to have hypersensitivity reaction, ABC should be stopped and should never be restarted. Other less severe side effects include nausea, malaise, headache and diarrhea.

NVP and EFV

NVP and EFV are the 2 NNRTI used for ART. NNRTI directly inhibit viral reverse transcriptase without the need for intracellular phosphorylation. Both act against HIV 1 only. NNRTI are potent inducers of hepatic cytochrome P450 and hence induce metabolism of other drugs as well as their own metabolism lead to many drug interactions.

Nevirepine (NVP)

Nevirepine (NVP) is the only NNRTI recommended for use in infants and is the component of all 3 drug FDC currently available. It is well absorbed orally and is extensively metabolized by liver. NVP should never be used alone except when it is given for prophylaxis. Rifampicin decreases the NVP concentration by 20 to 58 percent. For this reason and because of occurrence of hepatotoxicity with both drugs, Rifampicin and NVP are not used together. NVP is preferred in adolescent girls where EFV is contraindicated because of teratogenicity. The potentially life-threatening side effects associated with the use of NVP are hepatotoxicity and skin rash including Stevens Johnson syndrome. It has a higher incidence of rash as compared to other ART drugs.

To decrease the incidence of side effects associated with NVP use, it is given by introducing in small doses (Lead in Period) and gradually the dose is increased. During the lead in period, less dose is given for first 14 days of therapy that leads to decreased incidence of side effects. NVP being an enzyme inducer induces its own metabolism and hence leads to decrease of its own blood levels

after 14 days. Hence, the dose has to be increased after 14 days to achieve optimum effect. However, if the child is already on an EFV-based regimen, and should be put back on NVP, a lead-in dose of NVP is not required.

Dose

160 to 200 mg/m² to a maximum dose of 200 mg twice daily.

Efavirenz (EFV)

Efavirenz (EFV) is NNRTI and is used in CLHA with concomitant active TB. It is less well absorbed orally but has longer half life as compared to NVP. It is not currently recommended for children <3 years of age because of nonavailability of pharmacokinetic data and no consensus regarding dosage. Its bioavailability is increased with a fatty meal. The common side effects are rash, CNS toxicity and teratogenicity. Hence, it is contraindicated in psychiatric patients and adolescent females not using any contraception method. For decreasing CNS side effects, it is given as a bed time dose or 2 to 3 hours after food. The patient should be warned regarding restriction of risky activities during initial 2 to 4 weeks of therapy.

Dose

15 mg/kg/day.

Protease Inhibitors (PIs)

Protease inhibitors (PIs) viral replication by inhibiting the enzyme protease that helps in assembly of new viral particles. As they act at a late step of viral cycle, they are effective in both newly and chronically infected cells. Under their effect, HIV infected cells produce noninfectious viral progeny, hence prevent further infection. RTV is an exception because it is not used for its antiviral property. Rather it is used because of its inhibitory effect on hepatic metabolism and hence it boosts the effect of other PIs. The side effects of PIs include dyslipidemia, lipodystrophy, hepatotoxicity, hyperglycemia, coagulopathy, osteoporosis and vascular necrosis.

Lopinavir (LPV)

Lopinavir (LPV) is the most commonly used PI. It is effective against both HIV 1 and HIV 2. It is used as boosted LPV with RTV (LPV/r). A high fat meal increases its absorption. Hence, it should be given with food. The common side effects are pain abdomen, GI upset and hepatotoxicity. Monitoring of hepatic function is required in children taking LPV especially in children with pre existing liver disease.

ART Regimens

Fixed drug combinations (FDCs) are used for ART to improve adherence. FDC tablets supplied under the national initiative cover children with >5 kg body weight.

For children <5 kg body weight, ARVs have to be in the form of syrups or suspension. It is recommended not to cut adult drugs for administration to children as this may result in inappropriate dosing.

Current ART Regimens for Use in Children Under NACO

The standard first-line regimen used for ART is triple drug therapy (2NRTI + 1 NNRTI). The commonly used NRTI are Zidovudine (AZT), Stavudine (d4T), Lamivudine (3TC) and Abacavir (ABC). The commonly used NNRTI are Efavirenz (EFV) and Nevirepine (NVP).

The first-line regimens for use in children have been labeled as PI, PIa, PII, PIIa, PIII, PIIIa, PIIIb, PIV and P IV a (Table 1).

Regimen PV is the pediatric second-line ART regimen recommended by NACO.

CHOICE OF FIRST LINE ANTIRETROVIRAL THERAPY

- For children not exposed to NNRTI, AZT+ 3TC+NVP is the preferred regimen
- For children exposed to maternal or infant NVP or other NNRTIs used for maternal treatment or PMTCT, the regimen is AZT+3TC+LPV/r as there is a risk of viral resistance to NVP in those exposed to NVP.
- If exposure to ARV is unknown, the regimen is 2NRTI+1 NNRTI.

Special Circumstances

- Anemia/neutropenia: If CLHA has hemoglobin <9.0 gm/dL or neutrophil count <500cells/mm³, avoid AZT and replace it with d4T.
- In children with concomitant active TB, NVP should be avoided and EFV should be used. EFV should not be used in children <3 years age/weight <10 kg and adolescent girls due to its teratogenicity in first trimester.
- Avoid NVP in adolescent girls with CD4 counts >250 cells/mm³ as there is risk of hepatotoxicity.
- For adolescents more than 12 years of age with hepatitis B, the preferred regimen is TDF+ FTC or 3TC+ NNRTI.
- Triple NRTI regimen (AZT/d4T+3TC+ABC) is used in cases of infant and children <3 years of age with active TB and pregnant adolescent girls with CD4 counts >250 cells/mm³.

For most ART drugs, tablets and capsules are available in sufficiently low doses for accurate dosing in children but some drugs do not have solid formulations in doses appropriate for pediatric use.

Initiation of ART in children may lead to rapid weight gain of child, hence the child must be weighed at each visit and the dosage of ART drugs should be changed accordingly to avoid under dosing.

Table 1: Current first line ART regimen for children

<i>National paediatric ART regimen</i>	<i>Type of regimen</i>	<i>Regimen</i>	<i>Remarks</i>
Regimen PI	First-line regimen	Zidovudine+Lamivudine + Nevirapine	Preferred pediatric regimen for starting ART
Regimen PI(a)		Stavudine + Lamivudine + Nevirapine	This regimen is for children starting ART who have Hb ≤ 9 g/dl
Regimen PII		Zidovudine+Lamivudine + Efavirenz	Preferred for children on antituberculosis treatment; Hb >9 g/dL and age >3 yr and weight >10 kg
Regimen PII(a)		Stavudine + Lamivudine + Efavirenz	For children on antituberculosis treatment; Hb ≤ 9 g/dl and age >3 yr and weight >10 kg
Regimen PIII	Alternative first-line regimen	Abacavir + Lamivudine + Nevirapine	For patients not tolerating AZT or d4T on a NVP-based regimen
Regimen PIII(a)		Abacavir + Lamivudine + Efavirenz	For patients not tolerating AZT or d4T on a EFV-based regimen
Regimen PIII(b)		Abacavir + Lamivudine + Lopinavir/Ritonavir	For patients not tolerating AZT or d4T on a LPV/r-based regimen e.g. infants started on LPV/r due to prior exposure to PPTCT regimens containing NNRTI (NVP or EFV).
Regimen PIV		Zidovudine + Lamivudine + Lopinavir/Ritonavir	For patients not tolerating both NVP and EFV, and Hb >9 g/dl
Regimen PIV(a)		Stavudine + Lamivudine + Lopinavir/Ritonavir	For patients not tolerating both NVP and EFV and Hb ≤ 9 g/dl

Side Effects of Antiretroviral Therapy (ART)

Antiretroviral therapy ART drugs have side effects that vary from mild to severe. The following grading system has been proposed for assessing the side effects of ART drugs:

Grade 1 (mild): Symptoms are mild and can be treated with simple drugs, e.g. the use of antihistaminics for rash. Grade 1 reactions do not require discontinuation of therapy.

Grade 2 (moderate): Lead to mild to moderate limitation of activity and require no/moderate medical intervention. ART drugs should be continued but if the side effects persist or if the child does not improve on symptomatic treatment, consider single drug substitution.

Grade 3 (severe): Lead to significant limitation of activity and sometimes hospitalization is required. The offending drug should be substituted without discontinuing ART.

Grade 4 (life-threatening): Lead to extreme limitation of activity and require complete stoppage of ART drugs. ART should be started only after the acute event has been managed and the regimen should be changed.

The common side effects seen with ART drugs are following:

- **Hematological:** Anemia and neutropenia are common side effects and are seen most commonly with AZT. This has an important implication for children residing in malaria endemic areas and also because children

with HIV are malnourished and anemia might be present at the time of initiation of ART.

- **Mitochondrial toxicity:** Because of their effect on mitochondrial metabolism, ART drugs can cause mitochondrial toxicity. The common side effects are lactic acidosis, pancreatitis, hepatotoxicity and peripheral neuropathy. d4T and ddI are the commonly offending drugs.
- **Lipodystrophy:** Abnormalities include fat maldistribution and body habitus changes, hyperlipidemia, hyperglycemia, insulin resistance, diabetes mellitus, osteopenia, osteoporosis and osteonecrosis. These are most commonly seen with d4T.
- **Allergic reactions:** Including skin rashes and hypersensitivity reactions are more common seen with the NNRTI drugs most common with NVP.

Table 2 depicts the common side effects of ART drugs and the drugs that can be used for substituting the ART drug.

Substitution and Switch

“Substitution” is “replacement of a single ARV drug for reasons of toxicity, drug-drug interactions, or intolerance” (usually within the same class) whereas “switch” refers to “replacement of the entire first line regimen in cases of treatment failure” (identified by clinical and/or immunological and/or virological monitoring).

Follow-up of Children on Antiretroviral Therapy (ART)

Children on ART should be followed up once every month for initial 6 months. In patients on NVP, the first follow-up should be at 15 days (the 'lead-in period') followed by the monthly schedule.

Clinical evaluation at every visit should include evaluation for efficacy of treatment which includes clinical improvement including weight gain. Clinical staging using the WHO T staging should be performed. T staging uses the same WHO clinical staging used in initial evaluation and takes into account any new events. Opportunistic infections, if any should be detected and managed. A clinical review for TB should also be done at every visit. Patient should also be assessed for IRIS. Monitoring for adverse drug reaction and counseling for adherence should be an integral part of clinical evaluation.

Treatment Failure and Second Line Antiretroviral Therapy (ART)

Second line drugs are used in case of clinical, immunological or viral failure. The drugs used for second line therapy are less effective, expensive and have more side effects. Hence, before starting a child on second line therapy, it is mandatory to ensure that adequate trial has been given to first line drugs (at least 24 weeks); adherence has been maintained (at least 90%) and all acute opportunistic infections have been treated and immune reconstitution inflammatory syndrome (IRIS) has been ruled out.

Clinical Failure

Refers to progressive neuro-developmental deterioration and/or growth failure despite adequate nutritional support and/or development of new OI or malignancy in an

Table 2: Common side effects/toxicity of antiretroviral drugs

<i>First-line ARV drug^a</i>	<i>Most frequent significant toxicity for the ARV drug</i>	<i>Suggested first-line ARV drug substitution</i>
Zidovudine	Severe anemia ^a or neutropenia ^b	Stavudine or abacavir
	Lactic acidosis	Abacavir
	Severe gastrointestinal intolerance ^c	Stavudine or abacavir
Stavudine	Lactic acidosis	Abacavir ^d
	Peripheral neuropathy	
	Pancreatitis	
	Lipoatrophy/metabolic syndrome ^e	Zidavudine or abacavir
Niverapine	Acute symptomatic hepatitis ^f	Efavirenz ^g
	Hypersensitivity reaction	Preferred substitution by either:
		• A third NRTI (disadvantage, may be less potent) or
	Severe or life-threatening rash (Stevens-Johnson syndrome) ^h	• PI (disadvantage, premature start of 2nd line ARV drug) ⁱ
Efavirenz	Persistent and severe central nervous system toxicity ^j	
	Potential teratogenicity (adolescent girl in 1st trimester pregnancy or of childbearing potential not receiving adequate contraception)	Niverapine
Abacavir	Hypersensitivity reaction	Zidovudine

a. Exclude malaria in areas where malaria is prevalent.

b. Defined as severe hematological abnormality that can be life-threatening and that is refractory to supportive therapy.

c. Defined as severe, refractory gastrointestinal intolerance that prevents ingestion of ARV drug regimen (e.g. persistent nausea and vomiting).

d. Abacavir is preferred in this situation as it is the least likely of the NRTIs to cause lactic acidosis; however, where abacavir is not available, zidovudine may be used.

e. Substitution of Stavudine may not reverse lipoatrophy, but may prevent further progression of the condition. In children, Abacavir or Zidovudine can be considered as alternatives.

f. Symptomatic Niverapine-associated hepatic toxicity is very rare in HIV-infected children prior to adolescence.

g. EFV is not currently recommended for children <3 years of age or <10 kg, and should not be given to postpubertal adolescent girls who are either in 1st trimester of pregnancy or are sexually active and not using adequate contraception.

h. Severe rash is defined as extensive rash with desquamation, angioedema, or serum sickness-like reaction; or a rash with constitutional findings such as fever, oral lesions, blistering, facial edema, conjunctivitis; Stevens-Johnson syndrome can be life-threatening. In most cases of nonlife-threatening Niverapine -associated rash, Efavirenz may be introduced with caution and monitored for adverse events. For life-threatening rash, most clinicians would not substitute Efavirenz due to the potential for NNRTI-class specific toxicity.

i. The premature introduction of the PI class of drugs in first-line regimens limits the choice of drugs in the event of treatment failure

j. Defined as severe central nervous system toxicity such as persistent hallucinations or psychosis

adherent child on ART. For CLHA with pulmonary or lymph node TB or severe recurrent pneumonia (all are stage 3 conditions), a trial of appropriate ATT and antibacterial therapy should be given before switching a child on to second line therapy.

Immunological Failure

Is defined as a drop in CD4 counts after initial immune recovery following ART initiation, to values at or below the age related CD4 cut offs given below or a failure of the CD4 count to rise above these threshold values. Recognition of treatment failure on the basis of immunological values relies on comparison with previous CD4 values, and underscores the need for CD4 measurement at the start of ART. At least 2 CD4 counts are required before declaring immunological failure.

In a fully adherent child ART failure is considered if:

- In 2 years to <5 years old child, the CD4 count is <200cells/mm³ or <10 percent
- In >5 years old child, if CD4 <100cells/mm³.

For children <2 years old, specialist advice should be sought before labeling immunological failure.

Virological Failure

Is recognized as persistent viral load above 5000 copies/ml after 24 weeks treatment in a fully adherent child.

At present, NACO does not recommend routine determination of viral loads in children on ART.

Note

If in a child the CD4 count fall but remain above the threshold level and there are no new clinical event, a switch of regimen is not recommended.

New or recurrent WHO clinical stage 4 conditions may warrant a switch in treatment regimen, although if the CD4 value remains above the age-related thresholds, it may be acceptable to delay switching.

Choice of Second Line Drugs

The following guidelines have been proposed for second line ART in children:

NACO regimen P 5 is second line ART in children. This includes:

ABC+ 3TC+ ddi+LPV/r

- After failure on a first-line NNRTI-based regimen, a boosted PI plus 2 NRTIs are recommended for second-line ART.

LPV/r is the preferred boosted PI for a second-line ART regimen:

- After failure on a first-line regimen of AZT or d4T + 3TC, ABC + 3TC is the preferred NRTI backbone option for second-line ART; ABC + ddi is an alternative.
- After failure on a first-line regimen of ABC + 3TC, AZT + 3TC is the preferred NRTI backbone option for second-line ART; AZT + ddi is an alternative.

- Treatment failure on an alternative triple NRTI regimen can be managed by using drugs from NNRTIs and PIs. The PI component remains essential in constructing a second-line regimen.
- If a child is on a regimen of LPV/r, and also requires ATT, add RTV (LPV/r+r) to a 1:1 ratio of LPV: RTV (superboosting) to achieve full therapeutic dose of LPV.
- If a PI was used as a substitute for a first-line NNRTI drug because of severe toxicity, should the PI fail, it is not considered safe to reintroduce the NNRTI class of drugs.
- As there is cross resistance between AZT and d4T, substituting one with the other is not recommended and both should be replaced with ABC.

Wherever possible, at least one new class of drugs should be used in a second-line regimen.

HIV and TB Coinfection

HIV infection increases the susceptibility to infection with *M. tuberculosis*, the risk of rapid progression to TB disease, and reactivation of disease in older children with latent TB. The comanagement of HIV and TB is complicated by the presence on drug interaction between ATT drugs and ART drugs. WHO proposed the following guidelines for any child with TB and HIV coinfection:

- Any child with active TB disease should begin TB treatment immediately, and ART should be started as soon as tolerated in the first 2 to 8 weeks of TB therapy, irrespective of the CD 4 counts or clinical stage.
- For children already on ART drugs, replace NVP with EFV in children >3 years age.
- For children <3 years age and not exposed to NNRTI, the preferred regimen is 2 NRTI+ NVP or 3NRTI.
- If child is on 2NRTI + NVP and substitution with EFV is not possible, ensure NVP is dosed at maximum dose of 200 mg/m² per dose twice daily.
- For those coinfecting with TB/HIV whose anti-TB treatment includes rifampicin, the dosage of RTV in the LPV/r regimen can be increased to a ratio of 1:1 in order to achieve adequate LPV exposure (superboosting; LPV/r+r).

Note: ART in children should be given using NACO weight band guidelines.

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Viral Encephalitis Including Japanese Encephalitis

Milind M Gore, KP Kushwaha

INTRODUCTION

Central nervous system (CNS) infections due to its preferred position and protection are rare, however, when any CNS abnormality happens it manifests as a very severe disease. In addition, residual damage due to loss of nervous tissue also leads to disabilities at various physical and mental levels. There are numerous medical conditions which may produce an encephalopathic illness; from traumatic to metabolic to immunopathological causes, which may mimic viral encephalitis, Encephalitis refers to an acute, usually diffuse, inflammatory process affecting the brain. While meningitis is primarily an infection of the meninges, a combined meningoencephalitis may also occur. An infection by a virus is the most common and important cause of encephalitis, although other organisms may sometimes cause an encephalitis. A number of metabolic conditions including liver and renal failure and diabetic complications may also cause confusion in diagnosis. (Kennedy, 2004). The time course of the viral encephalitis can be acute, subacute or chronic. Pathologically, there are encephalitis with direct viral entry into the CNS in which brain parenchyma exhibits neuronal damaging and viral antigens. In postinfectious autoimmune encephalitis is associated with systemic viral infections with brain tissue presenting perivascular aggregation of immune cells and myelin damaging (Domigues, 2009).

In order to capture all cases of encephalitis, WHO introduced a term acute encephalitis syndrome (AES). AES is defined as “a disease with acute onset of fever and a change in mental status (including symptoms such as confusion, disorientation, coma, or inability to talk) and/or new onset of seizures (excluding simple febrile seizures) in a person of any age at any time of year. (Soloman et al 2008). After enrolling the AES cases, differential diagnosis should therefore include viral encephalitides (e.g. conditions caused by arbo viruses and herpes viruses) and

infections that involve the central nervous system (e.g. bacterial meningitis, tuberculosis and cerebral malaria) (Dhillon and Raina, 2008).

Acute Encephalitis Syndrome in India

Average state-wise yearly incidence of AES in India for last seven years shows that Uttar Pradesh has the highest cases of AES followed by Assam and Bihar (<http://nvbdcp.gov.in/je-cd.html>) (Fig. 1). It should be noted here that a many of these reports are based on cases admitted in the tertiary government hospitals and thus patients not reaching the hospitals or taking treatment in private nursing homes are not listed. As diagnosis of etiological agent does not alter the treatment modalities no serious attempt is made to diagnose the viral agent. Monthly incidence of AES in various states indicates that in most states AES cases occur during rainy season (Fig. 2). In southern states like Andhra Pradesh and Tamil Nadu, cases can be seen in months of November to January due to south east monsoon in that region, while in northern India there is only one peak during August to October.

A detailed analysis of AES cases from 2008 to 2010 in Gorakhpur and Basti revealed that AES cases have been continuously occurring in eastern Uttar Pradesh since 2005. Most affected districts are Gorakhpur, Kushinagar, Mahrajganj and Deoria. Cases occur throughout the year with highest number of cases during July-October. (Figs 3 and 4.) Mean case fatality rate is 16.77 percent (Range 1.4 to 68%). Age distribution of cases over last three years in Gorakhpur region has indicated that most of the cases (48.4%) are in the pediatric age group and mainly in the age group of 1-10. (Fig. 5) Based on the projected population estimates of 2010 the average incidence of AES cases is 14.7 cases/100,000 population in four most affected districts while it is 6.34 cases/100,000 population in less endemic districts of Basti, Sant Kabir Nagar and Siddharth

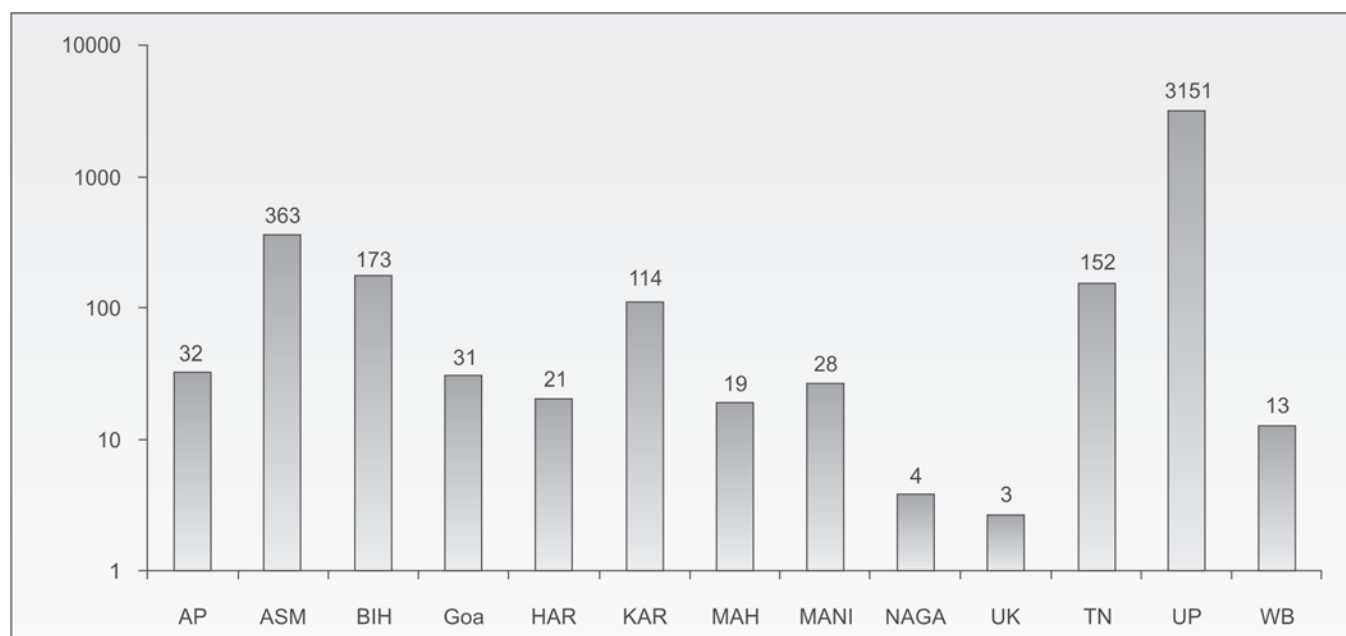


Fig. 1: Average incidence of AES cases in different states in India

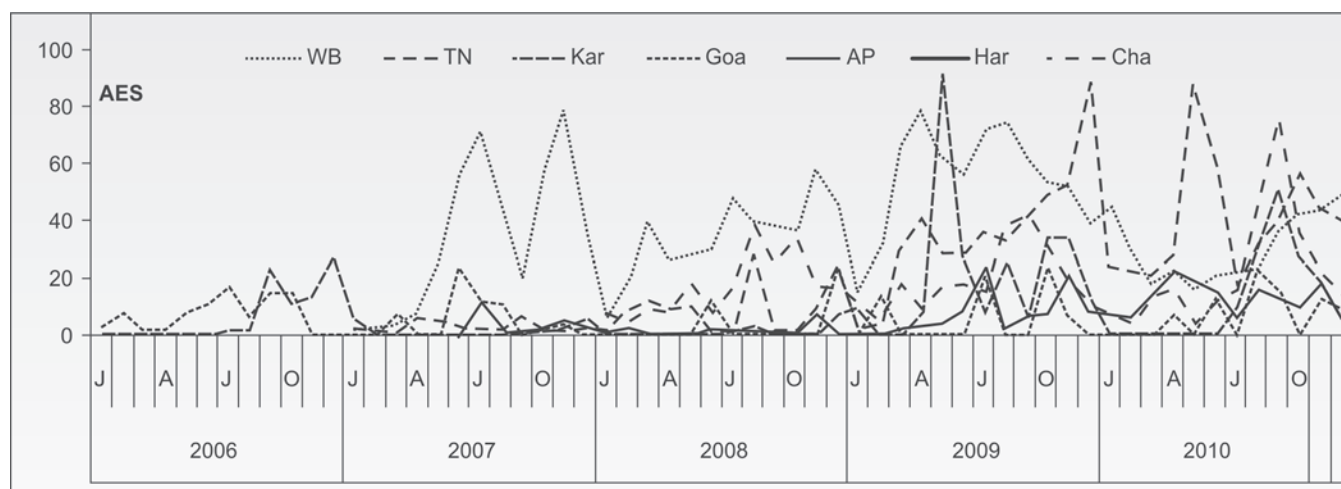


Fig. 2: Monthly distribution of AES cases in different states in India since 2006

Nagar. In Assam however as the rainy season starts earlier, cases of AES occur during April-September with peak activity during months of July and August. Most cases are encountered in age group >15 (65.9%) and cases in the pediatric age group are only 34.2 percent (Fig. 48.6).

Reporting of etiological diagnosis of AES cases depends on the quality of health information systems and the ability to clinically and serologically diagnose the disease. Diagnosis of bacterial and parasitic etiologies of AES is comparatively easier and is carried out on the basis of various clinical, pathological tests. In addition, various low cost diagnostic tests are also available. These cases mainly occur as sporadic cases and are treatable with drugs. In Gorakhpur about 5 percent of AES cases are diagnosed as

having bacterial meningitis while another 4 percent are of tubercular meningitis (NIV data).

Diagnosis of viral meningoencephalitis is difficult and requires elaborate laboratory facilities and thus largely goes undiagnosed. In India, major sporadic viral encephalitis cases are thought to be due to measles and herpes viruses. In addition, limited localized outbreaks of Chandipura, Nipah viruses have been reported by NIV (Gurav et al 2010, Chadha et al 2005, 2006, Rao et al 2004). Recently WN virus encephalitis cases have been reported from Assam (Khan et al 2011). In a prospective study in Delhi India during 2004-05 it was shown that measles and mumps encephalitis constitutes about 7 percent and 10 percent of the viral encephalitis cases. (Karmarkar et al

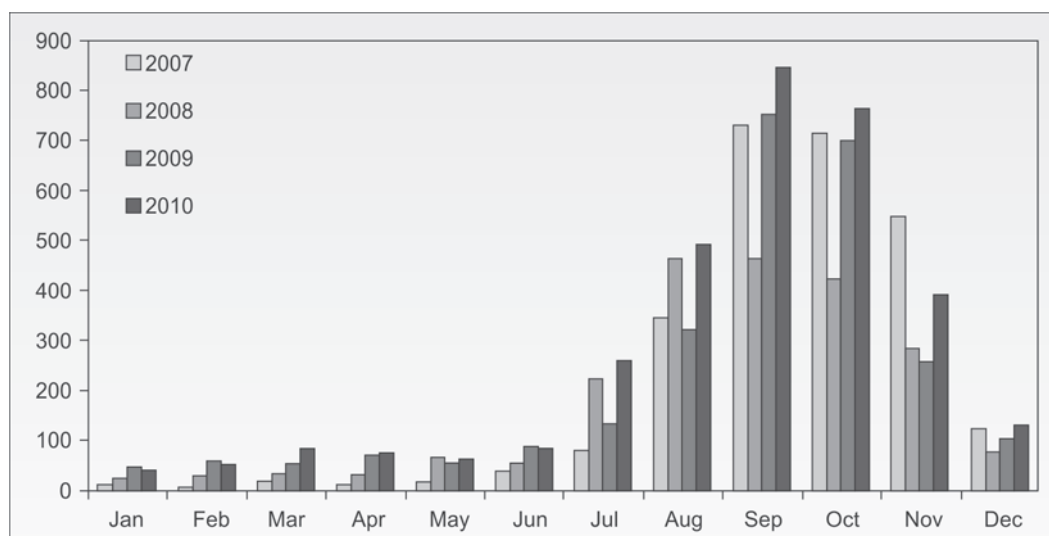


Fig. 3: Monthly distributions of AES cases in Eastern Uttar Pradesh (cases admitted in BRD Medical College, Gorakhpur during 2007-2010)

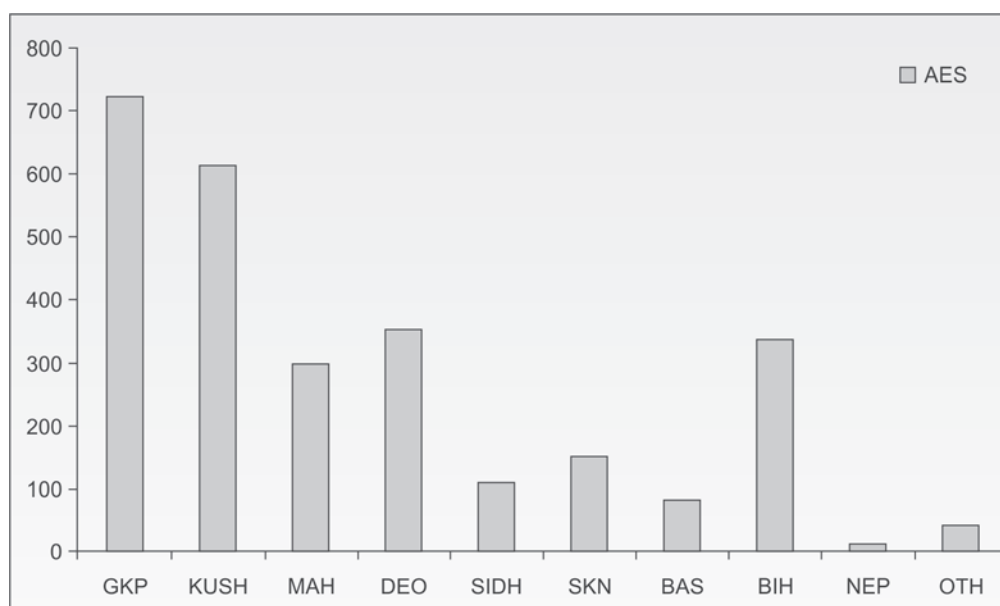


Fig. 4: Average distribution of AES cases in various districts on eastern UP between 2007 and 2010

2008). In another study in Mumbai, India 3.3 percent of the hospital admitted cases of measles showed CNS manifestations. (Raote and Bhawe, 1992). Measles encephalopathy was diagnosed in 5 percent of AES cases. (Kumar et al 1990). In a study from Aligarh as many as 21 percent cases were diagnosed as measles encephalitis (Beig et al 2010). In Vidarbha, Telangana and few districts of Gujarat Chandipura outbreaks also occur (Gurav et al 2010, Rao et al 2004, Chadha et al 2005). Sero-survey in Warangal district has shown that by the age of 15 years >70 of the population has neutralizing antibodies against CHPV (Dr B.V. Tandale, NIV personal communication).

Another major agent that is emerging in causation of viral encephalitis/meningoencephalitis is enterovirus. NIV reported isolation of enterovirus 76 from CSF as one of the agents causing encephalitis in eastern Uttar Pradesh. (Sapkal et al 2009) Subsequent years although the isolations and detection in the CSF has decreased to about 2 percent, detection of enteroviruses in rectal swab samples has been continuing in about 30 percent of the cases. Various enteroviruses, e.g. Coxsackie B3, A11, A22; ECHO 9, ECHO 30, EV 79/89, have been detected in these samples from Gorakhpur and surrounding area. It should be noted that the same areas also have the highest rates

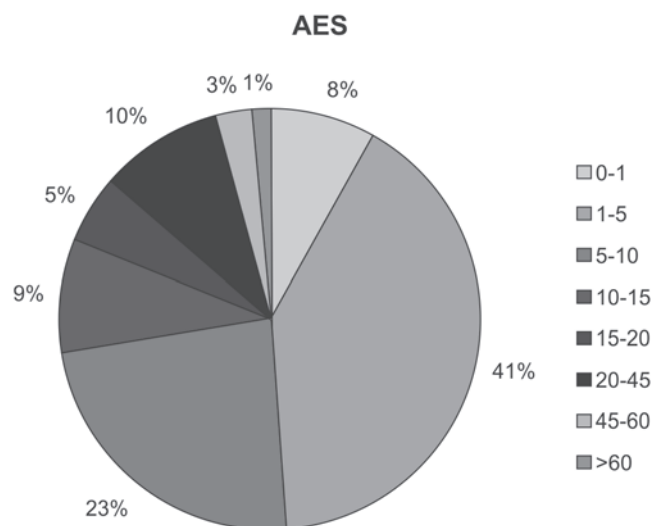


Fig. 5: Average age distribution of AES cases in eastern UP

of acute flaccid paralysis cases reporting every year. This area is however free from wild type polio virus. However, about 30 percent of the stool samples show presence of non polio enteroviruses. (<http://www.npsindia.org/bulletin.pdf>). In addition, a few studies have also reported detection of enteroviruses as one of the major causes of encephalitis. (Kumar et al 1990, Karmarkar et al 2008, Beig et al 2010). Recently, EV 75 has been detected from the CSF of AES cases from Karanataka (Lewthwaite et al 2010).

In South east Asia also enterovirus encephalitis is occurring as a regular feature. Taiwan, Thailand, Indonesia, Philippines have been reporting regular outbreaks of mainly enterovirus 71. Circulation of EV 71 as a causative agent of hand foot and mouth disease and myocarditis has also been reported regularly worldwide (Le et al 2010, Ooi et al 2010, Chen et al 2010, MMWR 2010).

Japanese Encephalitis

Japanese encephalitis (JE) is a vector-borne viral disease that occurs in South Asia, Southeast Asia, East Asia, and the Pacific (Solomon, 2006). An estimated 3 billion persons live in countries where the JE virus is endemic (UN Report, 2005) and the annual incidence of the disease is 30,000–50,000 cases (Solomon, 2006). Nearly half of the human population currently lives in countries where JEV occurs. The annual number of human deaths is 10,000–15,000, and the estimated global impact from JE in 2002 was 709,000 disability-adjusted life years (DALYs) (Solomon, 2006; WHO Report, 2008). The disease can cause irreversible neurologic damage. The JE virus (JEV) is mainly transmitted by the mosquito *Culex tritaeniorhynchus*, which prefers to breed in irrigated rice paddies. This mosquito species and members of the *Cx.gelidus complex* are zoophilic. Wading ardeid water birds (e.g. herons and

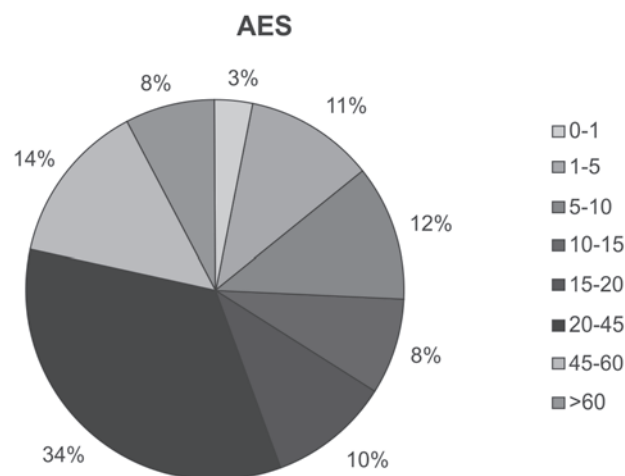


Fig. 6: Average age distribution of AES cases in Assam

egrets) serve as virus reservoirs but the virus regularly spills over into pigs, members of the family of equidae (e.g., horses and donkeys) and humans. Because infected pigs act as amplifying hosts, domestic pig rearing is an important risk factor in the transmission to humans. JE prevalence has been shown in these animals mainly by isolations and also by seroconversion. In India also, many studies have shown the dominance of *Culex tritaeniorhynchus* as a major vector. In Nepal sero-prevalence of JE in pigs, ducks, and horses was 48.11 percent, 26.79 percent, and 50.0 percent, respectively (Pant, 2006). A study in Gorakhpur area also gave similar figures in 2008 (NIV data). In Australia flying foxes have also been thought to be involved (Van den et al 2009).

Diagnosis

Diagnosis of JE is mainly done by IgM anti JEV antibody detection mainly in CSF of patients. In endemic region and during outbreaks serum IgM anti JE antibody can be taken as confirmed diagnosis. In pre ELISA days four-fold rise in Hemagglutination inhibiting (HI) antibodies against JE or four fold decrease in HI titer after 2 mercaptoethanol treatment was the only way of diagnosing a case. In recent years, availability of various good quality IgM capture ELISA kits have made it possible to quickly diagnose JE case. Sensitivity and the specificity of the various kits are comparable with minor differences (Lewthwaite et al 2010A). Use of monoclonal antibody based conjugate to detect the captured virus has also contributed to ease of operation of test. Many kits have now replaced mouse brain antigen source to tissue culture derived antigen increasing further the sensitivity of the test. In addition to this, detection of virus genome in CSF by reverse transcriptase polymerase chain reaction (RT-PCR) and quantitative PCR have also become available. This has

enabled to diagnose a JE case in the first three to five days (Swami et al 2008 Sapkal et al 2007). Test based on reverse transcription loop-mediated isothermal amplification (LAMP) has been developed (Chen et al 2010). Virus isolation from brain, CSF and peripheral blood leukocytes has also been used. (Sapkal et al 2007). In India, NVB-DCP has contributed immensely in increased surveillance network, establishment of diagnostic facilities at various medical colleges and hospitals, and regular supply of JE diagnostic kits made by NIV has made substantial gains in understanding the situation of JE encephalitis.

JE Outbreaks

JE is associated with rainfall and rice cultivation which are major mosquitogenic conditions. Thus, depending upon the rainfall pattern seasonality of JE varies. In India, since 2006 massive efforts are being made to understand the prevalence of JE amongst the AES cases. Major regional hospitals, ICMR laboratories and WHO surveillance network have contributed immensely in understanding the JE encephalitis situation in the country. Following data has been compiled from laboratories of RMRC Dibrugarh, NIV Gorakhpur Unit, Encephalitis group NIV Pune and NIV Bangalore Unit. NIV Pune and Bangalore Unit and RMRC Dibrugarh undertake diagnosis of JE for referred AES cases, while NIV Gorakhpur Unit carries diagnosis of JE for cases admitted in BRD Medical College, Gorakhpur respectively.

Despite the increasing attempts to centralize the case listing mechanisms, comprehensive data is still not available from most of the states. However, understanding of percentage positivity in referred samples gives an idea about the extent of the problem of JE in various states. Thus, about 3 to 6 percent of the cases from various districts of Maharashtra are JE IgM positive. Samples from

Rourkela in Odisha have also shown the JE positivity in -7.5 percent of cases during 2008 to 2010. Recent studies under the WHO surveillance program undertaken in selected center have given that about 10 to 20 percent of the total AES cases are JE in last few years. In Assam and other north eastern states JE positivity has been consistently high.

Data from Assam and Gorakhpur show a very divergent scenario of JE in India. In Gorakhpur JE constitutes 8 to 14 percent of the total AES cases. As the number of AES cases are very large actual number of JE cases are 176, 375 and 417 in year 2008, 09 and 2010. Maximum number of cases of JE occur in the age group 1 to 10 years. During 2008 no adult case of JE was detected, however during 2009 and 2010 31.8 percent of the JE cases are >15 year of age (Fig. 7). JE cases in UP occur during rainy season with peak activity in the months of August –October (Fig. 8).

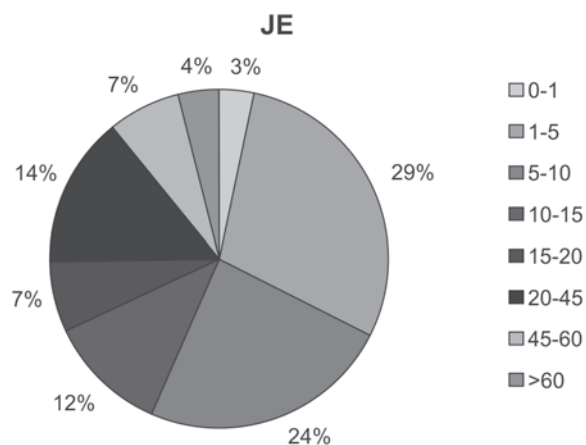


Fig. 7: Average age distribution of AES cases in eastern UP

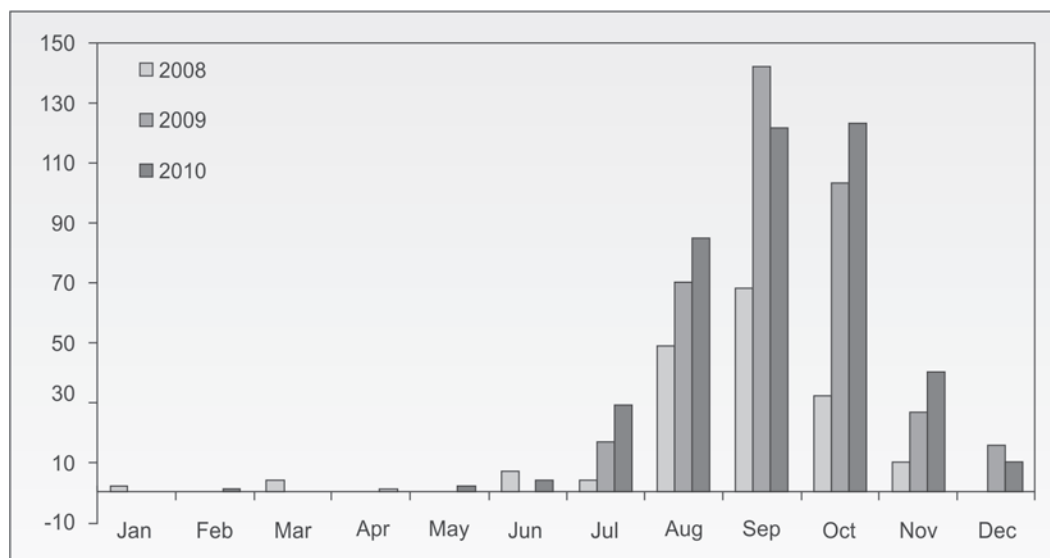


Fig. 8: Monthly distributions of JE cases in Eastern Uttar Pradesh (cases admitted in BRD Medical College, Gorakhpur during 2008-2010)

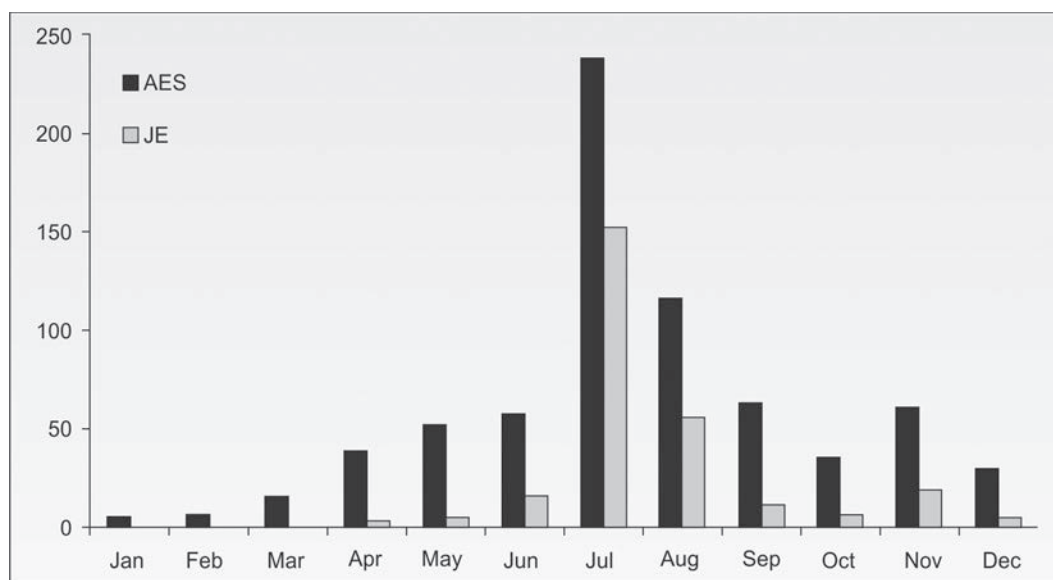


Fig. 9: Monthly distributions of JE cases in Assam during 2008-2010

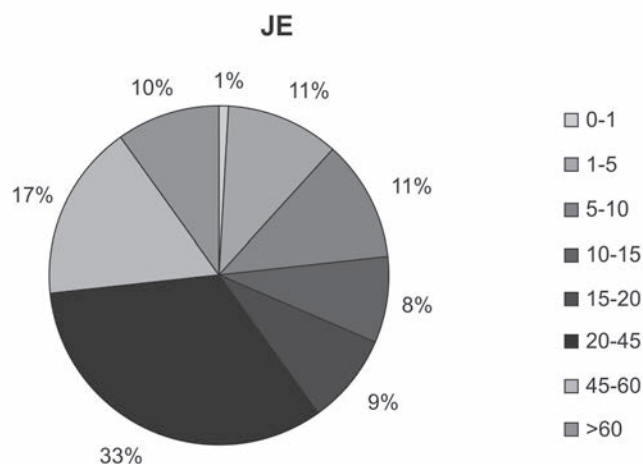


Fig. 10: Average age distribution of JE cases in Assam

Data from Assam however shows that the case positivity rate in Assam for JE is substantially and consistently higher. 47.7 percent, 36.7 percent and 33.3 percent during 2008, 09 and 2010, respectively (Fig. 9). As in the case of AES seasonality of JE also peaks during July Aug because of the early rains in north east. Another divergent feature of this region is the age distribution of JE cases. Majority of the JE cases occur in age >15 years (68.5%) (Fig. 10). Reasons for this deviation in an area where JE activity has been present for a very long time is intriguing.

In rest of the country as in case of AES, the pattern is associated with rainy season. In Andhra Pradesh during summer's incidence of AES is without JE component as many Chandipura encephalitis cases are also encountered (Fig. 11).

JE in South Asia and South East Asia

In many countries in South and South East Asia, JE is endemic. Surveillance of JE has improved and listing of cases of AES and diagnosis of JE has substantially improved the actual enumeration of JE cases. Seropositivity of JE on an average is in tandem of what is seen in India. In Nepal, and northern India, large outbreaks occur in the summer/rainy months; in tropical areas of southern Vietnam, southern Thailand, Indonesia, Malaysia, the Philippines, and Sri Lanka, cases occur more sporadically and peaks are usually observed during the rainy season (Vaughn and Hoke, 1992). In Nepal a recent study shows 18 percent of AES cases to be JE positive (Singh et al 2009), while in 2005 a detailed study gave an estimate of about 55.3 percent (Saxena et al 2009). A study carried out during 2004 to 2005 has given percent JE positivity as 32 percent. (Weirzba et al 2008) This was also a fall out of a situation in Gorakhpur area where a very large epidemic of JE occurred with JE seropositivity of about 30 percent in more than 8000 cases. (NVBDCP) Various estimates of the disease burden have been reported. In neighboring Bangladesh, JE contributed only 4 percent of the AES cases during 2003 to 2005. It is possible that majority of the nonJE cases are due to enteroviruses (Hossain et al 2010).

In countries of South East Asia JE cases occur on regular seasonal basis. In Vietnam about 26 percent cases were due to JE while 9.3 percent were due to enteroviruses. (Le et al 2010). In Thailand, JE remains an important cause with 15 percent cases showing JE positivity in Bangkok hospitals. In Southern Thailand, the JE etiology was at a higher rate (26%) (Olsen et al 2010).

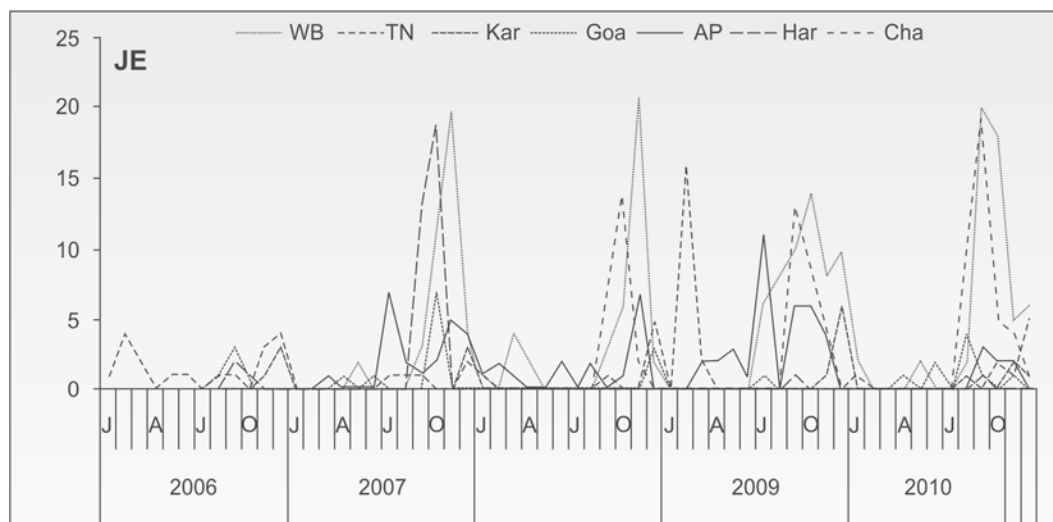


Fig. 11: Monthly distribution of JE cases in different states in India since 2006

In the absence of registering each case and providing diagnosis population based studies will always have bias. In Nepal study, it has been calculated to be 2.1/100,000 population. In another study, the rate was about 7.2 to 8.2/100,000 of children aged less than 10 years of age while it was 0.4/100,000 children with age >10 (Kari et al 2006) or even up to 24.1/100,000 (Weirzba et al 2008). In South India, a study showed the same as to be 15/10,000 children between 5 to 9 years (Gajanan et al 1995). Other studies in South East Asia also indicate the similar trends. In Gorakhpur region the average rate is 1.57/100,000 population in highly endemic four districts of Gorakhpur division while Basti division has the rate of 0.73/100,000 population.

Mortality due to JE has been estimated to be between 20 and 30 percent. In earlier studies it has been estimated to be about 37 percent (Kari et al 2006; Kumar et al 1990), 42 percent (Dhillon and Raina, 2008) while in recent studies it is about 20 percent (I.). Since last two years mortality in confirmed JE cases in Gorakhpur area has been seen to be 20 to 23 percent (NIV Data). In 2010 the mortality was reduced to 17.99 percent.

Molecular Epidemiology

Genetic studies suggest that JEV originated from an ancestral virus in the area of the Malay archipelago. The virus evolved, probably several thousand years ago into different genotypes (I–IV) and spread across Asia (Solomon et al 2003). The history of the clinical recognition and recording of JE dates to the 19th century. JE appeared as recurring encephalitis outbreaks in the summer season. The first clinical case of JE was recorded in 1871 in Japan. Half a century later, also in Japan, a large JE outbreak involving >6,000 cases was documented. Subsequent outbreaks occurred in 1927, 1934, and 1935. In 1924, an agent from human brain tissue was isolated; 10

years later, it was proven to be JEV by transfection into monkey brains. The role of *Cx. tritaeniorhynchus* as a vector and the involvement of wading ardeids and pigs as reservoir hosts were demonstrated in 1938 (Tsai, 1990). Extensive sequencing studies carried out throughout the region has resulted in identifying four genotypes of JE virus that are circulating. Until the early 1990s, only genotype-3 JE virus was identified in Japan, then, the genotype shifted to type-1 countrywide. In China, numerous genotype I JEV strains have been isolated from JE patients, mosquitoes and pigs while genotype III strains remain present in the circulation also. (Liu et al 2011, Wang et al 2010) In Japan, Genotype I was also isolated from horse (Shimajima et al 2011). In a comprehensive study in JEV isolates during 1983-2005 in South Korea, it was observed that Genotype 3 strains were predominant in Korea before 1993, when genotype 1 strain K93A07 was first isolated. The two genotypes were detected simultaneously in 1994 but since then, only genotype 1 has been isolated in South Korea (Yun et al 2010). Based on molecular epidemiological study of JEV in Vietnam, China and Japan, 8 subgroups of genotype 1 JEVs are circulating in East Asia and, at least, 4 of these subgroups are chronologically related and frequently introduced to Japan through China. Possibly, this subgroup distribution is due to bird migration and/or infected mosquitoes which carry viruses for long distances. While in Japan, a small population of genotype 1 is circulating locally. (Tang et al 2009; Morita, 2009; Fan et al 2010). Between 1935 and the 1990s, one of the Korean isolates fell into GII, demonstrating that GII has been circulating for at least 19 years longer than previously thought. (Schuh et al 2010) In India, all the strains that were isolated by various workers since 1956 were of genotype III. NIV has detected and isolated genotype I strains during outbreak of JE in Gorakhpur area (Fulmali et al 2011) (Fig. 12). A novel mutation S227T was detected

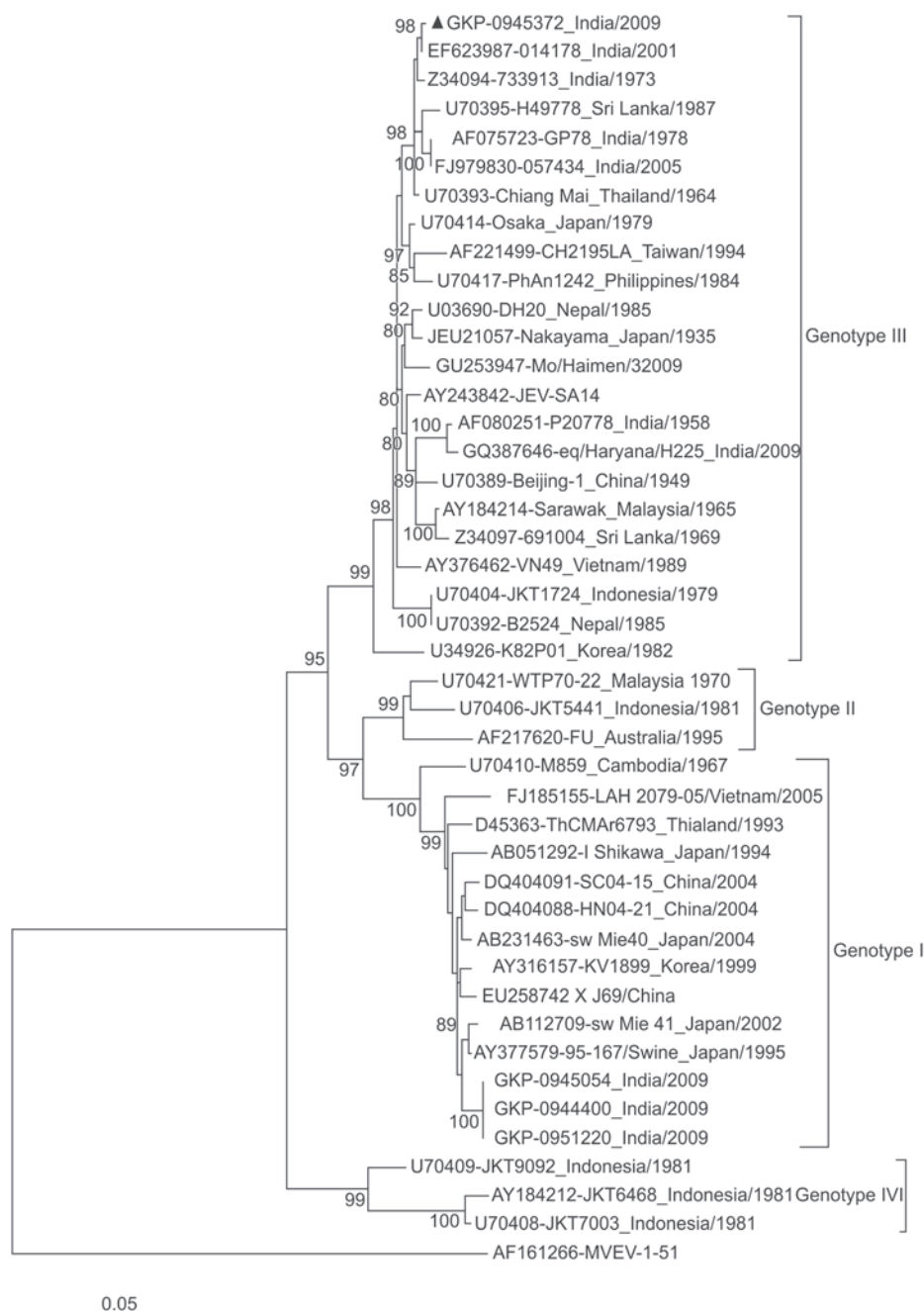


Fig. 12: Phylogenetic tree using a 1381 nt Japanese encephalitis virus envelope sequence directly amplified from CSF's collected in the acute phase of illness from hospitalized AES patients during September – November 2009. Phylogenetic analysis was performed by using nucleotide alignments, the maximum composite likelihood estimation algorithm (for the calculation of pairwise distances), and the neighbor-joining method (for tree reconstruction), as implemented in MEGA software (15). The tree was rooted within the Japanese encephalitis serogroup by using Murray valley virus (GenBank accession No. AF161266). The robustness of branching patterns was tested by 1,000 bootstrap pseudo replications. Each strain is abbreviated with accession number, strain name followed by country of origin and year of isolation. Bootstrap values are indicated above the major branch; 43 taxa comprised the ingroup, and all taxa were rooted with Murray valley encephalitis virus

corresponding to the loop region of domain II, E gene of JEV in comparison to Indian and other isolates from different parts of the world. (Pujhari et al 2010) The introduction of genotype I appears to be recent as even during the RTPCR analysis of CSFs in 2008 did not yield genotype I.

There are 10 fold differences in neutralization by antiserum against Beijing I strain that is used as vaccine in Japan (Nerome et al 2007). In Thailand JE strains from pigs and mosquitoes in 2003 to 2005 belonged to genotype I, which shows a switch from genotype III incidence that started during the 1980s. (Nitatpattana et al 2008) G I of JEV was introduced in China around 1979 and that JEV strains belonging to genotypes 1 and 3 circulate in China. (Wang et al 2007) In India, they are mainly G3, (Saxena et al 2009; Vrati, 2000, Sapkal et al 2007). Analysis using envelope, NS1, NS3, and NS5 genes revealed extensive divergence between the two Indian strains included (Uchil and Satchidanandam, 2008). Our studies on comparison of neutralizability of various strains it was observed that antisera raised against SA-14-14-2 vaccine virus could neutralize Genotype I viruses equally efficiently in comparison to genotype II strain isolated from India (Sapkal GN personal communication).

Clinical Course

Various clinical studies have documented features of clinical disease and the course of illness of JE. Symptomatic JEV infection manifests with nonspecific febrile illness, aseptic meningitis or encephalitis. Encephalitis manifests with altered sensorium, seizures and focal neurological deficit. Acute flaccid paralysis may occur due to anterior horn cell involvement. A wide variety of movement disorders especially transient Parkinsonian features and dystonia (limb, axial, orofacial) are reported in 20 to 60 percent patients. JE mainly affects thalamus, corpus striatum, brainstem and spinal cord as revealed by MRI and on autopsy studies. (Misra and Kalita 2010) A few studies have documented sequel for in patients' followed up to 3 to 6 months. As such about 28 percent cases have shown to have moderate and about 30 percent patients have severe sequel (Ooi et al 2008). In the clinical course of the disease patients have symptoms of fever, nausea, or headache (Chen et al 2009). In addition, during acute illness restricted eye movements, opsoclonus, upbeating nystagmus, and cogwheel rigidity may be seen. There was early and complete recovery of consciousness and eye signs. Parkinsonian features such as positive glabellar tap sign, mask like face, bradykinesia, tremors, and postural instability became apparent as these patients started walking. Reversible mutism was observed in three patients during the acute phase (Pradhan et al 1999) as a secondary feature. The diagnosis of markedly severe dystonia was based on increasingly frequent episodes of generalized dystonia with bulbar, respiratory, or metabolic derangement

or leading to exhaustion or pain. It was associated with marked axial dystonia resulting in opisthotonus and retrocollis in five patients, jaw-opening dystonia, teeth clenching, and oculogyric crisis and neck deviation, severe spasticity and rigidity in five patients, and focal muscle wasting (Kalita and Misra, 2000). This has become one of the differential diagnostic features for JE and non JE AES in recent times.

Pathological and radiological changes have been mainly restricted to thalamic region as evidenced by various CT and MRI studies. Leptomeningeal enhancement and low density lesions were the most common computed tomography findings. T2 hyperintensity lesions and leptomeningeal enhancement were seen in 5 patients. Two patients presenting with acute flaccid paralysis had high intensity lesions on the thalamus and basal ganglion (Chen, 2009) the presence of thalamic abnormalities suggested the diagnosis of JE but their absence did not exclude it. (Dung et al 2009) The EEG and MEP changes were also more frequently abnormal in the JEV group; however, there was no laboratory evidence of JE virus infection in patients with isolated brainstem involvement (Misra et al 2003). In study, using photon emission tomography (SPET), brain perfusion abnormalities observed depended on the stage of the disease. In the acute stage there was focal hyperperfusion to sites of the brain where JE virus is considered to replicate. In the subacute stage focal hypoperfusion was found to be possibly due to virus induced damage of cellular protein synthesis and in the chronic stage perfusion returns to normal due to regeneration of cellular organelles. Our results also confirm the high frequency of thalamic involvement in JE (Barai et al 2006).

In postmortem brain study edema, perivascular inflammation, hemorrhage, microglial nodules and acellular necrotic foci, as has been described. In addition, there was evidence suggestive of viral replication in the vascular endothelium, with endothelial cell damage; uneven binding of the vascular endothelial cells to Ulex europaeus agglutinin I and ultrastructural changes. There was an active astrocytic response, as shown by glial fibrillary acidic protein staining and activation of microglial cells was demonstrated by an increase in major histocompatibility complex class II expression (German et al 2006)

Therapy

No specific antiviral therapy is currently available, and management of patients is undertaken based on the symptoms. Interferon alpha-2a was tested in a double-blind placebo-controlled trial on children with Japanese encephalitis but with negative results (Gould et al 2008). Interferon inducing agents like aloe-emodin (Lin et al 2008), have shown some results in mouse models. Similarly, minocycline (Mishra et al 2009), Curcumin (Dutta et al 2009) and arctigenin (Swaroop et al 2008) as anti

oxidant and anti inflammatory agent have shown some promise in mice in protection from JE. Pentoxifylline has been tried in mice and probably showed its effect through the virus assembly (Sebastian et al 2009). Many of these drugs need to be tried in controlled trials under medical supervision.

Transmission and Vector Control

The emergence of JE can probably be explained by two factors. First, JE-endemic countries experienced an unprecedented population growth in recent decades. For example, in Eastern Asia, South-Central Asia, and Southeast Asia, the population more than doubled, from 1.7 billion in the mid 1950s to 3.5 billion 50 years later (UN Report, 2005). Second, rice-production systems, particularly irrigated rice farming, have increased both in cropping area and cropping intensity. Today, the total rice-harvested area of all JE-endemic countries (excluding the Russian Federation and Australia) is 1,345,000 km², an increase of 22 percent in the past 40 years.

Predicting outbreaks of JE based on the ecological conditions and mosquito density has always been difficult. In addition, ascertaining the infectivity was difficult. Antigen capture ELISA and recently quantitative RTPCRs have been used. (Samuel et al 2010, Yang et al 2010) Efficiency of field testing of these assays in predicting the outbreaks needs to be monitored. Using the remote sensing, satellite imagery and related techniques, large scale prediction of the outbreaks is being tried. The analysis of these methods in South Korea presented a statistically significant linear relationship between the two parameters, proportion of rice field land cover and log₁₀ of the average number of *Cx. tritaeniorhynchus* collected per trap night (Masuoka et al 2010, Richards et al 2010).

Environmental management for vector control, such as alternative wetting and drying of rice fields (also known as intermittent irrigation), can substantially reduce vector breeding while saving water, increasing rice yields, and reducing methane emission (Keiser et al 2005). However, an effective irrigation requires well-organized educational programs, sufficient water at specific times during the rice-growing cycle and an adequate infrastructure. Environmental management measures are most viable if they are readily integrated into a broader approach of pest management and vector management (WHO Report, 2008). Chemical control of vector populations with insecticides such as pyrethroids, organophosphates, and carbamates plays a marginal role in JE control. Although JE vectors are prone to develop insecticide resistance, usually this issue arises with insecticides that are not directly targeted to JE control, but rather are targeted to control of other pests (Karunaratne et al 2000). Relocating of pigs have been thought to help in breaking the transmission, however

a study in Australia indicated that as detection of JEV in mosquitoes after pig relocation could be shown pig relocation did not eliminate JEV risk. (Van den et al 2008) JE has been controlled in South Korea and Japan mainly on the basis of effective vaccination programs, mechanized farming practices and overall increase in the life style (Erlanger et al 2009; Arai et al 2004).

Vaccines

Traditionally, mouse brain derived inactivated purified JE vaccine (Biken) was used in Japan and other parts of the world for a long time. In order to avoid reactogenicity and to reduce the cost of vaccination tissue culture derived vaccines were developed. Currently, three vaccines are licensed or about to be licensed in many countries. 1. Live attenuated SA 14-14-2 vaccine being used in China Nepal, India. An inactivated Vero cell-derived vaccine based on the Beijing-1 strain is developed in Japan by Biken and Kaketsuken. Another promising vaccine candidate is the inactivated whole-virus vaccine IC-51 (Strain SA14-14-2) by the Austrian company Intercell. The third interesting vaccine candidate being in the late stages of clinical trials is the genetically engineered, Chimeric and live-attenuated vaccine ChimeriVax trade mark-JE by the UK/USA-based company Acambis (Paulke-Korinek and Kollaritsch, 2008)

Inactivated JEV vaccine (IC51, Ixiaro) has been licensed in Australia, the USA and Europe. A series of successful Phase III studies has been published. Results indicate a very good safety and efficacy profile. The vaccine promises to become a modern approach to active immunization against Japanese encephalitis (Jelinek, 2009). The single, high-dose regimen of this vaccine resulted in about 60 percent seroconversion rate at 10 days after administration, but it did not reach the almost 100 percent SCR achieved by the 2-dose standard administration at Day 35 (Schuller et al 2009). Vaccine immunogenicity was also observed in pediatric volunteers, with seroconversion rates not significantly different to an active comparator at 56 days post-vaccination (Duggan and Plosker, 2009). Also at 6 months, immunogenicity was higher with IC51 (seroconversion rate [SCR] 95 percent; geometric mean titer [GMT] 84) than other inactivated vaccine with JE-VAX (SCR 74%; GMT:34) At 12 months, the SCR was 83 percent and the GMT(41) remained above the protective titer of 1:10. Most people immunized with IC51 will have protective neutralizing antibody levels for at least a year (Schuller et al 2008, Dubischar-Kastner et al 2010).

Many studies on YF JE Chimeri VAX have been conducted and the vaccine has already being tested in phase II trials across the globe. Safety and immunogenicity of chimeric vaccine has been established (Chokephaibulkit et al 2010). Studies have shown that a single dose of ChimeriVax-JE gives complete protection; the cross-protective immunity elicited with ChimeriVax-JE is durable (>or=5 months) and broad, ChimeriVax-JE remains fully

attenuated in immunodeficient mice lacking type I and type II interferon responses (Lobigs et al 2009). In a long-term study booster dose at the end of 6 months 97 percent volunteers showed a seroprotective titers till month 60 (Nasveld et al 2010)

In China, various studies on attenuated vaccine against JE SA 14-14-2 have been conducted and have been reviewed. In addition to this in recent times, a few trials with single dose vaccine were conducted. In study in Nepal, of the 430 age-sex matched village controls, 234 (54.4%) were vaccinated. The protective effect of vaccine after 12 to 15 months was 98.5 percent (CI 90.1-99.2%) (Ohrr et al 2005) Similarly, in an earlier study, it was observed that among the 219 village controls, 114 had been vaccinated (52.1%) while only one of 20 JE cases had received live-attenuated JE vaccine. Five years after administration of a single dose, SA 14-14-2 provided a protective efficacy of 96.2 percent (CI 73.1-99.9%) (Tandon et al 2007) This was also seen in single dose study in efficacy that none of 20 JE cases had received JE vaccine compared with 326 of 557 age-sex matched village controls. The efficacy of a single dose of JE vaccine was 99.3 percent (CI 94.9-100%) (Bista et al 2001). In order to include JE vaccine in routine immunization and to reduce the cost of administration of vaccine, a combined vaccine trial of measles and JE was conducted in Philippines. It was observed that live JE vaccine and MV administered together are well tolerated and immunogenic in infants younger than 1 year (Gatchalian et al 2008)

In India, various studies on DNA vaccine have been conducted mainly by NII and IISc. (Huang et al 2009; Ramanathan et al 2009) A few studies on baculo virus based vaccine have been also conducted. NIV has a patent of Chimeric T helper B cell peptides that can induce partial protecting in mice (Dewasthaly et al 2001, 2007). NII group has been working on Vero cell based formalin-inactivated JEV P20778 virus vaccine. It induced high levels of protective immunity in mice (Appaiahgari and Vrati, 2004). NIV has been collaborating with Bharat Biotech International Ltd for development of inactivated vaccine using another Indian strain 821564.

The main pillar of JE control is the use of a live attenuated vaccine for humans, which was developed some 40 years ago (Igarashi, 2002). Currently, available JE vaccines are relatively safe and effective, but a drawback is that multiple doses are required (Solomon, 2006; WHO Report, 2008). Effective delivery of the vaccines to poor, rural communities therefore, remains a formidable challenge, and compliance and delivery costs have to be considered (Bharati and Vrati, 2006). Two vaccine candidates are in late-stage clinical development. The first one is a second-generation, live inactivated, single-dose vaccine grown in Vero cells. It is the yellow fever virus-based Chimeric vaccine and will soon enter the market (Solomon, 2006). The second candidate is an attenuated SA 14-14-2 virus strain,

adjuvanted with aluminum hydroxide and also grown in vero cells (WHO Report, 2008; Tauber and Dewasthaly, 2008). The vaccination of pigs represents another potential strategy to control JE but it is not widely used for 2 main reasons. First, the high turnover in pig populations would require annual vaccination of newborn pigs, which would be costly. Second, the effectiveness of live attenuated vaccines is decreased in young pigs because of maternal antibodies (Wada, 1987).

Present Situation

JE is concentrated in China, India, and the Southeast Asian peninsula. In countries such as Bangladesh, Cambodia, India, and Laos, where no specific diagnostic centers, vaccination programs and surveillance systems are in place, the incidence of JE appears to have increased in recent years. One of the major problems in India is correct surveillance of JE. After introduction of AES as a broader category to catch cases, confusion on correct diagnosis has increased. Thus, each government agency maintains different line lists, and the confirmation of cases poor. Thus, understanding the benefit becomes very difficult. In addition, private practitioners and nongovernmental hospitals are not required to report cases to central registry. On the contrary, in China, Japan, Nepal, South Korea, Sri Lanka, and Thailand, where vaccination programs are being implemented and regular surveillance is pursued, the incidence of JE is stable or declining. Despite the availability of WHO supported surveillance, the situation in North Korea, Myanmar, Pakistan, and Papua New Guinea remains largely unknown. However, under-reporting is substantial in most JE endemic countries; hence, it is conceivable that annual JE incidence is considerably higher than heretofore reported. For example, an estimate that used a representative incidence of 25/10,000 (not immunized), and a 1994 population estimate of 700 million children <15 years of age who live in JE-endemic areas suggested 175,000 cases annually with 43,750 deaths, and 78,750 cases with lasting sequel. Adjusted for vaccine coverage, the estimate is 125,000 cases per year (Sutherst, 2004).

In India, SA 14-14-2 was introduced as campaign mode in 2006. Another vaccine drive has been initiated and planned in 2010 and 2011. In addition, it has been made a component of routine immunization program. However, probable poor vaccination coverage, cold chain problems, highlighting of AEFI by media make it difficult for extensive vaccine coverage. This has resulted in lesser control of JE in highly endemic areas like UP. The problem is compounded by emergence of other encephalitic viruses like Enteroviruses and West Nile in Assam respectively.

Conclusion and Outlook

Discovered 125 years ago, JE has spread widely in the 20th century. Almost half of the human population now lives

in countries, where the disease is endemic. JE is a vector-borne epidemic with several features that are typical of an emerging infectious disease. The failure to halt the spread of JE in Asia and the Pacific region, despite the availability of an effective and inexpensive vaccine for 40 years, is of considerable public health concern. One of the main reasons for the proliferation of JE is the ecologic transformation caused by water resources development and management that create suitable breeding sites for vectors and intermediate hosts, which in turn influence, the frequency and transmission dynamics of these diseases (Sutherst, 2004). High-quality data on transmission and incidence of JE are lacking in various countries. Although clinical and serologic methods to diagnose and monitor JE are available, health systems in many developing countries are unable to differentiate encephalitis diagnoses. Examples of countries with successful JE control programs are Japan and South Korea. Before the 1950s, these countries experienced JE outbreaks, but incidence rates have remained stable for >2 decades. The following key control strategies and developments might explain the successful decline of JE in these countries: (1) large-scale immunization programs for humans, (2) pig immunization and the separation of pig rearing from human settlements, (3) changes in agricultural practices (e.g. enhanced mechanization and decrease of irrigated land), and (4) improved living standards (e.g. better housing and urbanization).

It is speculated that JE incidence is increasing mainly in low-income countries. However, because reliable figures about JE emergence are lacking due to the absence of rigorous monitoring systems, more research is needed to support or refute this claim. In any event, lack of political will and financial resources are two important reasons why JE is often given low priority. These factors might explain the paucity of JE immunization programs for children in low-income countries where the disease is endemic. Nevertheless, Sri Lanka and Nepal and Thailand and Vietnam have managed to successfully control JE.

The overall trend of JE has been declining over the past 3 decades and it is anticipated that this trend will continue in the long term. Indeed, China and India influence JE figures on a global scale because most people living in JE-endemic areas are concentrated in these two countries. The incidence of JE in China has declined since 1971, coincident with economic growth and development. Meanwhile, the national JE vaccination program has been integrated into the expanded program on immunization, and at present, >110 million doses of a live, attenuated vaccine (SA14-14-2 strain) are produced annually.

The incidence of JE in India is still increasing, and the case-fatality rate of reported cases is high, i.e. 10 to 30 percent. India currently has embarking on national vaccination program for children 1 to 15 years of age will be immunized. Overall trends for India are difficult to predict

because JE endemicity is heterogeneous and because socioeconomic conditions for control differ substantially from state to state. Coverage of immunization programs and changes in agricultural practices will further influence JE transmission. In Taiwan, for example, the average age for the onset of confirmed JE cases shifted from children <10 years toward adulthood, explained by a high coverage of vaccinated children. Climate change has been implicated in the increase of transmission of several vector-borne diseases.

The culicines that transmit JE are usually highly zoonophilic, and human outbreaks are therefore the result of a spillover of the virus from the animal reservoir into the human population. Studies in Sri Lanka showed that spillovers happen when there is rapid and dramatic buildup of *Culex spp.* populations to the extent that the number of human blood meals passes a threshold after which virus transmission begins. Such rapid buildups are a result of extreme weather conditions or of rice fields in semi-arid areas being flooded before rice is transplanted. Information on vector population dynamics would be very useful in early warning systems and could also help improve targeting of control programs. In conclusion, JE can be controlled, with effective surveillance systems and vaccines playing key roles. Although currently available vaccines are effective, the need for 3 to 4 injections compromises compliance and increases delivery costs (Bharati and Vrat, 2004). The advent of second-generation, cell-culture-derived vaccines will continuously replace mouse-brain and hamster kidney cell-derived vaccines. Such developments will hopefully boost current vaccination programs and deliver safer, more efficacious, and cheaper vaccines that comply with regulatory norms. Political will and commitment, financial resources, intersectoral collaboration (between the Ministries of Health and Agriculture and other stakeholders to set up vaccination programs for young children), as well as changing agricultural practices, pig vaccination, rigorous monitoring, and surveillance will go a long way in controlling JE.

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Influenza Vaccines

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Influenza viruses are responsible for respiratory infections and are important cause of mortality and morbidity among persons of all ages worldwide. Influenza viruses belong to the Orthomyxoviridae family of single-stranded RNA viruses, which include Influenza virus types A, B, and C. Influenza A and B cause majority of human infection.¹ Most seasonal local outbreaks and all worldwide outbreaks (pandemic) are due to Influenza A.¹ Last pandemic was seen in 2009. In April 2009, a novel influenza A virus (H1N1) emerged from Mexico² and has spread to other parts of world through human to human transmission so quickly that by June 11, 2009 World Health Organization (WHO) declared this as pandemic.³ This was the first influenza pandemic of this century and fourth overall since first influenza pandemic was recorded during World War I.⁴ Though 2009 H1N1 influenza pandemic officially ended on August 2010, but it is expected to be the predominant influenza virus that will remain responsible for influenza cases over next few flu seasons.⁵

MICROBIOLOGY

Although there is only one influenza B subtype, influenza A viruses are diverse and are characterized by combinations of their hemagglutinin (HA) and neuraminidase (NA) proteins, these are antigenic projections from the virus surface that facilitate viral entry and exit from human respiratory epithelial cells.⁶ There are 16 HA and 9 NA subtypes of influenza A, and although all can affect avian species, H1–3 and N1 and 2 are the principal antigenic types found in humans.¹ Influenza strains are additionally sub classified according to time and place of first isolation (e.g. A/California/7/04 strain).¹

Unlike most respiratory viruses, influenza viruses have evolved efficient mechanisms that promote antigenic variability. Point mutations in the surface protein genes of influenza, particularly the HA gene, can occur at a high

rate during viral replication and confer a selective advantage by facilitating evasion of host immune responses.⁶ Recent data also demonstrate that antigenic changes favorable to the virus can occur in non-immune individuals (particularly children) merely through binding to host cell receptors.⁷ This gives rise to new influenza strains of the same HA type, a phenomenon termed antigenic drift.⁸ These changes may render the host more susceptible to infection because existing antibodies may fail to protect against the new variant. A second mechanism of variation, known as antigenic shift, is less frequent but more dramatic and can occur either through cross-species transmission (e.g. poultry to humans) or by mixing of viral genes when there is simultaneous infection by more than one strain of influenza in a single human or nonhuman host.^{6,8} The influenza genome is segmented, allowing for the reassortment of genome segments so that one influenza strain (such as H3N1) can acquire a completely new HA or NA gene (such as H1 or N1) resulting in a new virus subtype (such as H1N1 or H1N2). These dramatic and sudden changes in influenza serotypes can result in pandemic influenza, particularly if hosts have no pre-existing protective immunity to the new virus and if there is ready spread from person-to-person in a sustained manner. Variability in influenza antigenicity necessitates annual modifications of influenza vaccines.⁸

Despite the potential diversity of influenza viruses, the predominant influenza strains that have caused epidemics and pandemics derive from only four HA subtypes: H1N1, H1N2, H2N2, and H3N2.^{1,6} Globally, the most common circulating influenza A viruses from 1994 to 2005 were H3N2 (90.6%), H1N1 (8%).⁹ However, this distribution changed significantly with the emergence and spread of the 2009 H1N1 pandemic virus;⁶ between April 2009 and March 2010 in the United States, 98% of the influenza A strains typed were the pandemic H1N1 strain.¹⁰ This was

the result of a triple reassortment (avian/human/swine) of recent North American H3N2 and H1N1 swine viruses and Eurasian avian-like swine viruses, followed by cross-species transmission from pigs to humans. It is antigenically distinct from other human and swine H1N1 influenza viruses¹¹ and by the end of the pandemic in August 2010 had caused >600,000 laboratory confirmed cases of infection.¹¹ The 2009 H1N1 virus strains are now considered the predominant seasonal influenza A strains; seasonal H1N1 virus strains have rarely been detected worldwide since 2009.¹²

EPIDEMIOLOGY

Influenza is one of the most common and important respiratory illnesses affecting all ages. In temperate countries, influenza exhibits a seasonal pattern, with peak activity during the winter months (December through March), and local outbreaks generally lasting 6 to 8 weeks before abating.¹³ The epidemic characteristic is less apparent in tropical countries.¹⁴ Influenza A predominates in most seasons, but epidemics of influenza B can occur.^{15,16} Infections typically spread throughout the general population via outbreaks in schools, nursing homes, and hospitals. The virus is stable in low humidity and at cold temperatures, conditions that favor its transmission.¹⁷ This in addition to the indoor crowding that occurs in winter months, could explain the seasonal pattern of influenza infections. The virus grows to high titer in respiratory secretions, promoting efficient transmission among persons in close contact via large particle droplets generated by coughing and sneezing.¹⁸ Small particle airborne transmission in the vicinity of an infected person may also occur.¹² These mechanisms, in addition to direct person-to-person spread by contact with respiratory secretions, or indirect spread through contact with virally contaminated surfaces where virus can persist for hours,¹⁸ account for the explosive nature of influenza outbreaks.

Influenza viruses infect on average 10 to 15% of the U.S. population annually,^{8,19,20} with rates of illness highest among children.²¹ Attack rates during outbreaks can be more than 40%, particularly among children and those with underlying medical conditions.²¹⁻²³ Seasonal influenza epidemics from 1976 through 2004 were responsible for >200,000 annual hospitalizations and >30,000 influenza-associated deaths annually in the United States.²⁴

However, there is significant variability by season, with H3N2-dominant years being associated with higher pneumonia and death rates than H1N1 years. The influenza death toll is considerably higher during pandemics compared with local epidemics,²⁵ due to the large numbers of persons infected and the lack of protective immunity against the new virus subtype. Pandemics occur infrequently (11 have occurred in the past 300 years) but can be devastating.²⁶ Recent global pandemics include those

of 1918–19 (Spanish flu, H1N1; responsible for 50 to 100 million deaths worldwide),²⁷ 1957–58 (Asian flu, H2N2; >1 million deaths), and 1968–70 (Hong Kong flu, H3N2; >700,000 deaths).²⁶ During the spring of 2009, a novel influenza A H1N1 virus of swine origin caused human infections, with a high fatality rate among previously healthy young and middle-aged persons.^{28,29} Despite initial concerns about a high lethality rate with this novel strain,^{28,29} most illnesses caused by the 2009 H1N1 virus were mild and self-limited.^{23,30} Overall case fatality rates were <0.5%.³¹

CLINICAL FEATURES

Following an incubation period of 2 to 5 days, the onset of symptoms of influenza is generally abrupt, a feature that can distinguish the virus from other viral respiratory infections. However, more gradual symptom onset may also occur.³² Fever is the most common finding, present in >90% of cases; other symptoms include a dry, non-productive cough (>80%), nasal congestion or rhinorrhea (>80%), headache, nonexudative sore throat and constitutional complaints (e.g. myalgias, malaise, fatigue, prostration).³²⁻³⁴ In previously healthy individuals, symptoms typically subside without treatment within 5 to 8 days. The course may be more protracted, and complications more frequent, in high-risk or immunocompromised patients.³⁵⁻³⁸ In addition, features of influenza often vary depending upon age. Attack rates are higher in children than in adults, maximal temperatures tend to be higher among children, and children more often have cervical adenopathy.³² Older adults may present with atypical symptoms such as malaise and confusion, lacking typical respiratory symptoms, although pulmonary complications are much more frequent in the elderly.³²

The risk factors for severe infection due to H1N1 influenza are also similar to seasonal influenza and include different chronic underlying medical conditions such as heart, lung, renal and liver disease, neurological and neuromuscular disorders, cancer, immunosuppression, as well as pregnancy.^{39,40} In addition, among patients with pandemic influenza compared with those with seasonal influenza (16% vs 1%) pregnancy was more frequent as was morbid obesity (body-mass index around 40) and American Indian/Alaska. Native race/ethnicity were risk factors for complications from 2009 H1N1 infection.^{12,22} However, there appears to be a shift of hospitalization and death cases to the younger age groups among those infected with H1N1 compared to seasonal influenza.² The age distribution and severity of disease are similar in different countries. CDC data as of July 31, 2009 showed the highest infection rate occurring in persons 5–24 years; the median age of confirmed influenza cases is 12 years.⁴¹ The incidence is lowest in people ≥65 years. The median age of hospitalized patients with H1N1 influenza is 20 years,

while the median age of deaths was 37 years and the highest rate of hospitalization was among children younger than 4 years. In contrast to seasonal influenza, the rates of hospitalization and death from H1N1 influenza were unexpectedly low in adults ≥ 65 years; 5% and 8% respectively.⁴¹

Persons with influenza may develop primary influenza pneumonia or secondary bacterial infection.^{32,42} Radiographic findings due to primary influenza pneumonia may be unimpressive relative to the degree of hypoxia that occurs.^{32,43} Acute respiratory distress syndrome (ARDS) may develop, likely mediated by a virus-induced cytokine storm.⁴⁴ Primary influenza pneumonia, characterized by diffuse interstitial infiltrates, severe hypoxia, and high mortality, is unusual except during pandemics or in individuals with chronic pulmonary disorders or valvular heart disease and increased pulmonary vascular pressure.^{22,32} Secondary bacterial pneumonia may complicate influenza.^{13,42} *Staphylococcus aureus* or *Streptococcus pneumoniae* infection, often with empyema,⁴² may occur 7 to 21 days following resolution of influenza infection. This heightened susceptibility to bacterial respiratory tract infections may be due to increased adherence of bacteria to influenza virus-infected respiratory epithelium,⁴⁵ decreased mucociliary clearance,³² and impaired function of polymorphonuclear leukocytes, macrophages, lymphocytes, and monocytes.⁴²

Non-respiratory complications of influenza are relatively infrequent but can be devastating. Encephalopathy, pericarditis, and rhabdomyolysis with renal failure may occur.⁴⁶ Central nervous system complications (e.g. encephalitis, myelitis, Guillain-Barré syndrome (GBS), and postinfectious encephalitis) are more common in children than adults.^{47,48} Reye syndrome, which is associated with a variety of viral infections, is perhaps the most severe postinfectious complication of influenza. It occurs primarily in children and manifests as neurological impairment, including delirium, seizure and coma, vomiting, respiratory arrest, and liver dysfunction with fatty infiltration.⁴⁹

Influenza and serious complications of influenza are more common in the elderly (age >65 years), children aged <2 years, adults or children with concurrent illness (e.g. pulmonary, cardiac, metabolic), immunosuppressed persons, and residents of chronic care facilities.^{12,32} Pregnant women are at increased risk for severe primary influenza pneumonia with respiratory failure, particularly during the third trimester.⁵¹ This was true of the 2009 H1N1 influenza pandemic; pregnant and postpartum women experienced severe disease and mortality related to influenza.⁵⁰

DIAGNOSIS

Most patients with influenza either fail to seek medical care due to self-limited nature of the disease or never

have the infection confirmed microbiologically when seen by their health care provider. However, laboratory diagnosis of influenza may be useful for management; targeted therapy can be initiated and unnecessary antibiotics avoided, infection control measures can be implemented, excess testing may be minimized, and health care costs can be reduced.^{1,52} Virus typing is also critical for disease surveillance and vaccine development.

An additional argument for using laboratory testing to confirm an influenza diagnosis is that the clinical diagnosis of influenza in all age groups is difficult to make and prone to error.^{53,54} This is in part because the sensitivity of clinical predictors depends on many factors, including influenza prevalence, age, underlying disease, vaccination rate, and duration of symptoms prior to presentation.^{55,56} The World Health Organization definition for influenza like illness (ILI), consisting of acute fever of $>38^{\circ}\text{C}$ and cough or sore throat in the absence of another diagnosis, was demonstrated to have a sensitivity of only 50 percent and specificity of 87 percent in differentiating 2009 H1N1 influenza from non-influenza illness in adult patients.⁵⁵ The clinical accuracy of diagnosing influenza may be much lower in children.^{54,57}

The gold standard for diagnosis was viral culture. Influenza virus can be isolated from nasal, nasopharyngeal swabs or oropharyngeal swab or combination of these are used.^{32,58} Endotracheal aspirate or bronchoalveolar lavage are taken for intubated patient. The swabs used are Polyester or Dacron swab that have a plastic shaft with synthetic tips. Cotton swab with wooden shaft are not recommended. Specimens are then immediately placed in viral transport medium and kept at a temperature of 4°C during transport to laboratory.⁵⁹ But the problem with virus culture are virus isolation is time consuming, taking 3 to 10 days using tissue culture^{60,61} and expensive and thus not always available. Moreover, although virus titers are often high early in the illness but they fall rapidly and culture may become negative only after 72 hours of symptoms.^{32,61} In one study, only 48 percent of hospitalized elderly persons with influenza confirmed by other diagnostic methods had a positive culture,⁵⁴ and the sensitivity of viral culture ranges in various studies between 50 and 90%.⁶¹ So a negative culture does not rule out infection.

Serological testing by detecting antibodies on paired acute (obtained within 1 week of disease onset) and convalescent (obtained 2 to 3 weeks later) sera, are used to diagnose retrospectively for epidemiological and research purposes but are not useful in the acute care setting.¹

The availability of easy-to-use rapid influenza diagnostic kit that detects viral antigens in respiratory secretions has improved the ability to rapidly diagnose influenza. Direct and indirect immunofluorescence assay are mostly used. These tests are relatively inexpensive, requires less infrastructure and usually provide result in around 1 hour

with a sensitivity of 50 to 90% and a specificity of 95% depending on the incidence, type of specimen and duration of symptoms prior to testing.^{1,61} These tests usually differentiate between influenza A and B infections.⁶² A patient with novel influenza A 2009 H1N1 may test positive for influenza A by the rapid tests but positive test for influenza A cannot differentiate between seasonal and novel influenza A 2009 H1N1 viruses.⁶³ The sensitivity and specificity of rapid tests for diagnosis of novel influenza A 2009 H1N1 is unknown. Initial studies suggest that sensitivity of rapid tests is significantly less compared to polymerase chain reaction in diagnosing novel influenza A 2009 H1N1.⁶⁴ So, a negative test does not rule out infection or an outbreak and rapid diagnostic tests are not essential in patients with typical influenza symptoms during confirmed outbreaks.⁶⁰

Another good method of detection is by detecting viral RNA by reverse transcription-polymerase chain reaction (RT-PCR). This is more sensitive than viral culture or antigen testing and has replaced culture as the gold standard for diagnosis.^{1,12,33,61} But, this testing is costly and not available widely.

Guidelines on categorization of Influenza A H1N1 Pandemic Novel Influenzas cases during screening for home isolation, testing treatment, and hospitalization by Govt. of India (Revised on 05.10.09).

In order to prevent and contain outbreak of Influenza-A H1N1 virus for screening, testing and isolation following guidelines are to be followed:

At first all individuals seeking consultations for flu like symptoms should be screened at healthcare facilities both Government and private or examined by a doctor and these will be categorized as under:

Category A

- Patients with mild fever plus cough/sore throat with or without body ache, headache, diarrhea and vomiting will be categorized as

Category-A: They do not require Oseltamivir and should be treated for the symptoms mentioned above. The patients should be monitored for their progress and reassessed at 24 to 48 hours by the doctor.

- No testing of the patient for H1N1 is required.
- Patients should confine themselves at home and avoid mixing up with public and high risk members in the family.

Category B

- In addition to all the signs and symptoms mentioned under Category-A, if the patient has high grade fever and severe sore throat, may require home isolation and Oseltamivir;
- In addition to all the signs and symptoms mentioned under Category-A, individuals having one or more of

the following high risk conditions shall be treated with Oseltamivir:

- Children with mild illness but with predisposing risk factors.
- Pregnant women;
- Persons aged 65 years or older;
- Patients with lung diseases, heart disease, liver disease, kidney disease, blood disorders, diabetes, neurological disorders, cancer and HIV/AIDS;
- Patients on long term cortisone therapy.
- No tests for H1N1 is required for Category-B (i) and (ii).
- All patients of Category-B (i) and (ii) should confine themselves at home and avoid mixing with public and high risk members in the family.

Category C

In addition to the above signs and symptoms of Category-A and B, if the patient has one or more of the following:

- Breathlessness, chest pain, drowsiness, fall in blood pressure, sputum mixed with blood, bluish discoloration of nails
- Children with influenza like illness who had a severe disease as manifested by the red flag signs (Somnolence, high and persistent fever, inability to feed well, convulsions, shortness of breath, difficulty in breathing, etc.)
- Worsening of underlying chronic conditions

All these patients mentioned above in Category-C require testing, immediate hospitalization and treatment.

TREATMENT

Influenza is generally a self-limiting illness that does not require any antiviral therapy, whether caused by seasonal influenza strains or by novel 2009 H1N1 strain. Antiviral treatment is recommended for suspected or confirmed influenza with severe, complicated or progressive illness or those who require hospitalization.^{12,58} Treatment is also recommended in outpatients with confirmed or suspected influenza if they are at risk for complications based on age (less than 2 yr or more than 65 yr), with underlying chronic medical conditions, pregnancy and immunocompromised patients.^{12,58} The optimal benefit of these medications occurs if they are administered within the first 48 hours of symptoms,⁵⁸ and they can reduce both the duration and severity of illness as well as the chance to develop severe disease or death.^{22,65-68} Although early initiation of antiviral therapy (within 48 hours of symptom onset) is required for optimal benefit, recent data have indicated benefit even in those who start treatment after 48 hours of symptom onset.^{67,69,70}

Two groups of drugs are currently available as anti-influenza medication. These include the adamantanes (Amantadine and Rimantadine) and newer neuraminidase

inhibitors (NAI) (Oseltamivir, Zanamivir and Peramivir). These two groups of drugs differ in pharmacokinetic properties, safety profile and sensitivity.

Adamantanes

Amantadine and rimantadine prevent viral replication within infected cells by blocking the influenza A virus M2 ion channel protein.⁷¹ Influenza B virus also got similar ion channels, but the adamantanes are ineffective against influenza B. Both were shown to be effective to treat^{16,72} uncomplicated infections due to sensitive influenza A. Overall, the duration of illness is shortened by around 1 day with either agent.⁷³ They were also found to be effective in prophylaxis.⁷⁴⁻⁷⁶ Adamantanes are associated with central nervous system toxicity (e.g. anxiety, insomnia, depression, hallucinations, seizures) as they stimulate catecholamine release, but rimantidine does not cause catecholamine release and CNS toxicity are not seen in them both can cause nausea, vomiting, and dyspepsia.^{73,75}

Unfortunately, widespread resistance to adamantanes among influenza A viruses has virtually eliminated the use of these drugs. Resistance can result from a single amino acid substitution within the viral M2 protein,^{9,77} and cross-resistance between amantadine and rimantadine is complete.^{73,78} In 2009 pandemic, resistance was detected among all 2009 H1N1 viruses tested in USA,⁷⁹ and high levels of resistance have been seen worldwide.⁹ Many treated patients shed adamantane-resistant influenza virus in the later stages of illness and this can result in outbreaks with drug-resistant virus. Therefore, the use of adamantanes for treatment or prophylaxis of current influenza viruses has been discouraged.^{12,80,81}

Neuraminidase Inhibitors (NAIs)

Currently NAIs are the drug of choice for prophylaxis and treatment of influenza. Apart from some sporadic cases, viral surveillance data indicate more than 99 percent influenza virus are still susceptible to NAIs. US FDA approved drugs are Oseltamivir and Zanamivir. They inhibit the viral NA enzyme by mimicking its natural substrate, N-acetylneuraminic acid (also called sialic acid), the cell surface receptor for influenza.⁸² Viral NA removes sialic acid from cell surface glycoproteins and thereby releases progeny influenza virus from infected host cells.⁷³ Neuraminidase inhibition leads to persistent attachment of virus to the host cell; viral replication and intensity of infection are thus reduced.⁷³ NAIs are active against both influenza A and B, but they are less active against influenza B.^{15,83,84} In comparison to adamantanes, NAIs have little toxicity. Whereas Oseltamivir is given by oral route, Zanamivir is given by inhalational route by dry powder inhalation. Dosing is similar to what is given in seasonal influenza and duration of treatment is 5 days. Long term therapy may be given in hospitalized patient with severe persistent

symptoms. Peramivir, another NAI, is under Phase 3 trial, given by Intravenous route was used in 2009 H1N1 pandemic to treat severely ill hospitalized patient successfully. Early treatment with NAIs was shown in randomized, controlled trials to shorten the course of illness.^{65,85-88} Duration of symptoms is typically decreased by 1 to 2 days in patients receiving NAIs compared with those receiving placebo,^{65,83,85,88} NAIs also reduce complications of influenza,⁸⁹ including sinusitis, bronchitis,⁸⁷ and otitis media.⁸⁸

Prophylaxis

Oseltamivir or Zanamivir is used for prophylaxis, in half dosage to what is used for treatment for total 10 days.⁹⁰ Prophylactic treatment is not indicated for healthy adult or children due to potential exposure in school or community. Prophylaxis is indicated for 'at risk' individual who may develop severe complication have been in contact with a person who have been diagnosed or suspected of having H1N1 influenza. Prophylaxis is also advocated for health care worker who come in close unprotected contact with diagnosed case of H1N1 influenza. Prophylaxis should be given within 48 hrs of exposure.⁹⁰

INFLUENZA VACCINE

Cornerstone for prevention of influenza and its complication is vaccine. In case of influenza, immunity response is provided by antibodies to surface antigen, particularly to HA antigen. But the problem is that antibody to one influenza type or subtype or antigenic variant confers little or no protection against other influenza types or subtypes or antigenic variant of the same type or subtype.⁹¹ Due to antigenic drift, this antigenic variant is quite frequent in influenza virus. But influenza vaccines are targeted against such an antigen which is prone to change therefore vaccines must be reformulated annually based on the changing pattern of influenza virus. This input regarding the changing pattern of influenza virus is usually given by World Health Organization (WHO).⁹² In February and September of each year, for the Northern and Southern Hemispheres, respectively, the influenza virus strains to be included in the coming season's vaccine are selected.⁹³ Two strains of influenza A (one H3N2 and one H1N1) and one of influenza B are selected and mixed in each vaccine to elicit broad serum immunoglobulin G (IgG) responses against surface HA and NA proteins of circulating strains. However, if significant antigenic change occur after this, as occurred in 2009, the vaccine may fail to cover the circulating influenza strains.⁹⁴ Another problem is, the current technology for developing influenza vaccines (i.e., egg-based manufacturing) is slow and existing supplies of vaccines can be inadequate in the face of a global pandemic.⁹⁵ As evidence of this, in response to the beginning H1N1 pandemic, the WHO made recommendations for vaccine strains in May 2009, but the virus replicated

poorly in embryonated chicken eggs, leading to vaccine shortages. Though production of vaccine in embryonated eggs has been safe and effective, but cell-culture based vaccine production is more rapid and it would also allow vaccination of persons with egg allergies.⁹⁶

Currently available seasonal influenza vaccines include the trivalent inactivated vaccines (TIVs) and live attenuated influenza vaccine (LAIV).⁹⁷ Both vaccines contain the same antigenic variants of influenza A and influenza B viruses which are predicted by WHO.⁸ Seasonal influenza vaccines are unlikely to protect against 2009 H1N1 influenza due to antigenic variation.^{11,98} It is observed that no cross reactive antibodies to 2009 H1N1 influenza virus developed in children receiving seasonal influenza vaccine.⁹⁸ Specific monovalent H1N1 influenza vaccines have been developed. Similar to seasonal influenza vaccine, both inactivated and live attenuated formulations against Influenza A (H1N1) 2009 are available and these are also produced by replicating the virus in embryonated hen eggs. The vaccines contain the strain A/California/7/2009 (H1N1) pdm.⁴¹ U.S.-licensed influenza vaccines do not contain adjuvants while some vaccine may contain adjuvants (with alum or MF-59) (Table 1).

In June 2010, first ever indigenous H1N1 vaccine was produced in India. This is an inactivated (whole virion) monovalent (H1N1) 2009 influenza vaccine. The vaccine is recommended for 18 years and above and should be administered by a single 0.5 ml intramuscular injection preferably in deltoid region.⁶⁴ Subsequently other indigenous vaccine including nasal live vaccine against influenza (H1N1) 2009 are started to be produced in India.⁹⁹

Whom to Vaccinate

Due to the short supply of influenza vaccine during the initial period of 2009 outbreak, the CDC' Advisory Committee on Immunization Practices (ACIP) recommended priority wise vaccination to five groups considered at the highest risk of influenza complications. These include:

- Pregnant women
- Close contacts of children less than 6 months of age

- Health care personnel
- Children and young adults 6 to 24 years of age and
- Persons 25 to 64 years of age with underlying medical conditions that are associated with increased influenza mortality and morbidity⁴¹

If the vaccine still does not fulfil the requirement of above group, ACIP recommended vaccination to 1st 3 groups. When vaccine becomes available then target population should be vaccinated as early as possible. Since 2010, ACIP started to recommend annual influenza vaccination of all persons ≥ 6 months age.

In India due to financial burden, use of influenza vaccine is very limited. After the pandemic of 2009, currently IAPCOI recommends influenza vaccine in all children with risk factors and also where the vaccine is requested by parents (after discussing benefits and limitations of the vaccine)

At risk individuals

- Congenital or acquired immunodeficiency
- Chronic cardiac, pulmonary, renal, liver, hematological disease and diabetes mellitus
- Children on long-term aspirin therapy
- Any neurologic disease that might cause respiratory compromise or impair the ability to handle secretions

Individual Vaccines (Table 2)

Inactivated influenza vaccines are basically of 3 types viz whole virus, split product and subunit vaccine. Whole virus vaccines are not used due to increased adverse reactions. Currently available vaccines are either split product vaccines (detergent treated) or subunit vaccines containing surface antigens in form of purified hemagglutinin and neuraminidase. Trivalent vaccines contain 15 μg of each of WHO recommended strain. Storage temperature is 2 to 8°C and should not be frozen.

Live attenuated vaccine is made by genetic reassortment of three influenza strains. It is also stored between 2 and 8°C. It is administered by a nasal spray that deposits the vaccine in nose and nasopharynx.

Table 1: Dosing schedule¹⁰⁰

Vaccine type	Age group	Dose	Route
Inactivated	6-35 months	0.25 ml, 1 or 2 doses, 4 weeks apart	Intramuscular
	>36 months	0.5 ml, 1 or 2 doses, 4 weeks apart	
	9 years	0.5 ml, 1 dose	
Live attenuated	2-49 year	0.2 ml sprayer, 1 or 2 doses, 4 weeks apart	Intranasal

* Children aged 6 months through 8 years who did not receive seasonal influenza vaccine during the 2010–11 influenza season should receive 2 doses at least 4 weeks apart for the 2011–12 season. Those children aged 6 months through 8 years who received ≥ 1 dose of the 2010–11 seasonal vaccine require 1 dose for the 2011–12 season. ≥ 9 years 1 dose. Revaccination annually.¹⁰⁰

* For adults and older children, the recommended site of vaccination is the deltoid muscle. The preferred site for infants and young children is the anterolateral aspect of the thigh.¹⁰⁰

Table 2: Comparison between inactivated and live influenza vaccine

	<i>Inactivated vaccine</i>	<i>Live vaccine</i>
Vaccine structure	Purified HA and NA antigen	“cold adapted” virus, ¹⁰¹ meaning it cannot replicate at temp. <25° C and thus is restricted to replicating in the upper airway.
Immune responses, whereas	Higher serum IgG response	Better IgA mucosal response at the site of entry. ⁸
Age of administration	>6 months	Healthy persons aged 5-49 years ¹⁰²
Route of administration	Intramuscular	Nasal
In person with underlying medical condition, pregnancy	Can be given	Not given due to higher risk of complication ¹⁰²

Vaccine Strain for 2011-12 Influenza Season

The 2011–12 U.S. seasonal influenza vaccine virus strains are identical to those contained in the 2010–11 vaccine. These include A/California/7/2009 (H1N1)-like, A/Perth/16/2009 (H3N2)-like, and B/Brisbane/60/2008-like antigens. The influenza A (H1N1) vaccine virus strain is derived from a 2009 pandemic influenza A (H1N1) virus.¹⁰³

Timing of Vaccination

The influenza vaccines should be given before the peak influenza season. In temperate countries the peak influenza season is in winters (December to March), in tropical countries like India illness occurs all over the year. So, the vaccine can be given at any time but generally given as soon as the new vaccine becomes available in the market or at the time of presentation to health care worker. Recently, WHO global influenza surveillance network have shown, in India, influenza peaks during monsoon (June to September). So, vaccine may be administered before monsoon, but new vaccine becomes available in India in late monsoon (around August).

Efficacy

If the vaccine strain match the circulating influenza virus strain, inactivated vaccines provide 70 to 100 percent protection among healthy adults and 30 to 60 percent among the elderly or young children.^{104,105} Serum antibody responses to influenza vaccination may be blunted in the elderly, immunocompromised individuals and preschool children compared with healthy school-age children or adults.⁷³ Protection against viruses similar to those in the vaccine generally lasts 6 to 8 months but can be much longer.⁹¹ A meta-analysis of 25 studies of healthy adolescents or adults (aged 14 to 60 years) found that TIV reduced serologically confirmed influenza by 70 percent compared with unvaccinated individuals.¹⁰⁶ In a study of children aged 5 through 8 years who received trivalent

inactivated vaccine (TIV) for the first time, the proportion of children with protective antibody responses was significantly higher after 2 doses than after 1 dose.¹⁰⁷

Both TIV and LAIV are effective in children and adults, and there are insufficient data to conclude there is an advantage of one over another.⁹¹ A randomized study comparing TIV to LAIV in healthy adults during the 2004–05 influenza season showed that LAIV was less effective than TIV, primarily due to reduced activity against influenza B viruses.⁹⁷ However, in children aged 6 to 59 months, LAIV was shown to be more efficacious than TIV, with 55 percent fewer cases of influenza in the LAIV group.¹⁰⁸ It has been postulated that LAIV may be more effective in young children or vaccine-naïve individuals because it may not replicate as well (and thus stimulate a less effective immune response) in an individual who already possesses some neutralizing antibodies to influenza.¹⁰⁹

The 2009 H1N1 monovalent vaccine was found to have immunogenicity similar to that of typical seasonal influenza vaccines.¹¹⁰

Vaccination in Children

As noted earlier, young children are at high risk for acquiring and transmitting influenza infections.^{13,33,34,111} Several studies in healthy children^{112,113} have demonstrated a 55 to 70 percent reduction in laboratory-confirmed cases of influenza after administration of TIV or LAIV. Both can also reduce the incidence of otitis media in infants.¹¹⁴ Furthermore, the efficacy rate improves from 89 percent with one dose to 94 percent with two doses 60 days apart.¹⁰¹

Vaccination of children in schools can reduce the incidence of influenza among family contacts¹¹² and the community at large.¹¹³ In Japan, implementation of a national child immunization program where >80 percent of school children received influenza vaccine prevented between 37,000 and 49,000 deaths (one death per 420 vaccinated children), principally in the elderly.¹¹³ When vaccination of children subsequently became optional, mortality rates increased. Results from these studies suggest that universal

vaccination of school-age or preschool children should be encouraged to develop herd immunity and benefit the community at large.¹¹⁵

Vaccination in Special Group

- Vaccination of health care workers (HCWs) is highly effective in protecting high-risk patients from influenza.^{116,117} Studies have found that vaccination of HCW in hospital can reduce mortality among hospitalised patient as well as lower worker sick leave.¹¹⁸ The CDC has recommended achieving high influenza vaccination rates of HCWs to prevent transmission between HCWs and patients.¹¹⁹
- Influenza vaccination is beneficial among elderly adults (>65 yr) living in the community or nursing homes.^{34,120} Vaccination was associated with reduction in the rate of hospitalization and mortality for pneumonia and influenza.
- Influenza vaccine also found to be beneficial in adult with concurrent medical illness and other high risk patients like in pregnancy, immunocompromised patient and recommended strongly in these group because of the potential for serious morbidity and mortality.³¹

ADVERSE EFFECT

Clinically important adverse effects are uncommon. With TIV, mild soreness of the arm at the site of vaccination for 1 to 2 days and fever, malaise, headache and arthralgia can occur. Hypersensitivity to other vaccine components can occur but is also very uncommon.⁹¹ Previously GBS was said to be rare adverse effect of influenza vaccination but now it has been shown that GBS was not associated with influenza vaccine. LAIV is well tolerated in children and adults.¹⁰¹ Mild upper respiratory tract symptoms (rhinorrhea, sore throat, nasal congestion) develop in 10 to 15 percent of persons receiving LAIV.^{8,101}

CONTRAINDICATION

Both vaccines are contraindicated in patients who are allergic to eggs, but even in this context serious hypersensitivity reactions to the vaccine are rare.¹²¹ Live vaccine should not be administered to immunocompromised individuals and in pregnancy, although inadvertent exposure to LAIV is not expected to lead to significant adverse events or prolonged viral shedding in persons with chronic medical conditions including human immunodeficiency virus infection.¹²²

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CHAPTER 50

Newer and Emerging Vaccines

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Vaccination is one of the most effective methods of intervention for prevention of diseases without improvement in overall socioeconomic status of a country. It is one of the most rapidly changing fields of medicine. Many vaccines against viral, bacterial, parasitic diseases and malignancies are under development, out of which only few have reached to clinical trials including malaria, dengue, HIV and hepatitis E vaccine. A brief review of new and emerging vaccines of global importance is presented.

MALARIA VACCINE

Malaria is a disease of global importance and afflicts more than 90 countries and territories in the tropical and subtropical regions. The World Health Organization (WHO) estimates 300 to 500 million malaria cases annually, with estimated mortality attributed to malaria ranging from 0.7 to 2.7 million/year globally.¹ Approximately 2.48 million cases are reported annually from South-east Asia, of which 75 percent cases are contributed by India alone. WHO has reported malaria mortality rate 15000 per year from India; however, a recent study by million death collaborators suggest much higher annual malarial mortality from India (205,000 overall and 55000 in children <14 years age).²

RTS,S/AS01 is a hybrid construct of the hepatitis B surface antigen fused with a recombinant antigen derived from part of the circumsporozoite protein. Given in three doses, it is formulated with an adjuvant (AS01 or AS02) and must be maintained in a cold chain³. The vaccine targets the parasite's circumsporozoite protein—the most prominent surface antigen on the sporozoite of the malaria parasite. The RTS,S vaccine triggers the immune system against *Plasmodium falciparum* when it enters the bloodstream or when it infects liver cells. This is the protein coat of the sporozoite, the parasite stage that is inoculated by the feeding anopheline mosquito, which then

invades liver cells and multiplies there before entering the bloodstream. Keys to the success of the vaccine are the immunogenic polymeric nature of RTS,S particles and the proprietary adjuvant AS01⁴. This vaccine has shown protection against *Plasmodium falciparum* malaria in children and infants in initial phase I trials. The vaccine had an acceptable side-effect profile and was immunogenic in children who were 6 weeks of age or older. In addition, the vaccine could be administered safely with other childhood vaccines and provided protection against severe malaria.^{5,6}

First results of recently published phase 3 trial of RTS,S/AS01 vaccine in African children has reported good efficacy and safety against both clinical and severe malaria. This randomized, controlled, double blind trial was designed to evaluate vaccine efficacy, safety, reactogenicity, and immunogenicity in children 6 to 12 weeks and 5 to 17 months of age after the administration of malaria vaccine. Initial results of the trial included 6000 children aged 5 to 17 months old enrolled at 11 centers in seven African countries. They were randomized to three doses of the new vaccine at one month intervals or a non-malaria comparator vaccine. During 12 months of follow-up, the incidence of the first or only episode of clinical malaria meeting the primary case definition was 0.44 per person-year in the RTS,S/AS01 group and 0.83 per person-year in the control group, resulting in a vaccine efficacy of 55.8 percent (97.5% confidence interval [CI], 50.6 to 60.4). At least one episode of severe malaria that met the primary case definition occurred in 57 of 2830 children (2.0%) in the RTS,S/AS01 group and in 56 of 1466 children (3.8%) in the control group, for a vaccine efficacy of 47.3 percent (95% CI, 22.4 to 64.2). Among children in the combined age categories, at least one episode of severe malaria that met the primary case definition occurred in 149 of 8597 children (1.7%) in the RTS,S/AS01 group and in 116 of

4364 children (2.7%) in the control group. Thus this anti-malarial vaccine halved the number of first clinical episodes of malaria and severe malaria in children in the 12 months after vaccination. The vaccine's protection was lower at the end of 12 months, suggesting that a booster may be needed. Results of one year efficacy in children aged 6 to 12 weeks are expected late next year and final efficacy and safety data for both age groups are expected in late 2014.⁷

Among adverse events, generalized convulsive seizures in the 7 days after RTS,S/AS01 vaccination occurred at a rate of approximately 1 per 1000 vaccine doses, a higher rate than that seen with the comparator rabies vaccine. All cases were associated with a history of fever, and all children recovered from the acute event. This increased risk of febrile reactions or seizures among RTS,S/AS01 recipients may be real, reflecting the reactogenicity of this highly immunogenic vaccine. Besides this, meningitis was reported more frequently in the RTS,S/AS01 group than in the control group, for a relative risk of 5.5 (95% CI, 0.7 to 42.6) in the older age category and 4.0 (95% CI, 0.5, 32.0) in the younger age category. There seems to be no plausible explanation for this, and it may well turn out to be a chance finding, but it cannot be ignored. Such questions highlight the importance of phase 4 studies of both safety and effectiveness with active surveillance if this vaccine is deployed.

These initial results show that the RTS,S/AS01 vaccine reduced malaria by half in children 5 to 17 months of age during the 12 months after vaccination and that the vaccine has the potential to have an important effect on the burden of malaria in young children. Additional information on vaccine efficacy among young infants and the duration of protection will be critical to determining how this vaccine could be used most effectively to control malaria.⁷ Although the vaccine is not 98 to 99 percent effective, as some vaccines against other diseases are, it may be further improved and is an important start in reducing malaria.

DENGUE VACCINE

Dengue viral infection has become an increasing global health concern with over two-fifths of the world's population at risk of infection. Dengue is a tropical disease affecting 110 countries throughout the world and placing over 3 billion people at risk of infection, affecting predominantly children. According to the World Health Organization 70 to 500 million persons are infected every year including 2 million who develop hemorrhagic form and 20,000 who die. It is the most rapidly spreading vector borne disease, attributed to changing demographics, urbanization, environment, and global travel. Dengue also carries a hefty financial burden on the health care systems in affected areas, as those infected seek care for their symptoms.^{8,9}

Due to the absence of specialized laboratories in most endemic regions and to the lack of specific clinical presentation, the incidence of dengue and its economic costs are certainly underestimated. Dengue is caused by an arbovirus belonging to the Flavivirus genus of the family Flaviviridae. There are four dengue virus serotypes and no cross protection between them. The disease is transmitted through the bites of mosquitoes belonging to the *Aedes* genus, mainly *Aedes aegypti*. There is no specific treatment for dengue. Prevention requires control of vector mosquitoes that is difficult to implement and maintain. The high human and economic costs as well as the absence of specific preventive measures underscore the need to develop a vaccine. However finding and distributing such a vaccine to populations at risk is hampered by numerous obstacles. The most notable challenges standing in the way of development of a candidate vaccine are as follows: absence of an animal model, which has important implications for the preclinical development strategy; need to develop a live attenuated vaccine; existence of 4 antigenically distinct serotypes with the resulting risk of competition between vaccine strains; immunologic risks related to antibody-dependent enhancement that has been hypothesized to be the cause of severe forms of the illness; absence of a well defined correlate of protection and preexisting vaccine, which will require the organization of large-scale preclinical trials to demonstrate the efficacy of the virus; complexity associated with industrial production of a tetravalent vaccine. Development and production of a safe and reliable vaccine are only the first steps to ensuring protection of the populations at risk.

Strategies with traditional attenuation, chimerization, engineered attenuation are in the more advanced stages. In addition, inactivated, subunit, virus-vectored, pseudo-infectious virus, DNA vaccines and recombinant subunits have been developed.¹⁰ The candidates include live attenuated tetravalent vaccines, chimeric tetravalent vaccines based on attenuated dengue virus or yellow fever 17D, and recombinant DNA vaccines based on flavivirus and nonflavivirus vectors.¹¹ Phase II clinical trials are now under way in children and adults in Mexico, Peru, and the Philippines. Similarly, two live attenuated tetravalent vaccine candidates are in Phase II clinical trials in dengue endemic regions. Although some level of success has been attained, several obvious obstacles still exist. For example, live attenuated dengue vaccines must elicit appropriately balanced tetravalent immunity, and they must be characterized by a good safety profile. The inactivated whole virion dengue vaccines were restricted by the low virus yields in typical dengue viral cultures. Recombinant subunit dengue vaccines may provide significant benefits over other approaches. For instance, subunit vaccines eliminate exposure to the virus, which means they are safer, and they are more easily manipulated through dose adjustments to

obtain a balanced immune response to all four serotypes of DV. However, subunit vaccines are recognized as poor immunogens, they require several immunizations and they must be formulated with a strong adjuvant to generate a sufficient immune response.

One of the subunit vaccines using lipidated consensus dengue virus envelope protein domain III (LcED III) have been studied in Taiwan in animal models. Single dose of this vaccine was capable of activating antigen-presenting cells and enhancing cellular and humoral immune responses. Besides this, single-dose of LcED III immunization was reported sufficient to elicit neutralizing antibodies against all four serotypes of dengue viruses in mice without extra adjuvant formulation. In addition, strong memory responses were elicited with quick, anamnestic neutralizing antibody responses to a live dengue virus challenge at 28 week postimmunization. These results demonstrate the promising possibility of a future successful tetravalent vaccine against dengue viral infections that utilizes one-dose vaccination with LcED III. However, this vaccine needs further phase III studies on safety and efficacy.¹²

Recent data suggest that dengue immunity could be elicited via either humoral or cell-mediated routes. Directing the immune response to serotype-specific epitopes from domain (D)III of the dengue virus envelope protein (Env) may induce effective levels of neutralizing antibodies. Removing serotypecross reactive epitopes from DIII, as well as DII, may reduce the potential for the vaccine to induce non-neutralizing antibodies associated with antibody-dependent enhancement (ADE) of infection. The use of consensus Env DIII sequences for each serotype, and perhaps even a single consensus sequence for all four serotypes of dengue virus, may direct the immune response to invariant neutralizing sequences, which might improve vaccine safety and long-term efficacy. Vaccines incorporating capsid and/or nonstructural (NS) proteins may be capable of inducing tetravalent cell-mediated immunity without ADE. However, the potential of cell-mediated immunity to contribute to pathology is not well understood, and modifications of NS proteins, such as truncated NS1, may be necessary for optimal vaccine safety.¹³ As of now, all of these dengue vaccines are under trials and no licensed dengue vaccine is available.

HIV VACCINE

An estimated 25 million people with HIV infection reside in sub-Saharan Africa. In resource poor settings, restricted treatment options and the cost of alternative treatment regimens are likely to magnify the limitations of antiretroviral treatment (ART) programs. Antiretroviral treatment can successfully reduce plasma HIV-1 RNA levels to <50 copies/ml, although it is less effective in those with advanced immunosuppression and higher viral loads.

ART has been linked to abnormalities of body fat metabolism and distribution, hyperlipidemia, insulin resistance, hyperglycemia, and lactic acidosis requiring regimen change in 40 percent of individuals within 1 year of starting treatment.^{14,15}

Therapeutic interventions that enhance immunologic function with concurrent ART may improve the long-term outcome of HIV infection. Immune recovery following appropriate ART is often incomplete and fails to elicit responses associated with protection from disease progression.¹⁶ This failure has been associated with dysfunctional T cell responses. Therefore, boosting the immune response via therapeutic intervention may significantly delay or inhibit progression to AIDS. Therapeutic vaccinations in rhesus macaques have demonstrated that immunity can be elicited, leading to lower viral load.¹⁷ Therapeutic vaccination for HIV is different from other vaccines in way that it primarily given not to prevent disease, but to promote immune recovery and prevent progression to advanced stage.

Prior studies have shown a reduction in plasma viremia in HIV infected individuals and evidence of enhanced HIV specific T cell responses after immunization.^{18,19} LFn-p24C consists of a detoxified anthrax-derived polypeptide, called lethal factor n-terminus (LFn), which has been fused to the HIV subtype C gag protein p24. Therapeutic immunizations using this LFn-p24C vaccine was studied in HIV infected patients from Uganda, Africa. This open label Phase I trial was designed to assess the safety, tolerability and immunogenicity of a therapeutic HIV-1 vaccine candidate. Thirty HIV positive volunteers receiving a stable regimen of antiretroviral therapy with CD4 counts >400 were recruited for the safety evaluation of LFn-p24C vaccine. The vaccine was well tolerated and HIV RNA levels remained undetectable following three immunizations. CD4 counts in vaccine recipients were significantly higher compared to the control individuals after 12 months. HIV-specific responses were associated with higher gain in CD4 counts following LFn-p24C immunizations. Volunteers were subsequently asked to undergo a 30-day period of observed treatment interruption and 30 percent individuals showed no evidence of viral rebound during treatment interruption. All demonstrated prompt suppression of viral load following resumption of ART. These initial data demonstrate the safety of LFn-p24C and suggest that adjunct therapeutic immunization may benefit select individuals in further boosting an immune response.²⁰ However, further phase II and III trials are required to establish role of therapeutic immunization in HIV infected patients.

HEPATITIS E VACCINE

Clinically indistinguishable from other types of acute viral hepatitis, hepatitis E virus (HEV) tends to be self-limited

and usually does not become chronic. A substantial majority of clinically apparent acute viral hepatitis among adults in much of Asia, the Middle East and North Africa is caused by HEV. An estimated one-third of the world's population living in the developing countries has been infected with HEV. Outbreaks of hepatitis E have been documented over a wide geographic area, primarily in developing countries with inadequate environmental sanitation; some of the large outbreaks involving tens of thousands of cases have occurred in India, China, and more recently in Uganda. In endemic areas hepatitis E predominantly affects adolescents and young adults aged 14 to 40 years with an overall fatality rate of 1 to 3 percent, however, pregnant women have a poor prognosis with mortality rates of 5 to 25 percent, and survivors have high rates of spontaneous abortion and stillbirth.²¹ In India, the lifetime infection risk is more than 60 percent, which translates to hundreds of thousands of illnesses annually. In patients with chronic liver disease, superinfection with hepatitis E virus often leads to a poor outcome. Every year, 13,000–26,000 deaths are estimated in patients with chronic liver disease in industrialized countries.²² Of particular concern in these countries is the development of chronic liver diseases among organ transplant recipients, HIV infected and other immunocompromised individuals infected with HEV.

At least four genotypes of hepatitis E viruses have been identified. Genotypes 1 and 2 were isolated from human beings and are mainly seen in developing countries. Genotypes 3 and 4 are zoonotic, with pigs being the principal reservoir; they have been identified in many sporadic cases and limited food borne outbreaks mainly affecting middle-aged and elderly men. Nevertheless, all hepatitis E viruses associated with human diseases can be considered as belonging to one serotype.²²

Natural infections in humans and experimental HEV infections in animal models elicit an antibody response which results in protective immunity. Rechallenge and passive immunoprophylaxis studies in animal models (macaques) have shown that antibodies to HEV can protect against HEV infection and hepatitis. Further, there is epidemiologic evidence that persons previously infected with HEV are protected during hepatitis E outbreaks. After natural infection anti-HEV IgG has been shown to persist for up to 14 years²³ and after experimental infection antibodies were detectable for up to 10 years in chimpanzees inoculated with HEV genotype 1 or 2.²¹ A major facilitator for conducting immunogenicity and vaccine efficacy studies has been the availability of a reliable, reproducible and readily available macaque model of HEV infection.

The capsid protein encoded by ORF2 of HEV is a 72 kDa protein and is a major protein in the virion. Antibody elicited in humans and experimentally infected animals against ORF2 is long lived, cross-reactive among diverse HEV genotypes and neutralizes HEV *in vitro*. Because of

its immunogenicity, ORF2 protein of HEV has been the antigen used for all vaccine studies.

Many virus proteins, HEV vaccine candidates expressed in insect cells, virus like particles and DNA vaccines have been studied in animal models.²¹ Out of these, only two vaccine candidates, baculovirus expressed 56 kDa protein (rHEV) and *E. coli* expressed HEV 239 protein have progressed to the stage of clinical evaluation.

Genotype 1 HEV recombinant protein (rHEV) vaccine, which provided protection in nonhuman primates and phase I trials was studied in phase II trial in Nepal. In this trial, 2000 anti-HEV negative-healthy adults ranging in age from 18 to 62 years, from the Nepalese Army were randomly assigned to receive either three 20 µg rHEV vaccine doses at 0, 1 and 6 months or a matched placebo; the vaccine group was followed for a median of 804 days. During the postvaccination follow-up period from 2 weeks after the last vaccine dose until the end of study (2 years), hepatitis E developed in 66 of 896 (7.4%) individuals in the placebo group compared to 3 of 898 (0.3%) in the vaccine group. Analysis of postvaccination anti-HEV responses in a randomly selected immunogenicity subgroup (80 subjects from the vaccine group and 160 subjects from placebo group) showed 81.3 percent of those who received the vaccine had an anti-HEV level of at least 20 Walter Reed (WR) antibody units/ml one month after the second vaccine dose and 100 percent achieved this level after the third vaccine dose. However, by the end of the study, the proportion of anti-HEV positive vaccinees declined to 56.3 percent. In contrast, in the placebo group the proportion of subjects with an anti-HEV level of 20 WR U/ml or more increased to 10.6 percent reflecting the background rate of infection. Overall, the vaccine was safe and achieved efficacy rates of 87.5 percent, 85.7 percent and 95.5 percent after the first, second and third doses, respectively. The proportion of subjects with adverse events was similar in the two study groups, except that injection-site pain was increased in the vaccine group ($P = 0.03$).²⁴ The results of this vaccine trial demonstrated that the rHEV vaccine could prevent clinically overt HEV infection. Unfortunately, no further progress on the development of this vaccine has been reported.

HEV 239 vaccine is a bacterially expressed recombinant peptide encompassing 368 to 606 AA of ORF2 of HEV genotype 1 Chinese strain and it is a particulate vaccine, consisting of 23-nm virus-like particles (VLPs) which are recognized by a panel of HEV specific murine monoclonal antibodies including two neutralizing antibodies. After its success in Phase II trials, this vaccine was studied in a large randomized, double blind placebo controlled phase III trial in Jiangsu province, China. Healthy adults aged 16–65 years were randomly assigned in a 1:1 ratio to receive three doses of HEV 239 (30 µg of purified recombinant hepatitis E antigen adsorbed to aluminium hydroxide) or placebo (hepatitis B vaccine) given intramuscularly

at 0, 1, and 6 months. Participants were followed up for 19 months. The primary endpoint was prevention of hepatitis E during 12 months from the 31st day after the third dose. Analysis was based on participants who received all three doses per protocol. All participants received at least one dose of the vaccine or placebo; of the 97,356 participants, who received all the three doses, 48,693 received the HEV 239 vaccine and 48,663 received the placebo. The vaccine was tolerated well and no vaccine-related adverse events were observed in a randomly selected reactogenicity subset of participants. During the 12 months after 30 days from receipt of the third dose 15 per-protocol participants in the placebo group developed hepatitis E compared with none in the vaccine group. Vaccine efficacy after three doses was 100.0 percent (95% CI 72.1–100.0). The protective efficacy of the vaccine was 95.5 percent after the first vaccine dose and 100 percent after the second or the third vaccine dose. No vaccination-related serious adverse event was noted. The levels of anti-HEV IgG antibodies elicited by vaccination were quantified in 11,165 participants in the immunogenicity subgroup. Of the 5567 participants in the vaccine group, 98.7 percent had a four times or more increase over baseline in IgG anti-HEV concentrations one month after the third vaccine dose. In contrast, only 2.1 percent of 5598 participants in the placebo group seroconverted during the same period.²²

Despite its several limitations, which include lack of data on the duration of protection afforded by the vaccine, safety and efficacy in younger age groups, pregnant women, and patients with chronic liver disease and immune disorders, the successful Phase III trial of HEV 239 vaccine is a major leap forward in the development of a vaccine against hepatitis E.

OTHER VACCINES

Many newer vaccines are under development; however, most of these are studied in animal models only. A viral-like particle (VLP) based vaccine has been studied against Epstein-Barr virus (EBV) infection. EBV is a ubiquitous human herpes virus, which can lead to infectious mononucleosis and different cancers. In immunocompromised individuals this virus is a major cause for morbidity and mortality. Transplant recipients who did not encounter EBV prior to immunosuppression frequently develop EBV-associated malignancies but a prophylactic EBV vaccination might reduce this risk considerably. Virus-like particles (VLPs) mimic the structure of the parental virus but lack the viral genome. Therefore, VLPs are considered safe and efficient vaccine candidates. A dedicated producer cell line for EBV-derived VLPs has been prepared which contains genetically modified EBV genome devoid of all potential viral oncogenes but provides viral proteins essential for the assembly and release of VLPs. Human B cells readily take up EBV-based VLPs and present viral

epitopes in association with HLA molecules to T cells. Consequently, EBV-based VLPs are highly immunogenic and elicit humoral and strong CD8(+) and CD4(+) T cell responses *in vitro* and in a preclinical murine model *in vivo*. These findings suggest that VLP formulations might be attractive candidates to develop a safe and effective polyvalent vaccine against EBV.²⁵

Similarly, severe acute respiratory syndrome (SARS) vaccine is also undergoing initial trials. SARS caused thousands of human infections worldwide and hundreds of deaths in just a few months. Evidence indicates that SARS coronavirus (SARS-CoV) has been circulating from animals to humans since before the 2002-2003 outbreak suggesting that another pandemic may occur. This possibility has focused continuous action on SARS vaccine research. Inactivated vaccines, viral and bacterial vector vaccines, recombinant protein vaccines, subunit vaccines, DNA vaccines, and live-attenuated virus vaccines have been studied in different animal models. While there is much evidence that various vaccine strategies against SARS are safe and immunogenic, vaccinated animals still display significant disease upon challenge.²⁶ Current data suggest that intranasal vaccination may be crucial and that new or combination strategies may be required for good protective efficacy against SARS in humans. Moreover, potential vaccine enhancement of SARS has also been shown in some studies.²⁷

Vaccines against hepatitis C, cytomegalovirus, herpes simplex, respiratory syncytial virus, diarrheal diseases, parasitic infections and bacterial diseases (*Staphylococcus* and *Streptococcus*) are also under studies.

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Older Vaccines Revisited

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INTRODUCTION

The Expanded Program of Immunization (EPI) was introduced in our country in the year 1978 with an aim to cover 6 childhood diseases.¹ In 1985 measles immunization was added to the EPI and thus the Universal Immunization Program (UIP) came into existence (Typhoid was dropped from the schedule in 1981).^{1,2} The UIP coverage includes BCG, DPT, OPV and measles. From then on till 2011 vaccines and vaccination programs have progressed by leaps and bounds. CDC and IAP regularly issue newer schedules for vaccination based on the available evidence and disease burden.^{1,3} However, at the national and public health sector level, introduction of newer vaccines has not made much progress since 1985 (with the exception of Hepatitis B and Hib in select districts).¹ This chapter cannot cover all aspects of immunization and the IAP 2011 guidebook is an ideal option for that. Here we intend to rediscover these old vaccines from a bygone era and highlight their relevance and importance in the 21st century.

BACILLUS CALMETTE-GUÉRIN (BCG)

The last publication of Advisory Committee on Immunization Practices (ACIPs) on BCG was in 1996.⁴ This tells about the lost importance of this vaccine in the developed nations; where the incidence of the disease is very low. The situation in India is however different. In addition to the highest prevalence of the disease in the world; the HIV pandemic is adding further to the disease burden in India.^{5,6}

The *Bacillus Calmette-Guérin* (BCG) vaccine was introduced in 1921 and till today is the only one available to prevent tuberculosis.⁶⁻⁸ The current vaccine strains are all descendants of the original *M. bovis* isolate that Calmette and Guérin passaged through numerous cycles during the 13-year period 1909 to 1921. Subsequent passages

under different laboratory conditions resulted in a variety of new BCG strains showing phenotypic as well as genotypic differences.⁵ After about a century of use, BCG still remains controversial with known variations in vaccine strains and efficacy.⁶ While most experts agree that BCG is efficacious against severe forms of childhood tuberculosis, its efficacy in adults is highly variable.^{5,9} It does not prevent the establishment of primary disease or reactivation of latent disease.⁵ As a result of the uncertain efficacy of the BCG vaccine, countries have developed very different BCG vaccination policies. Some countries, such as the United Kingdom, have or have had universal BCG vaccination programs, while others (including Canada and the United States) either only recommended BCG for high-risk groups or did not advocate BCG countrywide.⁶ India adopts a policy of universal immunization with BCG at birth. Regular boosters are currently not recommended in our country (16 countries have adopted the policy of BCG boosters).^{1,2,6} For details on individual country's policies "The World BCG Atlas" (available at www.bcgatlas.org) is an excellent source of information.

BCG Vaccination Policies

Clinicians cannot keep a track of BCG vaccination policies across all countries and most adult immigrants do not remember their/retain their childhood immunization records. The BCG world atlas is the only known comprehensive source of information on BCG vaccination across countries and over time.⁶ Most of the countries across the world have begun their BCG vaccination in between 1940 and 80. Currently nine countries have ceased universal immunization with BCG.⁶ Sixteen countries adopt the policy of BCG booster routinely and four out of these use two boosters after the initial dose.⁶ Eight countries routinely employ TST (tuberculin skin testing) after BCG

vaccination. The BCG coverage across the world is in the range of 70 to 100 percent.⁶

WHO Position Paper^{5,10}

- Countries with high burden of the disease should adopt the policy of universal BCG vaccination.
- Countries with a low burden of tuberculosis can choose to limit the vaccination to high risk groups.
- BCG vaccination is not routinely recommended for adults. Vaccination may be considered for those adults who are tuberculin negative and are in (unavoidable) close contact with a multidrug tuberculosis case.
- Repeat vaccination with BCG has no proven benefit.
- For Infants of HIV positive mothers WHO made these new recommendations in 2007:
 - a. For infants whose HIV status is unknown and show no clinical signs/ symptoms of HIV infection – BCG vaccination is recommended.
 - b. Infants who are HIV positive with or without clinical signs/ symptoms – BCG vaccination is not recommended.
 - c. For infants with clinical signs/ symptoms but unknown HIV status – BCG vaccination is not recommended. This applies only to infants who have not received BCG soon after birth; because HIV symptoms usually appear after 3 months.

IAP Recommendations¹

- IAP recommends routine vaccination with BCG at birth or six weeks (if birth dose is missed).
- Children till the age of 5 years can receive catch up vaccination.
- For a child who does not demonstrate a BCG scar; a second dose of BCG can be given till the age of 5 years.
- TST is not recommended at any stage.

POLIO VACCINES

As on October 5th 2011, 1002 cases of polio have been reported worldwide in past 12 months and about 290 in past 6 months (WHO data as on 5th October 2011).¹¹ This year only one case of (wild polio virus – WPV 1) was reported from India on 13th January 2011 from West Bengal (WHO data as on 5th October 2011).¹¹ There is a 40 percent decline in the number of polio cases this year compared to last year. Two effective polio vaccines are available for the past five decades – Salk inactivated polio vaccine (IPV) and sabin oral polio vaccine (OPV). The global polio eradication program was launched in 1988 and today only 4 countries—India, Pakistan, Afghanistan and Nigeria are polio endemic.^{1,11} WPV2 has been last isolated in 1999.^{1,11} In the year 2005 two new monovalent polio vaccines – mOPV1 and mOPV3 were introduced to enhance the supplementary immunization activities.¹

Polio Vaccination Policies

The last case of wild polio in the Americas and western hemisphere was isolated in 1991 and 1994 respectively^{12,13} with the use of OPV alone. The US shifted from an all OPV schedule to sequential IPV-OPV schedule in 1997 and from the year 2000 an all IPV schedule is in force.^{12,14} Many of the industrialized nations also have done the same. This is done to eliminate the burden of vaccine associated paralytic poliomyelitis (VAPP); a rare adverse event of OPV. The ACIP recommends a 4-dose schedule for IPV. These should be administered at 2 months, 4 months, 6 to 18 months and 4 to 6 years.¹⁵ The final dose of IPV should be administered after the age of 4 years regardless the number of previous doses.¹⁵ If a child is being immunized with DTaP-IPV/Hib combination vaccine at 2, 4, 6 and 15 to 18 months; then an additional booster dose of IPV/ IPV containing vaccine is needed at 4 to 6 years. This leads to a 5-dose schedule for IPV and is recommended by ACIP.¹⁵ This is quite different from the IAP recommendations which will be discussed later.

WHO Position Paper¹⁶

- OPV is highly heat sensitive vaccine and must be kept frozen or, after thawing it should be kept at temperatures of 2 to 8°C for a maximum of 6 months.
- OPV is the vaccine of choice for Global Polio Eradication Program. It has eradicated WPV2 from the world and eliminated WPV1 and WPV3 in 3 of 6 WHO regions.
- OPV alone along with birth dose is recommended for all polio endemic countries and in countries at high risk for importation of the disease.
- OPV alone preferably with birth dose is recommended for all countries with a moderate to high potential for transmission and importation of WPV.
- In countries with a high risk for importation of WPV, sequential IPV-OPV should be introduced only after immunization coverage is more than 95 percent. Initial 2 doses of IPV should be followed ≥2 doses of OPV to ensure sufficient level of protection in the intestinal mucosa and a decrease in the incidence of VAPP.
- IPV alone may be considered in countries with a very low risk of WPV importation and transmission. IPV alone is not an economically feasible option in the pre-eradication era.
- WHO recommends 3 doses of primary series of OPV at 6, 10 and 14 weeks or 2, 4, and 6 months
- When sequential IPV-OPV is used, IPV-OPV-OPV or IPV-IPV-OPV-OPV schedule is recommended in the primary series.
- Previously immunized persons travelling to polio endemic countries should be offered a single dose of polio vaccine before the journey.

The above recommendations were published in 2010 and pertain to polio vaccination in the pre-eradication era. In 2006 WHO had suggested methods to be adopted in post polio eradication era. A review of the same is due. According to the 2006 recommendations countries will have 2 options after polio eradication and OPV cessation – either to stop all polio vaccination or shift to an all IPV schedule.¹⁷ OPV alone or in combination is not an option in posteradication era, as it may lead to re-establishment of the disease.¹⁷

IAP Recommendations¹

- The IAPCOI recommends OPV at birth, 3 dose primary series and boosters at 15 to 18 months and 4 to 6 years. In addition OPV is recommended on all NIDs and SNIDs
- IPV should be offered to all children in addition to OPV at 6, 10, 14 weeks and a booster at 15 to 18 months. An alternative option is to schedule the first 2 doses after 2 months of age, with an interval of 8 weeks between the 2 doses. This reduces the total number of IPV doses required to 3.
- IPV can be offered as catch up vaccination for children up to 5 years of age in the form of 2 doses 8 weeks apart.
- Unlike the ACIP recommendations, a 5th year booster of IPV is not included; only OPV is indicated at 4 to 6 years.

DIPHTHERIA, TETANUS AND PERTUSSIS VACCINES

Vaccination with DPT had begun as early as the 1940's in certain parts of the world.¹⁸ Currently a wide variety of DPT, alone and in combination are available. These are: 1. DTwP (whole cell pertussis) 2. DTaP (acellular pertussis) 3. Tdap (for 10th year booster) 4. DT and 5. dT. The immunogenicity and efficacy for diphtheria and tetanus exceeds 95 percent after 3 doses. Protection against pertussis is lower; in the range of 61 to 89 percent with whole cell vaccines.^{19,20} The acellular pertussis vaccines have efficacy rates that approach the best whole vaccines.²¹ However, among the acellular vaccines, the multi-component acellular vaccines have higher protective efficacy than the 1 and 2 component vaccines.²¹ There are no safety concerns for whole cell vaccines and the WHO position paper acknowledges this as well. The only absolute contraindications for pertussis vaccination (whole cell and acellular) are anaphylaxis and encephalopathy (not attributable to any cause) within 7 days of vaccination.²²

DPT Vaccination Policies

ACIP had proposed the routine use of DTaP for United States in 1997.²² The recommendation is 5 doses in a primary series at 2, 4 and 6 months and boosters at 15 to 18 months and 4 to 6 years.²² At that point the

recommendation for the 10th year booster was the use of Td. With the availability of reduced diphtheria toxoid and acellular pertussis vaccines (Tdap), ACIP recommended the use of these for the 10th year booster and as catch up vaccination after 7 years age.²³ This was done to curb the rising incidence of pertussis among adolescents and adults. A year later in 2006 ACIP came out with recommendations for adults. In a nutshell adults aged 19 to 64 years should receive one dose of Tdap to protect against pertussis in addition to the other 2 diseases.²⁴ Tdap is also recommended in health care personnel and pregnant women (during postpartum period).^{24,25} Postpartum women should receive one dose of Tdap before discharge from hospital, if 2 or more doses have elapsed since the last dose of Td. ACIP recommends vaccination with Td during pregnancy if 10 or more years have elapsed since the last booster. If the mother has sufficient protection against tetanus, then Td can be substituted with Tdap during immediate postpartum period. Further details on this can be found in the 2008 ACIP publication on this matter.²⁶ Currently there is no data on safety of Tdap in pregnancy. In special circumstances where there is high risk of pertussis Tdap may be given during 2nd or 3rd trimester after informed consent.²⁶ An April 2011 provisional recommendation from ACIP suggests the use of a single dose of Tdap among health care workers (if not received previously) irrespective of the previous dose of Td.²⁷

WHO Position Paper²⁸⁻³⁰

- Vaccination with DPT should begin with a primary series of 3 doses during infancy with 1 to 2 boosters by the age of 4 to 7 years.
- For children 1 to 7 years of age who are not previously immunized, 2 doses 2 months apart followed by a booster 6 to 12 months later is recommended.
- After 7 years of age Td should be used for vaccination. If feasible Tdap should be used instead of Td.
- Pregnant women who have received complete childhood immunization should receive at least 1 dose of Td during the first pregnancy. If the childhood immunization schedule is incomplete then 2 doses at least 4 weeks apart are recommended.
- WHO does not differentiate between wP and aP for national immunization programs. In resource poor settings it recommends the use of wP as the vaccine of choice.
- WHO Position paper believes that there is insufficient evidence to recommend routine use of pertussis containing vaccines for adolescents and adults. This schedule can prevent pertussis in the above mentioned age groups, but has little impact on pertussis in infancy – where the morbidity is highest. Hence, WHO recommends that a high coverage of primary immunization should be the first priority followed by the two boosters.

- Only vaccines containing aP should be used after 6 years.
- Similar to ACIP, WHO finds that there is insufficient evidence to recommend the vaccination of pregnant women with pertussis containing vaccines
- If the economics and logistics permit, WHO recommends the vaccination of health care workers with pertussis containing vaccines.

IAP Recommendations¹

- IAPCOI universally endorses the use of wP containing vaccines.
- Three doses at 6, 10, and 14 weeks followed by boosters at 15 to 18 months and 4 to 6 years is recommended.
- Catch immunization schedule is similar to the WHO recommendation.
- IAPCOI suggests the use of Td as the 10th year booster; catch up vaccination after 7 years and in all situations where TT is used.
- IAP recommends the use of Tdap for 10th year booster for those who can afford the vaccine. In addition IAP also endorses most of the recommendations suggested for Tdap by ACIP.
- After 7 years catch up vaccination can be done with one dose of Tdap followed by 2 doses of Td.

MEASLES

Measles is a disease that occurs only in humans and is transmitted by respiratory droplets. With the absence of an intermediary host; measles has generated a lot of interest for a potential eradication. Hence, the measles vaccination garners a lot of importance at the national and international level. Maternal antibodies provide protection for the first 6 to 9 months of infancy. A number of live attenuated vaccines are available against measles either as monovalent measles vaccine or measles containing vaccine (MCV). The MCVs are MMR (measles, mumps and rubella) and MMRV (measles, mumps, rubella and varicella).³¹ Most measles vaccines are derivatives of the original Edmonston strain, isolated in 1954 by Enders and Peebles.³² Strains derived from this include the Schwarz, Edmonston – Zagreb, AIK-C and Moraten strains. Nucleotide sequence analysis has not revealed much of a difference between these strains. The vaccines underwent trials in 1958 and were licensed for human use in 1963.^{32,33}

Measles Vaccination Policies

Measles vaccination was introduced in the US in 1963 and in 1993 transmission of indigenous measles transmission was interrupted completely.³² By 1989 the US had already adopted the policy of 2 doses of measles in the form of MMR. The 2nd dose was initially planned at 11 to 12 years; but later the age was brought down to 4 to 6 years.³³ The Enders-Edmonston strain, grown in chick embryo

fibroblast culture is the only vaccine available in the US.³⁴ The idea of 2 doses in measles vaccination is different from other vaccines. The second dose is not a booster dose. It is given so that persons who do not respond to first dose of measles vaccine will mount an immune response after second dose.³⁵ All people born after 1957 should receive at least one on dose of MMR. All women of childbearing age should receive one dose of MMR unless contraindicated (This is for protection against Rubella).³⁴ HIV infected children who are not severely immunocompromised should receive first dose of MMR soon after 1st birthday and 2nd dose after 28 days.^{34,36} Those children at risk for measles should receive one dose of measles vaccine at 6 to 12 months followed by the earlier mentioned schedule of MMR.^{34,36} In infants >6 months age measles vaccine can be used as post exposure prophylaxis within 72 hours of exposure.³⁴

WHO Position Paper³¹

Like the wild measles virus, measles vaccine causes both a stimulating and suppressing effect on the immune system. This suppressing effect is harmless generally, but forms the basis for not giving BCG with measles (for those who did not receive BCG earlier). The median percentage of children, who seroconverted after 1st dose of measles vaccine at 8 to 9 months, was 89.6 percent when compared to 99 percent of those at 11 to 12 months. Vaccination before 6 months fails to produce seroconversion due to immaturity of immune system as well as neutralizing maternal antibodies.³⁷

- Measles vaccines are safe, effective, inexpensive and provide long lasting immunity. Hence, all countries should aim at providing 2 doses of measles vaccine in their immunization programs.
- Countries aiming at control of measles and reducing mortality should aim at ≥ 90 percent measles coverage. Vaccination coverage of ≥ 95 percent for both the doses of measles vaccines helps in achieving elimination of measles.
- In areas with high measles transmission, the first dose of measles/MCV should be administered at 9 months. All unvaccinated children after 9 months should receive their vaccine as soon as possible. In countries with low risk of measles transmission, the first dose may be administered at 12 months.
- MCV2 should be added to national immunization schedule after ≥ 80 percent coverage with MCV1 is achieved. Till then countries should concentrate on improving MCV1 coverage and conduct supplementary immunization activities (SIAs). However, there are situations under which a country may choose to introduce MCV2 without satisfying the above criteria. The details of this can be found in the WHO position paper.

- The optimal timing of 2nd dose of measles is 15 to 18 months. However, it can be given any time 1 month after the first dose.
- Measles vaccination should be offered to children with HIV infection. The WHO recommendation is similar to the ACIP recommendations mentioned earlier.

IAP Recommendations¹

Even after 5 decades of availability and 2 to ½ decades of UIP measles coverage is around 71 percent in our country. Indian measles vaccines are usually made from the Edmonston-Zagreb strain grown on human diploid cells or chick embryo cells.

- IAP recommends the first dose of measles vaccine at 9 months age. In the event of an outbreak the first dose may given as early as 6 months.
- A second dose of measles vaccine, preferably MMR should be introduced in UIP at 18 months age for states with >80 percent coverage with 1st dose of measles vaccine.
- For states with <80 percent coverage SIA should be optimized to reduce mortality from measles.
- In addition IAP recommends 2 doses of MMR at 12 to 15 months and 4 to 6 years. The second dose of MMR is to protect those who fail seroconversion against mumps, and less commonly rubella, with the first dose of the vaccine.

CONCLUSION

There are several vaccines which may now be called as older ones; like HIB, Hepatitis B and MMR to name a few. However, this chapter was mainly intended to cover the oldest of the lot; those vaccines that were introduced in 1985 and even before that. The UIP has not undergone any major changes from its inception. In 2006 Hepatitis B, second dose of measles and Japanese B encephalitis have been introduced into UIP.³⁸ The implementation is occurring in a phased manner. Though a significant dent has been made to the mortality caused by the vaccine preventable diseases, a lot more needs to be achieved. The UIP coverage in India is >70 percent in only 11 states, 50 to 70 percent in 13 states and <50 percent in the remaining states.³⁸ These remaining states are the most populous states and they bring overall national average to less than 50 percent.³⁸ There are several bottle necks preventing high immunization coverage. Weak surveillance system, lack of epidemiological data, limited economics and lack of trained manpower are just a few of them. The government with the help of NTAGI (National Technical Advisory Group of Immunization) and other organizations is aiming to improve the existing UIP and make immunization of all children of our country a dream come true.

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Rabies Prophylaxis: The Current Guidelines

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INTRODUCTION

Rabies is a major public health problem throughout the world and more so in the Africa and Asia. It is a zoonotic disease caused by RNA viruses in the family Rhabdoviridae, genus *Lyssavirus*. It is invariably fatal once it occurs and has mortality rate of almost 100 percent. Rabies virus is transmitted in the saliva of rabid mammals via a bite. After entry to the central nervous system, these viruses cause an acute, progressive encephalomyelitis. The incubation period usually ranges from 1 to 3 months after exposure, but can range from days to years. Rabies can be prevented by avoidance of viral exposure and initiation of prompt medical intervention when exposure does occur. As a part of its mandate to provide guidance, World Health Organization (WHO) issues a series of regularly updated position papers on vaccines against diseases that have an international public health impact. In August 2010, WHO published a position paper on rabies vaccines, which incorporates the most recent developments in the field of human rabies vaccines, in particular with regard to immunization schedules.¹ The current position paper replaces the previous position paper on rabies vaccines published in the weekly epidemiological record in December 2007 by WHO. The following article is based on this position paper and discusses strategies to prevent infection with rabies after being bitten or exposed to an infected animal or suspected animal.

EPIDEMIOLOGY

Rabies is a viral zoonosis that is widely distributed across the globe in >100 countries and territories. Rabies infects domestic and wild animals and spreads to the human through close contact with infected saliva. More than 95 percent of human rabies infections come from dogs. At the global level, ≥ 15 million people receive rabies

prophylaxis annually, the majority of them live in China and India. Rabies is almost invariably fatal, once clinical symptoms have developed. In a number of countries, deaths due to rabies are under-reported. The most of the estimated 55,000 deaths caused by rabies each year occur in rural areas of Africa and Asia. In India alone 20,000 deaths (that is, about 2/1,00,000 population at risk) are estimated to occur annually. Although all age groups are susceptible, rabies is most common in children aged <15 years; on average 40 percent of postexposure immunizations are given to children aged 5 to 14 years, and the majority of those immunized are males.^{2,3}

In industrialized countries, human rabies is close to being eliminated owing to the vaccination of domestic dogs and the implementation of other control measures. In Thailand also the mass vaccination of dogs and widespread immunization of humans following exposure have significantly reduced the number of human rabies deaths.

RABIES

Virology

The rabies virus (RABV) belongs to the genus *Lyssa* virus in the family Rhabdoviridae. There are 11 species classified under *Lyssa* virus genus and all are known to cause progressive human encephalitis. The RABV is the major representative and its RNA encodes 5 proteins, including the G glycoprotein that carries the main antigenic sites.

Transmission

Human infection usually occurs following a transdermal bite or scratch by an infected animal. The other mode of transmission is person's mucosa or fresh skin wounds coming in contact with infected saliva. Human-to-human transmission by bite is extremely uncommon except for

transplantation of an infected organ. Ingestion of raw meat or other tissues from animals infected with rabies is not a known source of human infection. The incubation period depends upon the amount of virus inoculated, the degree of innervation at the site of viral entry and the proximity of the bite to the central nervous system (CNS). The typical incubation period is 1 to 3 months but may vary from <1 week to >1 year. Inoculated virus is transported to the CNS via the peripheral nerves. In brain, it multiplies and disseminates rapidly, again via the nervous system to many different tissues including the salivary glands and resulting in progressive fatal encephalomyelitis.

Diagnosis

Almost 60 to 70 percent will have furious rabies characterized by hyperactivity and fluctuating consciousness, hydrophobia or aerophobia, or both and resulting in death in few days due to cardiorespiratory arrest. Paralytic rabies represents as much as 30 percent of human cases and has a less dramatic and longer course often misdiagnosed and under-reported. The paralytic form of rabies is often misdiagnosed and this contributes to the under-reporting of the disease. No tests are available to diagnose rabies infection in humans before the onset of clinical disease. At the stage of clinical manifestations, saliva, urine, extracted hair follicles and CSF may be tested by virus isolation or by polymerase chain reaction, and serum or CSF may be tested for antibodies to rabies virus. Skin biopsy specimens or postmortem brain biopsy may be examined for rabies antigen fluorescent antibody test or a direct rapid immune-histochemical test. A rapid tissue culture isolation test may also be used.

Note: Rabies differs from many other infections in that the development of clinical disease can be prevented through timely immunization even after exposure to the infecting agent.

RABIES VACCINES

Since their development more than four decades ago, concentrated and purified cell-culture and embryonated egg based rabies vaccines (here jointly referred to as CCVs) have proved to be safe and effective in preventing rabies. These vaccines are intended for pre-exposure prophylaxis as well as post-exposure prophylaxis, and have been administered to millions of people worldwide. Some countries in Asia and Latin America still depend partially on rabies vaccines derived from animal nerve tissues for postexposure prophylaxis. The production and use of nerve tissue vaccines is not recommended by WHO due to severe side effects and less immunogenicity.³ CCVs consist of rabies virus that has been propagated in cell substrates such as human diploid cells (embryonic fibroblast cells), fetal rhesus diploid cells, vero cells (kidney cells from

the African green monkey), primary Syrian hamster kidney cells, primary chick embryo cells or in embryonated duck eggs.⁴ The more recently developed vaccines based on chick embryo cells and vero cells have safety and efficacy records comparable to those of the human diploid cell vaccines and are less expensive. No rabies vaccines are supplied in multidose vials for intramuscular injection. Rabies vaccines prequalified by WHO do not contain preservatives such as thimerosal. The shelf-life of these vaccines is ≥ 3 years, provided they are stored at $+2^{\circ}\text{C}$ to $+8^{\circ}\text{C}$ and protected from sunlight. Following reconstitution with the accompanying sterile diluent, the vaccines should be used immediately, or within 6 to 8 hours if kept at the correct temperature. All CCVs should comply with the WHO recommended potency of ≥ 2.5 IU per single intramuscular dose. (0.5 ml or 1.0 ml volume after reconstitution, depending on the type of vaccine).

Intramuscular and Intradermal Administration

The cost of CCVs for intramuscular administration limits their widespread use in many areas where canine rabies is prevalent. Intradermal administration of these vaccines offers an equally safe and immunogenic alternative that requires only 1 to 2 vials of vaccine to complete a full course of postexposure prophylaxis, thereby reducing the volume used and the direct cost of vaccine by 60 to 80 percent compared with standard intramuscular vaccination.⁵ There is no evidence that intradermal administration requires vaccines with potency higher than that recommended for intramuscularly-administered rabies vaccines.^{6,7} Intradermal regimens have been successfully introduced for postexposure prophylaxis in countries such as India, the Philippines, Sri Lanka and Thailand.⁵ Intradermal regimens require sufficient trained staff to ensure correct storage, reconstitution and injection.

Vaccine Efficacy and Immunogenicity

Rabies is a fatal disease. Therefore, randomized controlled human trials involving untreated comparison groups cannot be carried out for ethical reasons. Direct assessment of vaccine-induced protection is based on the efficacy of post-exposure prophylaxis following category II or III exposure to animals confirmed to be rabid through laboratory analysis. The efficacy of vaccine can be also made indirectly through immunogenicity studies. All CCVs induce a prompt and high rabies-virus neutralizing antibody response to the viral G protein. WHO's specified minimum titer of 0.5 IU/ml of serum, measured by the rapid fluorescent focus inhibition test (RFFIT) or the fluorescent antibody virus neutralization test (FAVN) is a widely used reference. In healthy vaccines, this level should be achieved in most individuals by day 14 of a post-exposure regimen, with or without simultaneous administration of rabies immunoglobulin and irrespective of age.

When new rabies vaccines are introduced, their immunogenicity is evaluated by comparing the rabies-virus neutralizing antibody titers induced by the vaccine being tested with those induced by a vaccine of demonstrated efficacy. Studies from Thailand and several other countries in South-East Asia have established the immunogenicity and effectiveness of CCVs for both pre-exposure and post-exposure prophylaxis. The feasibility of using them either intramuscularly or intradermally in all age groups, including infants, has been clearly demonstrated. In both pre-exposure and postexposure use, these vaccines induce an adequate antibody response in almost all individuals. Prompt postexposure use of CCVs combined with proper wound management and simultaneous administration of rabies immunoglobulin is almost invariably effective in preventing rabies. However, delays in starting or incomplete prophylaxis may result in failure, particularly following bites in highly innervated regions, such as the head, neck or hands or following multiple wounds.

Duration of Immunity

The development of immunological memory after vaccination with CCVs is critical for the establishment of long lasting immunity against rabies in humans. Individuals who had received their primary series 5 to 21 years previously showed good anamnestic responses after booster vaccination. Long-term immunity is also achieved with intradermal immunization and may persist even when antibodies are no longer detectable. The anamnestic response to a booster vaccination is seen with both *pre* as well as postexposure prophylaxis.

Adverse Events Following Immunization

In general, CCVs have been shown to be safe and well tolerated. However, in 35 to 45 percent of vaccinees, minor and transient erythema, pain and/ or swelling may occur at the site of injection, particularly following intradermal administration of a booster. Mild systemic adverse events following immunization (AEFI), such as transient fever, headache, dizziness and gastrointestinal symptoms, have been observed in 5 to 15 percent of vaccinees. Serious AEFIs mainly of allergic or neurological nature rarely occur.⁸

Contraindications and Precautions

For pre-exposure prophylaxis, previous severe reaction to any components of the vaccine is a contraindication to further use of the same vaccine. Because rabies is a lethal disease, no contraindications exist to postexposure prophylaxis following high-risk exposure. This is also the case for postexposure prophylaxis during infancy or pregnancy and for immunocompromised individuals, including children with HIV/AIDS. People taking chloroquine for malaria treatment or prophylaxis may have a reduced

response to intradermal rabies vaccination. These patients should receive the vaccine intramuscularly. As with all other immunizations, vaccinees should if possible be kept under medical supervision for at least 15 to 20 minutes following vaccination.

Replacing Nerve-tissue Vaccines with CCVs

With time, the CCVs have become more affordable particularly with intradermal administration schedules. But still some of the Asian and Latin American countries are producing and using nerve-tissue vaccines. These vaccines induce more-severe adverse reactions and are less immunogenic than CCVs. It is therefore imperative that production and use of nerve-tissue vaccines be discontinued as soon as possible and replaced with CCVs.

Intradermal Administration of CCVs

For administration by the intradermal route, CCVs should meet the same WHO requirements for production and control as required for rabies vaccines delivered intramuscularly. In addition, the immunogenicity and safety of intradermally administered vaccines should be demonstrated in appropriate clinical trials using the WHO recommended postexposure prophylaxis regimen and a volume of 0.1 ml per intradermal site.⁶ New postexposure regimens, particularly those using intradermal administration, even if shown to be safe and efficacious, must have clear practical or economical advantages, or both, over existing regimens if they are to be endorsed. In countries where intradermal administration is an approved route for postexposure prophylaxis, manufacturers of vaccines proved to be safe and efficacious by this route should be requested to state that their vaccine can be used intradermally.

RABIES IMMUNOGLOBULIN

Rabies immunoglobulin should be administered in all people with category III exposure and to those with category II exposure who are immunodeficient. Human rabies immunoglobulin has a relatively slow clearance (the half-life is about 21 days), so it is the preferred product, particularly in cases of multiple severe exposures and bites on the head, face and hands. However, human rabies immunoglobulin is in short supply and available mainly in industrialized countries. Where it is not available or affordable, equine immunoglobulin or F(ab')₃ products of equine immunoglobulin should be used, although the F(ab') have a faster clearance than human rabies immunoglobulin. Most of the new equine immunoglobulin preparations are potent, highly purified, safe and considerably less expensive than human rabies immunoglobulin. However, they are of heterologous origin and carry a small risk of anaphylactic reaction (1/45 000 cases). There are no scientific

grounds for performing a skin test prior to administering equine immunoglobulin because testing does not predict reactions, and it should be given whatever the result of the test. The treating physician should be prepared to manage anaphylaxis which, although rare, could occur during any stage of administration.⁹

PRE-EXPOSURE PROPHYLAXIS

Pre-exposure prophylaxis is recommended for anyone who will be at continual, frequent or increased risk of exposure to the rabies virus, either as a result of their residence or occupation (for example, laboratory workers dealing with RABV and other lyssa viruses, veterinarians and animal handlers). Travelers with extensive outdoor exposure in rural high-risk areas where immediate access to appropriate medical care may be limited should also be vaccinated regardless of duration of stay. Children living in or visiting rabies-affected areas are at particular risk. WHO encourages the implementation of carefully designed studies on the feasibility, cost-effectiveness and long-term impact of incorporating CCVs into the immunization programs of infants and children if canine rabies is a public health problem.

Intramuscular Administration for Pre-exposure Prophylaxis

Pre-exposure prophylaxis requires intramuscular doses of 1 ml or 0.5 ml (volume depending on the type of vaccine) to be given on days 0, 7 and 21 or 28. For adults and children aged ≥ 2 years, the vaccine should always be administered in the deltoid area of the arm; for children aged < 2 years, the anterolateral area of the thigh is recommended. Rabies vaccine should not be administered in the gluteal area, as the induction of an adequate immune response may be less reliable.

Intradermal Administration for Pre-exposure Prophylaxis

Intradermal administration of 0.1 ml volume on days 0, 7, and 21 or 28 is an acceptable alternative to the standard intramuscular route. To lead to significant savings, intradermal immunization sessions should involve enough individuals to utilize all opened vials within 6 to 8 hours.

Requirements for Booster Injections

Booster doses of rabies vaccines are not required for individuals living in or travelling to high-risk areas who have received a complete primary series of pre-exposure or postexposure prophylaxis with a CCV. Periodic booster injections are recommended as an extra precaution only for people with frequent occupational exposure. If available, antibody monitoring of personnel at risk is preferred to the administration of routine boosters. For people who are potentially at risk of laboratory exposure to high concentrations of live rabies virus, antibody testing should be done every 6 months. Those professionals who are not at continual risk of exposure through their activities, such as certain categories of veterinarians and animal health officers, should have serological monitoring every 2 years. Because vaccine-induced immunity persists in most cases for years, a booster would be recommended only if rabies virus neutralizing antibody titers fall to < 0.5 IU/ml.

POSTEXPOSURE PROPHYLAXIS

The indication for postexposure prophylaxis depends on the type of contact with the suspected rabid animal:

For category I exposures, no prophylaxis is required; for category II, immediate vaccination is recommended; and for category III, immediate vaccination and administration of rabies immunoglobulin are recommended. For categories II and III, thorough washing and flushing (for about 15 minutes, if possible) with soap or detergent and

Table 1: WHO definitions of categories of exposure for the use of rabies biologicals

<i>Category of exposures</i>	
Category I	Touching or feeding animals licks on intact skin (that is no exposure);
Category II	Nibbling of uncovered skin minor scratches or abrasions without bleeding;
Category III	Single or multiple transdermal bites or scratches contamination of mucous membrane with saliva from licks/ licks on broken skin; exposures to bats.
<i>Prophylaxis recommended</i>	
For category I exposures no prophylaxis is required;	
For category II immediate vaccination is recommended; and	
For category III immediate vaccination and administration of rabies immunoglobulin are recommended.	
For categories II and III thorough washing and flushing (for about 15 minutes if possible) with soap or detergent and copious amounts of water of all bite wounds and scratches should be done immediately or as early as possible.	

Table 2: Rabies postexposure prophylaxis—general considerations and wound management

- Wound management should be done immediate and is essential even if the person presents long after exposure
- It consists of immediate washing and flushing for 15 minutes with soap and water, or water alone and disinfection with ethanol (700ml/L) or iodine (tincture or aqueous solution).
- Postpone suturing if possible; in case suturing is necessary ensure that RIG has been applied locally; Apply antimicrobials and tetanus toxoid if necessary
- No contraindications if modern purified rabies vaccines are used;
- Use the vaccine regimens and routes of administration as recommended
- Initiation of PEP should not be delayed by dog observation.
- Pregnancy and infancy are not contraindications to PEP

copious amounts of water of all bite wounds and scratches should be done immediately or as early as possible. Where available an iodine-containing, or similarly viricidal, topical preparation should be applied to the wound.

When it is impossible to complete postexposure prophylaxis with the same CCV, another CCV should be used instead. However, since no study has been done yet on vaccine immunogenicity following changes in the route of vaccine administration (for example, from intramuscular to intradermal) during postexposure prophylaxis, such changes should be the exception. Postexposure prophylaxis may be discontinued if the suspect animal is proved by appropriate laboratory examination to be free of rabies or, in the case of domestic dogs, cats or ferrets, the animal remains healthy throughout a 10-day observation period starting from the date of the bite. Factors that should be taken into consideration when deciding whether to initiate postexposure prophylaxis include the epidemiological likelihood of the implicated animal being rabid, the category of exposure (I–III) and the clinical features of the animal, as well as its availability for observation and laboratory testing. In most situations in developing countries, the vaccination status of the implicated animal alone should not be considered when deciding whether to give or withhold prophylaxis.

Intramuscular Administration for Postexposure Prophylaxis

The postexposure vaccination schedule is based on injecting 1 ml or 0.5 ml (the volume depends on the type of vaccine) into the deltoid muscle (or anterolateral thigh in children aged <2 years) of patients with category II and III exposures. The recommended regimen consists of either a 5-dose or a 4-dose schedule:

- *5 Dose regimen:*
 - The 5-dose regimen prescribes 1 dose on each of days 0, 3, 7, 14 and 28.
- *4 Dose regimen*
 - The 4-dose regimen prescribes 2 doses on day 0 (1 in each of the 2 deltoid or thigh sites) followed by 1 dose on each of days 7 and 21.

- An alternative for healthy, fully immunocompetent, exposed people who receive wound care plus high quality rabies immunoglobulin plus WHO-prequalified rabies vaccines, is a postexposure regimen consisting of 4 doses administered intramuscularly on days 0, 3, 7 and 14.¹⁰

Intradermal Administration for Postexposure Prophylaxis

The 2-site regimen prescribes injection of 0.1 ml at 2 sites (deltoid and thigh) on days 0, 3, 7 and 28. This regimen may be used for people with category II and III exposures in countries where the intradermal route has been endorsed by national health authorities.

Postexposure Prophylaxis for Previously Vaccinated Individuals

For rabies-exposed patients who can document previous complete pre-exposure vaccination or complete post-exposure prophylaxis with a CCV, following schedules can be used:

- *1-site 2-day Regimen:* 1 dose delivered intramuscularly or intradermally on days 0 and 3 is sufficient. Rabies immunoglobulin is not indicated in such cases. This 1-site 2-day intradermal or intramuscular regimen also applies to people vaccinated against rabies who have demonstrated rabies-virus neutralizing antibody titers of ≥ 0.5 IU/ml.
- *Single-visit-4-site Regimen:* The patient may be offered a single-visit 4-site intradermal regimen consisting of 4 injections of 0.1 ml equally distributed over left and right deltoids or prescapular areas. Vaccination cards recording previous immunizations are invaluable for making correct decisions.

Immunization of Immunocompromised Individuals

In immunocompromised individuals including patients with HIV/AIDS, a complete series of 5 doses of intramuscular CCV in combination with comprehensive wound management and local infiltration with human rabies immunoglobulin is required for patients with category II and III exposures. When feasible, the rabies-virus neutralizing

antibody response should be determined 2 to 4 weeks following vaccination to assess the possible need for an additional dose of the vaccine.

Rabies Immunoglobulin for Passive Immunization

Rabies immunoglobulin for passive immunization is administered only once, preferably at, or as soon as possible after, the initiation of postexposure vaccination. Beyond the seventh day after the first dose, rabies immunoglobulin is not indicated because an active antibody response to the CCV is presumed to have occurred. The dose of human rabies immunoglobulin is 20 IU/kg body weight; for equine immunoglobulin and F(ab')³ products, it is 40 IU/kg body weight. All of the rabies immunoglobulin, or as much as anatomically possible (but avoiding possible compartment syndrome), should be administered into or around the wound site or sites. The remaining immunoglobulin, if any, should be injected intramuscularly at a site distant from the site of vaccine administration. Rabies immunoglobulin may be diluted to a volume sufficient for all wounds to be effectively and safely infiltrated.⁶

COORDINATED RABIES CONTROL

As demonstrated in industrialized countries and in most of Latin America, eliminating rabies from dog populations significantly reduces human exposure to the disease. Mass vaccination of dogs is the single most cost-effective intervention to control and eliminate canine rabies. However, successful rabies control also depends on measures such as managing the dog population, mainly by promoting responsible dog ownership; compulsory notification of rabies in humans and animals; ensuring the availability of reliable diagnostic procedures; conducting postmortem examinations to confirm the cause of death in people suspected to have been infected with rabies; and improving coordination between all public sectors involved in rabies control.¹¹

How can dog bites be prevented?

Dog bites are a largely preventable public health problem and adults and children can learn to reduce their chances of being bitten. Before bringing a dog into household, it is better to consult with a professional to learn what breeds of dogs is the best fit for household. Dogs with histories of aggression are not suitable for households with children. It is better to spend some time with a dog before buying or adopting it and use caution when bringing a dog into a household with an infant or toddler.

If a dog is brought into home, it's better to neuter the dog to reduce aggressive tendencies and not to play aggressive games with him. Teach the dog, submissive behaviors and properly socialize and train him. One should immediately seek professional advice from veterinarians if the dog develops aggressive or undesirable behaviors. To help to

prevent children from being bitten by dogs, teach them the basic safety tips like not to approach an unfamiliar dog; not to run from a dog or scream but remain motionless; roll into a ball and lie still if knocked over by a dog; avoid direct eye contact with a dog; do not disturb a dog that is sleeping, eating, or caring for puppies and if bitten, immediately report the bite to an adult.

SUMMARY

Rabies is a viral zoonosis of mammals. Rabid dogs are the dominant source of infection in humans, in whom rabies virus causes acute, progressive encephalitis that is invariably fatal. Each year, rabies causes about 55,000 human deaths, many in children living in rural areas of Asia and Africa. The disease is grossly under-reported; it is estimated that without postexposure prophylaxis about 3,27,000 persons would die from rabies in Africa and Asia each year. In industrialized countries and in most urbanized areas of Latin America human rabies is close to being eliminated owing to the vaccination of domestic dogs and the implementation of other control measures. Cell-culture-based rabies vaccines have proven to be safe and effective in preventing rabies and have been administered to millions of people worldwide. All these vaccines can be administered intramuscularly, but some are also recommended for vaccine-saving intradermal use. When used according to WHO's recommendations, neutralizing antibody concentrations of ≥ 0.5 IU/ml are achieved in practically 100 percent of healthy vaccinees and so far, no cases of rabies have been reported in individuals with such antibody concentrations. Cell-culture-based vaccines are safe and usually well tolerated although in 35 to 45 percent of vaccinees, minor and transient erythema, pain and or swelling may occur at the site of injection, particularly following intradermal administration. Mild systemic adverse events such as transient fever, headache, dizziness and gastrointestinal symptoms, have been observed in 5 to 15 percent of vaccinees.

Pre-exposure prophylaxis is recommended for anyone who will be at continual, frequent or increased risk of exposure to rabies virus, either by nature of their residence, travel or occupation. Children living in or visiting rabies-affected areas are at particular risk. The protection is long lasting (at least 10 years) and booster doses are only recommended for people whose occupation puts them at continual or frequent risk of exposure. The indication for postexposure prophylaxis depends on the type of contact with the suspected rabid animal: category I – touching or feeding animals, licks on intact skin; category II – nibbling of uncovered skin, minor scratches or abrasions without bleeding; category III – single or multiple transdermal bites or scratches, contamination of mucous membrane with saliva from licks, licks on broken skin, and exposures to bats. For category I exposures, no prophylaxis is required; for category II, immediate vaccination

is recommended; and for category III, immediate vaccination and administration of rabies immunoglobulin are recommended. The position paper provides details on various WHO-recommended schedules for intramuscular as well as intradermal pre and postexposure vaccination, the correct use of rabies immunoglobulin, as well as on other measures to be observed following possible exposure to rabies virus.

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Infections in the Immunocompromised Hosts

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Immunosuppressed individuals constitute one of the rare but very fragile population from the pediatric age group. The numbers of immunocompromised individuals are increasing out of the increased survival secondary to the better management in these individuals. The outcome of immunosuppressed individuals whether inherited or iatrogenic primarily depends on the timely initiation of the appropriate management steps. The discussion in this chapter is going to focus on the basic immunopathological issues, types of infection, and their early diagnostic tools and about the appropriate management strategies in these immunosuppressed individuals.

Immunity is primarily interplay between antigens and antibodies. Antigen is a live or inactivated substance (e.g. protein, polysaccharide) capable of producing an immune response while antibodies are protein molecules (immunoglobulin's) produced by B lymphocytes to help eliminate a foreign antigen. One of the primary functions of the immune system is to prevent or cure infectious diseases and the tool used to achieve this function is immunity. Immunity helps in recognizing self vs. nonself, protects from infectious disease, usually indicated by the presence of antibodies and very specific to a single organism. The immunity is primarily of two types, the innate immunity and adaptive immunity. The basic features of innate immunity are, it's the 1st line of defense and provides initial defense against infection, it's relatively non-specific, not enhanced by immunization but necessary for the establishment and enhancement of adaptive immunity. Adaptive immunity (acquired or specific immunity) develops slowly, has got a broad activity against antigens and has a high degree of specificity. It is enhanced by immunization and activity heightened by cross talk with the innate immune system via cytokines.

The specific immunity can be acquired either naturally (Active: antigens enter the body naturally, e.g. natural

infections or Passive: antibodies pass from mother to fetus via placenta) or artificially (Active: antigens are introduced in body through vaccines and they produce antibodies or Passive: preformed antibodies in immune serum are introduced into body by injection, e.g. varicella-zoster immunoglobulin). Flow chart 1 summarizes the basic functioning of immune system.

Infections in the immunocompromised differ significantly from those in the immunocompetent. They can be more serious, more often life-threatening, more difficult to diagnose and are caused by more unusual organisms. Children can be immunocompromised for a variety of reasons. Since immunocompromised host are a heterogeneous population and no stringent criteria can be laid down to define an immunocompromised host. The complete details of the immunocompromised conditions are given in Table 1. They can also be classified as primary and secondary. *Primary* disorders are genetically inherited disorders of T cell, B cell or combined, complement and phagocytic dysfunctions. *Secondary* causes of immunocompromised hosts are-HIV, malignant neoplasms, transplant recipients (solid organ transplant or bone marrow transplant), chronic liver diseases, asplenia or postsplenectomy and therapy related. Therapy related can be immunosuppressive drugs (e.g. steroids, tacrolimus, and cyclosporin, etc.), chemotherapy drugs and secondary to Radiation therapy.¹

Degree of immunosuppression depends either on the severity of underlying disease or the doses of the given immunosuppressive agents. Drug-induced immunosuppression is a dose-dependent phenomenon. These immunosuppressed patients are incapable of mounting adequate cellular and humoral immune responses to infection including typical and atypical ones. Suboptimal immune response put these patients at an increased risk of a complicated clinical course even to the common

Flow chart 1: Overall basic interplay of human immune system

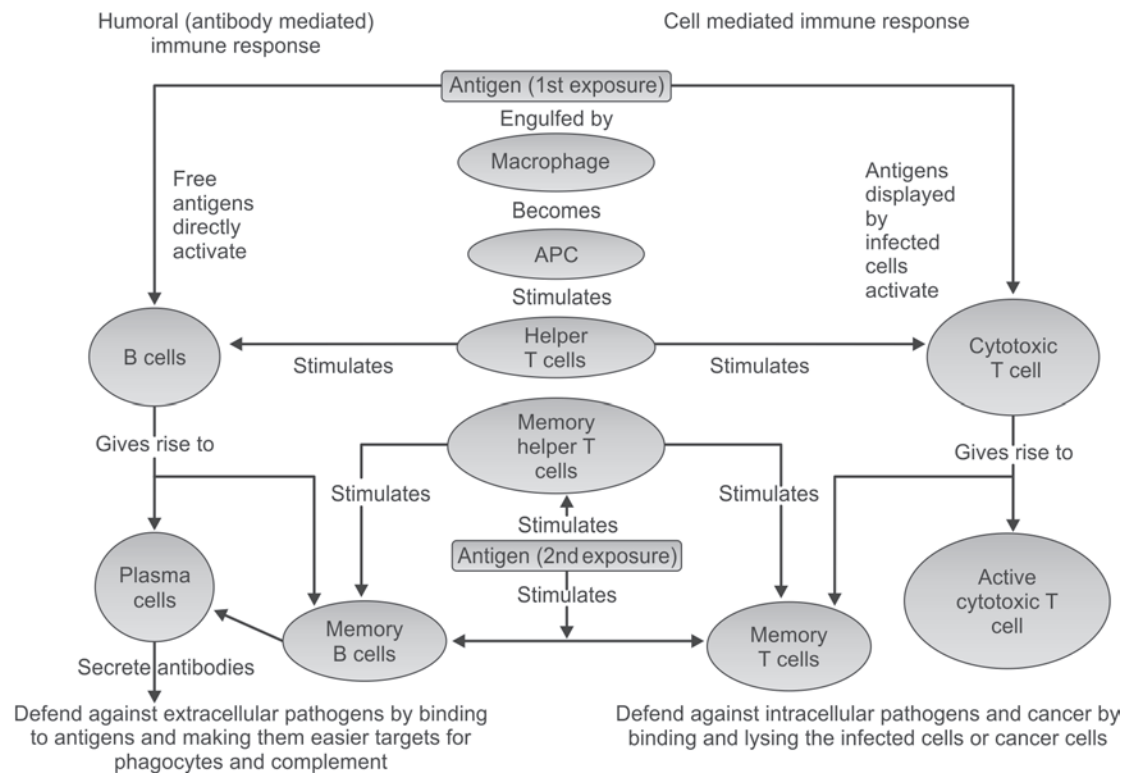


Table 1: Conditions associated with immunosuppression²⁻¹⁰

Congenital conditions:²⁻⁷ Usually they present either in the neonatal period or in the infancy

<i>B-cell defects</i>	<i>Macrophage, cytokine, and miscellaneous defects</i>	<i>Phagocyte deficiency or dysfunction</i>
<ul style="list-style-type: none">• Common variable immunodeficiency• IgG heavy-chain deletion• Kappa-chain deficiency• Selective IgA deficiency• Selective IgM deficiency• Transient hypogammaglobulinemia of infancy or early childhood• Thymoma with agammaglobulinemia• X-linked (Bruton) agammaglobulinemia• X-linked hyper-IgM syndrome• X-linked hypogammaglobulinemia with growth hormone deficiency	<ul style="list-style-type: none">• Mendelian susceptibility to mycobacterial diseases (MSMD)• IL-1 receptor–associated kinase 4 (IRAK4) deficiency• Apolipoprotein L-I deficiency• Toll-like receptor mutations• Plasminogen activator inhibitor-1 4G/4G promoter genotype• Anti-interferon-γ antibodies• RANTES promoter gene polymorphisms• Whim syndrome—CXCR4 mutations• IL-6 polymorphisms• Dectin-1 deficiency• IL-12 receptor deficiency	<ul style="list-style-type: none">• Chediak-Higashi syndrome• Chronic granulomatous disease• Chronic idiopathic neutropenia• Cyclic neutropenia• Glycogen storage disease 1b• Hyper-IgE/recurrent infection (Job) syndrome (Janus kinase protein tyrosine kinase 2 [Tyk2])• Kostmann syndrome• Leukocyte adhesion deficiency (including CD11 or CD18 deficiency)• Myeloperoxidase deficiency• Shwachman-Diamond syndrome
<i>T-cell defects</i>	<i>Complement deficiencies</i>	
<ul style="list-style-type: none">• Multiple carboxylase deficiency (Biotin-dependent)• Chronic mucocutaneous candidiasis• DiGeorge (velocardiofacial) syndrome• Short-limbed dwarfism or cartilage-hair hypoplasia	<ul style="list-style-type: none">• Deficiencies of C1q, C1r, C1s, C4, C2, C3, or C5-9• Deficiencies of factor D, factor P, factor I, factor H, or properdin	

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Combined B-cell and T-cell defects	Syndromes	Other conditions
<ul style="list-style-type: none"> Adenosine deaminase deficiency Ataxia-telangiectasia syndrome Intestinal lymphangiectasia Janus kinase 3 (JAK3) deficiency Omenn syndrome Reticular dysgenesis Swiss-type severe combined immunodeficiency T-cell receptor deficiency Wiskott-Aldrich syndrome X-linked lymphoproliferative syndrome X-linked severe combined immunodeficiency 	<ul style="list-style-type: none"> Griscelli Syndrome—Partial albinism with immunodeficiency Rendu-Osler disease—Hemorrhagic hereditary telangiectasia PAID Syndrome—Partial albinism, immunodeficiency, and progressive white matter disease Autoimmune polyendocrinopathy syndrome type 1 Rubinstein—Taybi syndrome Hermansky—Pudlak-2 syndrome CHARGE syndrome Other dysmorphism or immunodeficiency syndromes 	<ul style="list-style-type: none"> Asplenia Kartagener syndrome Galactosemia and other metabolic conditions Trisomy 21 and other genetic disorders
<i>Acquired and iatrogenic conditions:⁸⁻¹⁰ These conditions may interfere directly with the immune system or may disrupt barrier function</i>		
Acquired conditions	Iatrogenic conditions	
<ul style="list-style-type: none"> HIV Disease Malnutrition Acquired asplenia Acquired lymphedema Other conditions that injure or bypass barrier function <ul style="list-style-type: none"> Parasitic infections Animal and insect bites or scratches 	<ul style="list-style-type: none"> Chemotherapy or radiotherapy Leukemia or lymphoma, hematopoietic Stem cell transplant, solid tumors <p><i>Immunosuppression</i></p> <ul style="list-style-type: none"> Bone marrow or stem-cell transplantation Solid organ transplantation <p><i>Others</i></p> <ul style="list-style-type: none"> Therapy for autoimmune or inflammatory disorders TNF-alpha inhibitors Monoclonal antibodies and related small molecules Steroids for nephrotic syndrome 	

Table 2: Type of infections associated with a particular congenital condition^{6,11,12}

Condition	Type of infection	Name of the etiological agents
<i>Conventional conditions</i>		
<i>Asplenia:</i> congenital or acquired	Capsulated agents survives due to asplenia	Bacterial: <i>Streptococcus pneumoniae</i> , <i>Haemophilus influenzae</i> , <i>K. pneumoniae</i> , <i>Neisseria</i> species, <i>Edwardiella</i> Protozoa: Malaria and Babesiosis
<i>Trisomy 21</i>	Otitis media and upper respiratory infection	<i>Candida</i> organisms.
B-cell defects	Sinopulmonary and respiratory tract infections	Viral: Rotaviral, Parvovirus B19 Bacterial: <i>S. Pneumoniae</i> ; <i>H. influenzae</i> ; <i>S. aureus</i> ; <i>Pseudomonas aeruginosa</i> ; <i>M. pneumoniae</i> ; <i>Giardia lamblia</i> ; and <i>Salmonella</i> , <i>Shigella</i> , and <i>Campylobacter</i> species.
Common variable immunodeficiency:	Respiratory tract infections and gastrointestinal	Bacterial: <i>Salmonella</i> , or <i>Campylobacter</i> Viral: Enteroviruses Protozoa: <i>Giardia</i> , <i>Cryptosporidium parvum</i> Fungal: <i>P. Jiroveci</i>
Selective IgA deficiency:	Sinopulmonary and gastrointestinal	Bacterial: <i>Salmonella</i> , or <i>Campylobacter</i> Protozoa: <i>Giardia</i>
X-linked (Bruton) agammaglobulinemia:	Sinopulmonary	Bacterial: <i>S. Pneumococcal</i> , <i>S. Aureus</i> Viral: Enteroviruses, Echovirus and Rotavirus Protozoa: <i>G. lamblia</i> Fungal: <i>P. Jiroveci</i>

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Condition	Type of infection	Name of the etiological agents
Congenital conditions		
X-linked hyper-IgM syndrome:	Oral ulcers and perirectal abscesses	Bacterial: Mycobacterial, Salmonella Viral: CMV and Adenovirus Protozoa: <i>Entamoeba histolytica</i> , <i>Giardia</i> and <i>Cryptosporidium</i> Fungal: <i>P. jiroveci</i> (Recurrent Abscesses), <i>Cryptococcus</i>
T-cell defects	Sinopulmonary, gastrointestinal, skin and mucus membrane infections	Bacterial: <i>Mycobacterium avium-intracellulare</i> complex Viral: Herpesviruses Fungal: <i>Candida</i> and <i>P. jiroveci</i>
Chronic mucocutaneous candidiasis:	Skin and mucus membrane infections	Candidal infection
DiGeorge (velocardiofacial) syndrome:	Recurrent sinopulmonary and Gastrointestinal infections	Bacterial: <i>S. pneumoniae</i> Fungal: <i>Candida</i> species, and <i>P. jiroveci</i> Viral: CMV and HSV
Cartilage-hair Hypoplasia: Combined B and T-cell defects	Life-threatening varicella infections Failure to thrive and thrush	Varicella and other enteric virus infections MC infection is with <i>P. jiroveci</i> infection, other common are as follows: Bacterial: <i>S. pneumoniae</i> , <i>P. aeruginosa</i> , <i>Legionella pneumophila</i> , <i>L. monocytogenes</i> , <i>Nocardia</i> species, <i>Mycobacterium</i> species Viral: VZV, HSV, CMV, Epstein-Barr virus (EBV), respiratory viral infections Protozoa: <i>Toxoplasma</i> species, <i>Cryptosporidium</i> , <i>Strongyloides</i> Fungal: <i>P. jiroveci</i>
Ataxia-telangiectasia syndrome:	Severe sinopulmonary infections and bronchiectasis	Bacterial: Capsulated bacterial infections Viral: Herpes Simplex, Herpes Zoster and Uncomplicated Varicella Fungal: <i>Candida</i>
Wiskott-Aldrich syndrome:	Bacteremia and skin infections	<i>S. Pneumoniae</i> , <i>H. influenzae</i> , <i>P. jiroveci</i> , <i>Candida</i> species, CMV, HSV, EBV
X-linked lymphoproliferative syndrome: Macrophage, cytokine, and miscellaneous defects	LN and extra lymphatic organ involvement	EBV
RANTES promoter gene polymorphisms:	Sinopulmonary and gastrointestinal infections	Bacterial: Mycobacterial, <i>Salmonella</i> and <i>Listeria</i>
Toll-like receptor mutations:	Respiratory and urinary tract (Upper)	Respiratory syncytial virus infection
Phagocyte deficiency or dysfunction	Respiratory tract, neonatal sepsis and CNS infections	Bacterial: Meningococcal Respiratory syncytial virus, CMV and parainfluenza virus Fungal: <i>Aspergillus</i> Protozoa: <i>Cysticercosis</i>
	Skin, soft tissue and mucus membrane infection	Bacterial: <i>S. aureus</i> , <i>Nocardia</i> , <i>P. aeruginosa</i> , <i>Serratia</i> , streptococci, <i>Burkholderia</i> , and <i>Chromobacterium</i> species Fungal: <i>Candida</i> and <i>Aspergillus</i>
Chediak-Higashi syndrome:	Recurrent skin and mucosal infections	Infections with <i>S. aureus</i> and streptococci
Chronic granulomatous disease:	Skin, soft tissue and mucus membrane infection	Bacterial: Catalase-positive bacteria's including <i>S. aureus</i> , <i>S. Marcescens</i> , <i>Burkholderia cepacia</i> , <i>Granulibacter Bethesdensis</i> , <i>Nocardia</i> species, <i>Chromobacterium</i> species Fungal: <i>Candida</i> species, <i>Aspergillus</i> species
Hyper-IgE (Job) syndrome:	Skin, soft tissue and mucus membrane infection	Bacterial: <i>S. aureus</i> and Streptococci Fungal: <i>Candida</i> or <i>Aspergillus</i> species
Leukocyte adhesion deficiency:	Recurrent necrotic skin and soft-tissue infection, poor wound healing, delayed cord separation, gingivitis and periodontal abscesses	Bacterial: <i>P. aeruginosa</i> , <i>S. aureus</i> , <i>E. coli</i> , <i>B. Cepacia</i> , <i>Serratia</i> , <i>Klebsiella</i> and <i>Fusarium</i> Fungal: <i>Candida</i> and <i>Aspergillus</i> species
Complement deficiencies	Recurrent sinopulmonary infections	Bacterial: <i>S. Pneumoniae</i> , <i>H. influenzae</i> and <i>Neisseria</i> species
Deficiency of C1q, C1r, C1rs, C4, C2, C3, or C5-9:		
Deficiency of factor D, factor P, factor I, factor H, or properdin:	Meningococcal infection	Meningococcal infections

infections and the situation is further complicated by the atypical clinical presentation and there by delayed clinical diagnosis. Delayed clinical diagnosis also results in inadequate treatment and increased mortality and morbidity in these patients. The type of infection and the time of infection depend mainly on the present immune status of the patient and the likely immune system reconstitution time line.

Types of Infection in Immunocompromised

As such any infectious agent can complicate any immunocompromised condition but there are few trade mark infections which are commonly found in few conditions and knowing them help in the differential diagnosis of an immunocompromised child. Tables 2^{6,11,12} and 3^{12,13} gives brief details of common infectious agents in a particular condition. It is beyond the scope of the chapter to deal

Table 3: Type of infections associated with a particular acquired/iatrogenic condition^{12,13}

<i>Acquired or Iatrogenic conditions</i>		
Malnutrition	Respiratory, gastrointestinal, tuberculosis, malaria	Bacterial: Mycobacteria and atypical mycobacteria & Salmonellosis Viral: Measles, HIV Fungal: <i>P. jiroveci</i> Protozoa: <i>Plasmodium</i>
Hematologic or oncologic conditions	Almost every system can be affected but the commoner presentation are septicemia/bacteremia, line related infections, lung and gut infections	Bacterial: Coagulase-negative staphylococci, Viridans streptococci, <i>S. aureus</i> , <i>P. aeruginosa</i> , <i>S. pneumoniae</i> , <i>S. Pyogenes</i> , <i>Aeromonas</i> , <i>Mycobacteria</i> and other gram-positive and gram-negative organisms Viral: CMV, HSV, VZV, or community respiratory viruses Fungal: <i>Candida</i> , <i>Aspergillus</i> , <i>Mucor</i> , <i>Rhizopus</i> , <i>Trichosporon</i> and <i>P. jiroveci</i> Protozoa: <i>Strongyloides</i> species, <i>Toxoplasma</i> species
Neutropenia	Septicemia, line related, lung and gut infections	Bacteria: <i>E. coli</i> , <i>K. pneumoniae</i> , <i>Enterobacter</i> species, <i>Citrobacter</i> species, <i>P. aeruginosa</i> , <i>S. aureus</i> , <i>Clostridium septicum</i> , coagulase-negative staphylococci, streptococci, enterococci, anaerobes Fungal: <i>Candida</i> and <i>Aspergillus</i> and a variety of yeasts
Corticosteroid therapy	Sinopulmonary and gastrointestinal infections	Bacterial: <i>S. aureus</i> , <i>S. pneumoniae</i> , <i>Legionella</i> , <i>Listeria</i> Viral: VZV Protozoa: <i>Strongyloides</i> Fungal: <i>P. jiroveci</i> , <i>Candida</i> and <i>Nocardia</i> (now considered as fungus)
Inhaled corticosteroids	Oral thrush and community-acquired pneumonia (CAP)	<i>Candida</i> and organism causing CAP
Inhibitors of TNF- α	Reactivation of tuberculosis, CNS and gut infections	Bacterial: <i>M. tuberculosis</i> , atypical mycobacterial infections and <i>Listeria</i> Viral: HSV encephalitis Fungal: Histoplasmosis and <i>Candida</i> Protozoa: <i>Falciparum</i> malaria
Other monoclonal antibodies Eculizumab (C5 inhibitor)	Invasive meningococcal infection	Meningococcemia
Natalizumab (Inhibitor for cellular adhesion molecule α 4-integrin)	Progressive multifocal leukoencephalopathy	JC virus
Transplantations Bone marrow or hematopoietic stem cell transplant	Any organ system can be affected but the commoner presentations are septicemia, lung, gut, skin and soft tissue. (Usually the type of infection depends on the time since transplant)	Bacterial: Aerobic gram-negative rods, coagulase-negative Staphylococci, Streptococci, <i>S. aureus</i> , <i>C. difficile</i> Viral: Respiratory and enteric viruses, CMV, VZV, HSV, EBV, HHV 6 or 7, Parvovirus B19, Polyomaviruses, Rotavirus and Adenovirus Protozoa: <i>Toxoplasma</i> Fungal: <i>Candida</i> , <i>Aspergillus</i> , <i>P. jiroveci</i> , <i>Fusariums</i> species; Zygomycosis; other molds, such as <i>Pseudallescheria</i> species

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Acquired or Iatrogenic conditions

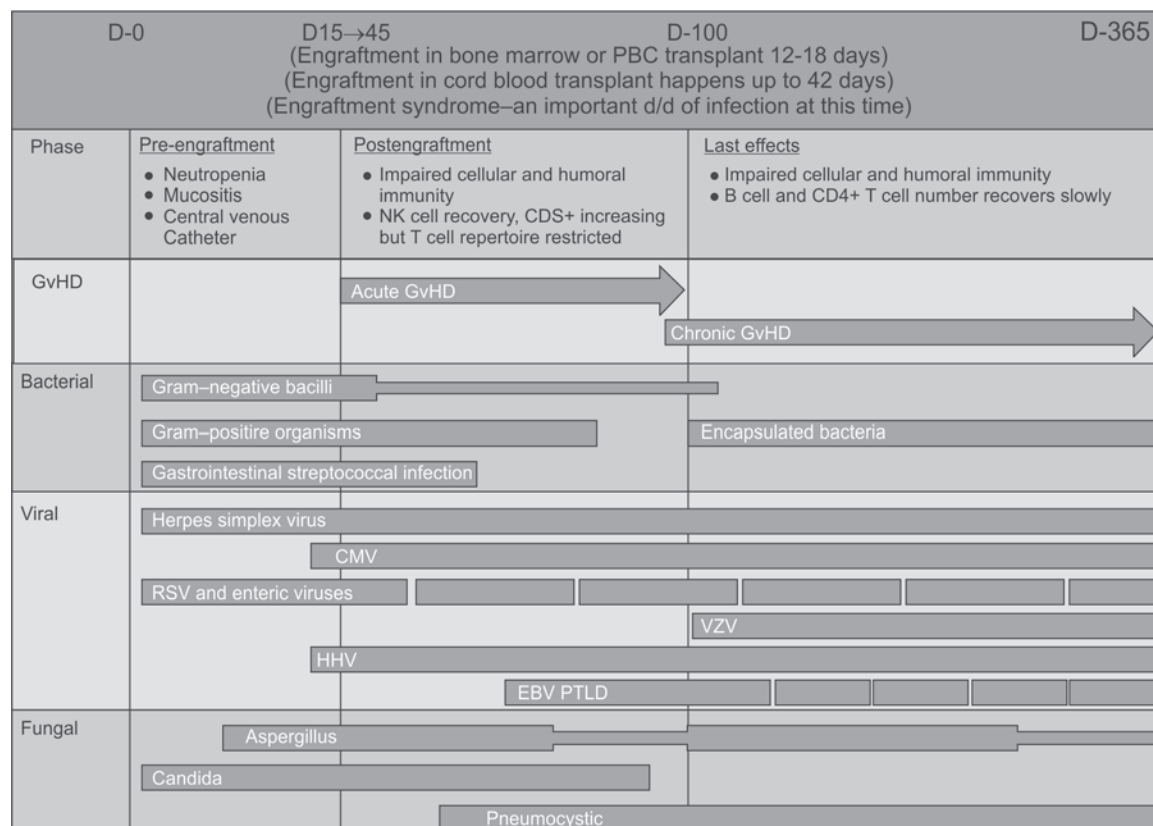
Solid organ transplant	Reactivation of old infections (tuberculosis), but usually the infections are transplant specific	Viral Infections nonspecific to organ transplant- Respiratory syncytial virus, influenza, CMV, VZV, HSV, EBV, BK virus, JC virus Heart or Heart Lung Transplant: <i>P. jiroveci</i> and <i>Toxoplasma</i> species Renal transplant: Adenovirus and BK virus and early post-transplant infections particularly with aspergillosis, cryptococcosis and zygomycosis
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with individual bacterial infections and a broad guideline for the bacterial management would be discussed under the febrile neutropenia and the commoner viral and fungal infections would be covered under separate headings.

The patients of hematopoietic stem cell transplant (HSCT) deserve a special mention. It's thought to be secondary to the immune reconstitution following HSCT and the type and the timing of infection depend on the recovery of various facets of immune system. The details of the immune recovery are given in the next chapter, i.e. "Vaccination of the immunocompromised host". Whether, It's secondary to allogenic or autologous (high dose chemotherapy followed by patient's own stem cell rescue, collected and cryopreserved at an earlier time) HSCT the

chances of infection are very high. The period of immunodeficient time is prolonged in the patients of allogenic HSCT in comparison to autologous HSCT. A brief timeline for the type of infections is given in the Figure 1.¹⁴

One of the big group among the immunocompromised hosts is constituted by the kids postchemotherapy and then presenting as febrile neutropenia. The most recent guideline of the Infectious Diseases Society of America (IDSA),¹⁵ states that in patients with febrile neutropenia the gram-positive bacteria are responsible for ~ 60 percent of microbiologically confirmed cases and the important ones are coagulase-negative staphylococci, vancomycin resistant enterococci, *S. aureus*, *pneumococcus* and *streptococcus viridans*. The recent years have shown an



D: Day; GvHD: graft versus host disease; CMV: cytomegalovirus; RSV: respiratory syncytial virus; VZV: varicella zoster virus; HHV: human herpes virus; EBV PTLD: Epstein Barr virus post-transplant lymphoproliferative disease; Bars: thicker the bar commoner the infection, thinner the bar vice versa.

Fig. 1: Time line for infection in patients with HSCT¹⁴

increase in the incidence of gram-positive bacteria may be secondary to the invasive procedures in these kids. Gram-negative bacteria are the second common group and the significant ones are *P. aeruginosa* and enterobacteria, especially *Klebsiella* spp. and *E. coli*, many of which, depending on local epidemiology, are extended-spectrum beta-lactamase (ESBL) producers.¹⁵ The likelihood of an infection varies from the unit to unit and hospital to hospital based on their practices. The guidelines given here are to be seen as a suggestion in their perspectives. Other etiologic agents, such as fungi and mycobacteria, may affect, with lower frequency, febrile neutropenic patients and are normally related to more severe and prolonged episodes of neutropenia (neutrophil $<500/\mu\text{L}$ and neutropenia for more than 10 days), to previous and prolonged wide spectrum antimicrobial use or antifungal prophylaxis and bone marrow or hematopoietic stem cell transplantation.¹⁶

DIAGNOSIS OF INFECTION

The diagnosis of sepsis in immunocompromised host is the pivotal step in the management and the clinical diagnosis should always be supported with lab diagnostics. The clinical diagnosis of infections in immunocompromised individuals is always a challenge as the clinical picture is always subtle secondary to the suboptimal inflammatory response in these kids. Having said that, usually it might not be possible to establish an infectious agent in the laboratory so early clinical diagnosis or suspicion holds the key for early interventions and thereby decreasing the mortality and morbidity. Definitive diagnosis might not always be possible and delaying the treatment might lead to devastating outcome in these patients so clinical suspicion of an infection is a good enough reason to start the targeted treatment (antibiotics, antiviral or antifungals) in these kids pending the lab results and then treatment to be titrated as per the course of the illness.

Since these patients are a heterogeneous population, but still if the patient is with a known diagnosis and is on immunosuppressive agents, making a clinical diagnosis is not difficult. If it's a new patient there are few clinical parameters which connote a possible immunocompromised condition and these are >10 episodes of acute otitis media, >2 episodes of pneumonia, >2 life-threatening infections per year, unusual pathogens causing infection, poor response of the normal pathogens to the standard of therapy, recurrent episodes of autoimmune phenomena, infections causing worsening of the chronic illnesses, poor immune response to vaccines, family history of immunodeficiency or similar infections, failure to thrive and developmental delays, chronic eczema, diarrhea and thrush.¹⁷

To establish a diagnosis, the laboratories tests to be done initially and then as add-on according to the suspected clinical condition are listed in Table 4.¹²

MANAGEMENT

Given the vast scope of the subject it might not be possible to include all the infections in the given chapter. We will cover the management of the bacterial illnesses under febrile neutropenia, and then the common and important viral and fungal infections would be discussed in brief.

Febrile Neutropenia

Any patient with neutropenia and fever is grouped in febrile neutropenia but majority of the patients fall into either of the two categories. First category involves patients which are neutropenic secondary to the bone marrow failure syndromes (single or multilineage), cyclical neutropenia, or benign neutropenia of the infancy (autoimmune neutropenia). Second group contains the patients who are neutropenic secondary to the chemotherapy given. Febrile neutropenia usually is used for neutropenia secondary to the chemotherapy.

Infectious Diseases Society of America (IDSA) guidelines define neutropenia as a neutrophil count of 500 cells/mm^3 or less or a count of $<1,000 \text{ cells/mm}^3$ with a predicted decrease to $<500 \text{ cells/mm}^3$ and fever in a neutropenic patient is defined as a single measurement of oral temperature of more than 38.3°C or a temperature of $>38.0^\circ\text{C}$ for $>1 \text{ h}$.¹⁸ The combination of the above two is known as febrile neutropenia. The diagnosis of febrile neutropenia warrants an immediate antibiotic support based on the risk grouping. Infectious disease society of America in their consensus guideline gave the criteria to divide the patients in to either low risk group or the high risk group for the initial decision of antibiotic selection and management strategies.¹⁸ Table 5 summarizes the commonly used criteria to group patients in the risk categories.^{18,19}

Once the patient is assigned a risk group the management starts. There is no gold standard hard and fast rule for antibiotic selection and the Figure 5 gives only the suggestions. A detailed antibiotic policy as per the prevalent common infections in the hospital and their culture sensitivity reports is a sound antibiotic policy for any individual unit and should be followed up closely.

Infectious Disease Society of America (IDSA) 2010, recommendations for the evaluation and treatment of patients with fever and neutropenia.¹⁵ A summary (strength of recommendation is given in parenthesis)

Role of risk assessment and what distinguishes high-risk and low-risk patients:

Assessment should be done at presentation of fever (A-II), this may determine the type of empirical antibiotic therapy (oral vs intravenous), if an admission needed (inpatient vs outpatient), and the duration of antibiotic therapy (A-II). Most high-risk patients should be initially admitted to the hospital for empirical therapy (A-II). Low-risk patients are candidates for oral empirical therapy (A-II).

Table 4: Lab work to be done as per the suspected condition¹²

<i>Blood test</i>		<i>Cultures</i>	<i>Radiological</i>	<i>Microbiological</i>
Initial lab work, non-specific to condition	CBC with differential with morphology ESR and C-reactive protein Renal and liver function tests and coagulation studies if indicated Blood urea, Creatinine, electrolytes, liver transaminases, total and direct bilirubin and amylase	Cultures: Every immunocompromised patient if febrile need a vigorous search for infection through various cultures. Depending on the various factors like, central venous line <i>in situ</i> , previous known infection, and productive sputum or discharges a blood culture and a culture of the other body fluids is taken up. If CVL <i>in situ</i> , a pair of blood culture (one from CVL and second from peripheral phlebotomy) is taken ideally. We need to repeat the blood cultures daily in order to increase the yield.	Depending on the organ system of presentation, may order for chest X-ray or ultrasound of the chest or abdomen or CT scan of the head (with or without contrast, as advised by the initial condition)	Rapid antigen testing as indicated and includes, group A streptococci, <i>C. difficile</i> , <i>Cryptococcus</i> species, RSV, influenza virus, adenovirus and parainfluenza
<i>Additional test to be done as per the suspected condition</i>				
B cells evaluation	Ig levels IgG subclass levels Isohemagglutinins Lymphocyte subpopulations (CD19 or CD20)	Daily blood cultures if patient stays febrile or suspected of running infection and add other cultures as and when required	CXR/CT chest to look for a thymus and/or lymphoid tissue	Antibody production after vaccination (e.g. diphtheria, meningococcal, pneumococcal and Tetanus)
T cells evaluation	Lymphocyte subpopulations Assessment of delayed-type hypersensitivity reactions	Daily blood cultures if patient stays febrile or suspected of running infection and add other cultures as and when required	CXR/CT chest to look for a thymus and/or lymphoid tissue	Mitogen-stimulation assays
Phagocytic evaluation	Absolute neutrophil count Numbers of CD11(a, b and c subset) and CD18 β -receptor	Daily blood cultures if patient stays febrile or suspected of running infection and add other cultures as and when required	CXR/CT chest to look for a thymus and/or lymphoid tissue	Chronic granulomatous disease assay (formerly nitroblue tetrazolium test)
Complement evaluation	Total hemolytic complement MBL levels (mannose-binding lectin) Specific complement components, e.g. C3, C4, etc.	Daily blood cultures if patient stays febrile or suspected of running infection and add other cultures as and when required	CXR/CT chest to look for a thymus and/or lymphoid tissue	CH50 evaluation

Table 5: Risk groups assignments in patients with febrile neutropenia

	<i>Low risk for severe infection</i>	<i>High risk for severe infection</i>
Factors	ANC $\geq 100/\text{mm}^3$ AMC $\geq 100/\text{mm}^3$ Normal chest X-ray Nearly normal hepatic and renal function tests Duration of neutropenia of < 7 days Resolution of neutropenia expected in < 10 days No intravenous catheter–site infection Early evidence of bone marrow recovery Malignancy in remission Peak temperature of $< 39.0^\circ\text{C}$ No neurological or mental changes Nontoxic appearance and no abdominal pain No comorbid complications ^a	ANC $< 100/\text{mm}^3$ Toxic appearance Comorbid complications ^a Abnormal chest X-ray Abnormal hepatic and renal function tests Resolution of neutropenia expected in > 10 days Intravenous catheter <i>in situ</i> Malignancy not in remission Signs of CNS involvement

ANC: Absolute neutrophil count; AMC: absolute monocyte count; a: shock, hypoxia, pneumonia or other deep-organ infection, vomiting, or diarrhea.^{18,19}

Multinational Association for Supportive Care in Cancer (MASCC) scoring system (B-I) may be used to put the patient in Risk groups.

- High-risk patients have a MASCC score <21 (B-I) and Low-risk patients have a MASCC score >21 (B-I).

What specific tests and cultures should be performed during the initial assessment?

Complete blood cell (CBC) count with differential leukocyte counts; serum creatinine, blood urea nitrogen; electrolytes, hepatic transaminases and total bilirubin and a chest X-ray with respiratory signs and symptoms (A-III). Two sets of blood cultures are recommended (AIII). Blood culture volumes should be limited to 0.1 percent of total blood volume (CIII):

- If CVC (central venous catheter) present—Collect simultaneously from each lumen of CVC, and from a peripheral vein site.
- If no CVC—Two blood culture sets from separate venipunctures should be sent.

Culture specimens from other sites of suspected infection should be obtained as clinically indicated (A-III).

What empiric antibiotic therapy is appropriate?

High-risk patients require hospitalization for IV empirical antibiotic therapy; monotherapy with an antipseudomonal β -lactam agent, such as cefepime, a carbapenem (meropenem or imipenem-cilastatin), or piperacillin-tazobactam, is recommended (A-I). Other antimicrobials (aminoglycosides, fluoroquinolones, and/or Vancomycin) may be added to the initial regimen for management of complications (e.g. hypotension and pneumonia) or if antimicrobial resistance is suspected or proven (B-III). Vancomycin or other agents active against gram-positive cocci are not recommended as a standard part of the initial antibiotic regimen for fever and neutropenia (A-I) but may be considered for suspected catheter-related infection, skin or soft-tissue infection, pneumonia, or hemodynamic instability. Modifications to initial empirical therapy may be considered for patients at risk for infection with the following antibiotic-resistant organisms, (B-III):

- MRSA (methicillin-resistant *Staphylococcus aureus*): Consider early addition of Vancomycin, Linezolid, or Daptomycin (B-III).
- VRE (vancomycin-resistant *Enterococcus*): Consider early addition of linezolid or daptomycin (B-III).
- ESBLs (Extended-spectrum β -lactamase): Consider early use of a carbapenem (B-III).
- KPCs (*Klebsiella pneumoniae* carbapenemase): Consider early use of polymyxin-colistin or tigecycline (C-III).

Penicillin-allergic patients—usually tolerate cephalosporins, but those with severe reaction should avoid β -lactams and carbapenems and be given combinations

such as ciprofloxacin plus clindamycin or aztreonam plus vancomycin (A-II).

Low-risk patients should receive initial oral or IV empirical antibiotic doses in a clinic or hospital setting; and then they may be transitioned to outpatient oral or IV treatment as per their progress (A-I).

Ciprofloxacin plus amoxicillin-clavulanate in combination is recommended for oral empirical treatment (A-I). Other option includes levofloxacin or ciprofloxacin monotherapy or ciprofloxacin plus clindamycin (B-III). Patients receiving fluoroquinolone prophylaxis should not receive therapy with another or the same fluoroquinolone (A-III). (Issue - use of quinolones in the early childhood is of concern. Few pediatric oncology centers uses oral Cephalosporine (Cefpodoxime) also)

How to make antimicrobials modifications?

Modifications should be made based on clinical and microbiologic data (A-II). Persistent fever without an obvious cause and otherwise stable, rarely need a change to the initial antibiotic regimen (A-I).

Documented infections should be treated with antibiotics as per the culture and sensitivity report (A-I). If vancomycin was started initially, and there is no evidence for gram-positive infection, it may be stopped after 2 days (A-II). Patients who are hemodynamically unstable even after the standard agents for neutropenic fever should have a broadened antibiotic coverage for resistant gram-negative, gram-positive, and anaerobic bacteria and fungi (A-III).

Low-risk patients who are on IV or oral antibiotics, clinically stable but in hospital should be offered a simplified antibiotic coverage (A-I) and a transition to outpatient care with daily follow-up. If fever persists or recurs within 48 h in outpatients, hospital readmission is recommended, with management as for high-risk patients (A-III).

High-risk patients should be offered an empirical antifungal coverage that have persistent fever after 4 to 7 days of a broad-spectrum antibacterial regimen and no identified fever source (A-II).

Duration of antibiotic therapy?

In *documented infections*, the duration of therapy depends on the organism and site; appropriate antibiotics to be given at least during the neutropenia (until ANC is >500 cells/mm³) or longer if clinically necessary (B-III).

In *nondocumented fevers*, the initial antibiotics to be continued until there are signs of marrow recovery. Once ANC exceeds 5000 cells/mm³, antibiotics can be stopped (B-II).

If patient is afebrile with resolved clinical signs of nondocumented infections and initial course of antibiotics completed but are still neutropenic, should be given appropriate oral antibiotic prophylaxis until marrow recovery (C-III).

Antibiotic prophylaxis?

Appropriate prophylaxis (unit policy based on microbiological data) should be given for high-risk patients (BI). Addition of a gram-positive active agent is generally not recommended (A-I). Antibacterial prophylaxis is not routinely recommended for low-risk patients (A-III).

Empirical or pre-emptive antifungal therapy?

In *high risk* patients where fever is persisting or recurring after 4 to 7 days of antibiotics, should be considered for empirical or pre-emptive (evaluated with CT chest and sinuses with ultrasound abdomen and reports are normal) antifungal therapy (A-I). There is no consensus for selecting a specific empirical antifungal agent for a patient who is already receiving antimold prophylaxis, but switching to a different class of antimold antifungal with intravenous route should be considered (B-III).

In *low risk patients*, routine use of empirical antifungal therapy is not recommended (A-III).

Antifungal prophylaxis?

In *high risk* patients prophylaxis against *Candida* infection is recommended (A-I). Fluconazole, itraconazole, voriconazole, posaconazole, micafungin, and caspofungin are all acceptable agents depending on the units policy. Patients who are undergoing intensive chemotherapy for acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) should be offered anti-aspergillus prophylaxis (B-I).

In patient with autologous or allogenic hematopoietic stem cell transplant, prophylaxis against *Aspergillus* infection before engraftment has not been shown to be efficacious. However, in patients with prior invasive aspergillosis, a mold-active agent is recommended (A-III).

In *low risk* patients antifungal prophylaxis is not recommended (A-III).

Antiviral prophylaxis?

Patients undergoing allogeneic HSCT or leukemia induction therapy and are seropositive should receive a herpes simplex virus (HSV) antiviral prophylaxis with Acyclovir (A-I). Treatment for HSV or varicella-zoster virus (VZV) infection is only indicated if there is clinical or laboratory evidence of active viral disease (C-III).

Influenza virus infection should be treated with neuraminidase inhibitors if the infecting strain is susceptible (A-II). In a situation like influenza exposure or outbreak, if a neutropenic patient presents with influenza-like illness, should receive treatment empirically (C-III). Routine treatment of RSV infection in neutropenic patients with upper respiratory disease should not be given (B-III).

Hematopoietic growth factors (G-CSF or GM-CSF)?

Hematopoietic growth factors should be considered for patients in whom the anticipated risk of fever and

neutropenia is >20 percent (A-II) but are not generally recommended for treatment of established fever and neutropenia (B-II).

Catheter-related infections?

Differential time to positivity (DTP) >120 min (CVC related samples are positive earlier than then the taken from peripheral vein) of qualitative blood cultures performed on specimens simultaneously drawn from the central venous catheter (CVC) and a peripheral vein suggests a central line-associated blood stream infection (CLABSI) (A-II).

- CLABSI caused by *S. aureus*, *P. aeruginosa*, fungi or mycobacteria, catheter removal is recommended in addition to systemic antimicrobial therapy for at least 14 days (A-II). Catheter removal is also recommended for tunnel infection or port pocket site infection, septic thrombosis, endocarditis, sepsis with hemodynamic instability, or blood stream infection that persists despite >72 h of therapy with appropriate antibiotics (A-II).
- CLABSI caused by coagulase-negative staphylococci, the catheter may be retained using systemic therapy with or without antibiotic lock therapy (B-III).
- Prolonged treatment (4-6 weeks) is recommended for complicated CLABSI, defined as the presence of deep tissue infection, endocarditis, septic thrombosis (A-II) or persistent bacteremia or fungemia occurring 72 h after catheter removal in a patient who has received appropriate antimicrobials (A-II for *S. aureus*, C-III for other pathogens).

VIRAL INFECTIONS

Viral infections are a common cause of the serious disease in immunocompromised hosts. In the last twenty years, several potent new antiviral agents have become available for the effective management of infections like herpes simplex virus (HSV), varicella-zoster virus (VZV), and cytomegalovirus (CMV).²⁰⁻²³ In the last decade, major advances in rapid diagnostic techniques for viral infections have further helped to markedly improve the efficacy of antiviral treatment. Last few years have seen the refined antigen detection assays, polymerase chain reaction (PCR) and Shell-vial cultures helping the clinician to detect viral infections at an early stage and making timely therapeutic decisions. It will be beyond the scope of the chapter to include all the viral infection here but the common infections will be discussed here in brief (Table 6).

Influenza

Influenza (flu) virus is a RNA virus from the family orthomyxoviridae and affects birds and mammals. Influenza viruses make up three of the five genera of the family orthomyxoviridae²⁴ influenza virus A, B and C. For

Table 6: Management strategies for the common viral infections in the settings of immunocompromised hosts

<i>Virus</i>	<i>First line treatment</i>	<i>Second line treatment</i>	<i>Diagnosis</i>	<i>Comment</i>
HSV	Acyclovir (IV, oral), high dose IV—250 mg/m ² Q8H x 10 D Use 500 mg/m ² for visceral Oral: <2 yrs—200 mg QID 2-6 yrs—400 mg QID >6 yrs—800 mg QID Valacyclovir (oral), high dose PO—500 mg BID x 10 D	Foscarnet (IV)* IV—60 mg/kg Q8H Cidofovir (IV) IV—1 mg/kg alternate days	Serology, viral cultures, viral antigens and viral DNA PCR and Tzanck smear from the lesions	Give preferably in central line if using IV and monitor serum creatinine
VZV	Acyclovir (IV, oral), high dose IV—500 mg/m ² Q8H x 14 D Oral- <2 yrs—200 mg QID 2-6 yrs—400 mg QID >6 yrs—800 mg QID VZV immune globulin in <96 hrs <5 years—250 mg IV stat 5-10 years—500 mg IV stat and >10 years—750 mg IV stat	Famciclovir* PO—500 mg three times a day	Viral cultures, viral antigens and viral DNA PCR	Give preferably in central line if using IV and monitor serum creatinine
ADV	Cidofovir (IV) IV—5 mg/kg/week x 3 wks as induction and then 5 mg/kg/alternate wks x 3 wks (continue as per unit policy)	Vidarabine (IV)* IV—10 mg/kg/day x 5-7 Days in one course (number of courses as per unit policy)	Viral cultures, viral antigens by immunofluorescence in urine, stool and blood and viral DNA PCR	Coadministered with Probenecid and monitor serum creatinine
CMV	Gancyclovir (IV) Induction: IV—5 mg/kg Q12H Consolidation: IV—6 mg/kg once daily x 5 D/wk Cytogam (CMV immunoglobulin) IV—50 mg/kg once a wk	Foscarnet (IV)* Induction: IV—60 mg/kg Q12H Consolidation: IV—90 mg/kg once daily x 5D/wk	Serology, viral cultures, viral antigens and viral DNA PCR	May cause neutropenia (consider G-CSF) Neurotoxicity in patients with renal impairment
RSV	Ribavirin (inhalation, IV, oral) Aerosolized—6 g over 18 h/day at 20 mg/ml, for 7 days via a respiratory small particle aerosol generator 'SPAG unit') and + IVIg (500 mg/kg/dose alternate days for four doses)	Palivizumab# (Humanized RSV monoclonal antibody) IV—15 mg/kg single dose (courses number as per unit policy)	Immunofluorescence and enzyme immunoassay for RSV antigen in nasopharyngeal washings or bronchoalveolar lavage	Therapeutic benefit in RSV infection unclear outside allogeneic stem cell
HBV	Pegylated Interferon α-2a (180 µg once weekly) + Lamivudin (Oral) PO—3 mg/kg/day x 48-56 wks		Serology and HBV DNA PCR	Prevention of acute liver failure in patients with active HBV replication
Influenza	Oseltamivir (oral) x 10 D <15 kg—30 mg BD 15-25 kg—45 mg BD 25-40 kg—60 mg BD >40 kg—75 mg BD (150 mg BD x 10 days in severe infection)	Zanamivir (inhalation) x 5 mg inhalation once daily x 10 D	Viral culture, serology, rapid antigen testing, immunofluorescence assays and viral PCR	Administer as early as possible (<48 h) after diagnosis. Infants safety not established and use not recommended \$—Administer as early as possible (<48 h) after diagnosis

Contd...

Contd...

<i>Virus</i>	<i>First line treatment</i>	<i>Second line treatment</i>	<i>Diagnosis</i>	<i>Comment</i>
EB virus	Donor leukocyte infusion rituximab (Anti-CD20) (IV)	EBV specific cytotoxic T lymphocytes Chemotherapy	EBV PCR for viral load Post-transplant lymphoproliferative disease- Tissue biopsy for evidence of Lymphoproliferation + Ebstein barr virus load	Data from EBV associated lymphoproliferative disease after transplantation

HSV: herpes simplex virus; VZV: varicella zoster virus; ADV: adenovirus; CMV: cytomegalovirus; RSV: respiratory syncytial virus; HBV: hepatitis B virus; EBV: Epstein-Barr virus; #: no randomized study, small case series with conflicting results; *: evidence from case reports only

Influenza-A virus, wild aquatic birds are the natural hosts. Occasionally, viruses are transmitted to other species and sometimes cause devastating outbreaks in domestic poultry or give rise to human influenza pandemics.²⁵ The type-A viruses are the most virulent human pathogens among the three influenza types and cause the most severe disease and latest pandemic of swine flu (2009) is one of the examples. The virulence increases exponentially in immunosuppressed patients. Influenza-B almost always infects humans²⁶ and is less common than influenza A. Influenza B viruses are less genetically diverse, with only one serotype²⁶ and because of this less antigenic diversity immunity to influenza B is usually acquired at an early age. Influenza-C is less common than the other types and usually causes mild disease in children.

Flu in humans present as sore throat, cough, fever, chills, malaise, myalgia, headache, fatigue and nausea and vomiting particularly in the children.²⁷ Although it is often confused with other influenza-like illnesses, especially the common cold but influenza is a more severe disease. Flu can occasionally cause either direct viral pneumonia or secondary bacterial pneumonia.²⁸ Influenza is transmitted through the droplets containing the viruses. Influenza can also be transmitted by direct contact with bird droppings or nasal secretions, or through contact with contaminated surfaces, though the most important means of transmission is not clear.²⁹ Influenza viruses can be inactivated by sunlight, disinfectants and detergents.^{30,31} As the virus can be inactivated by soap, frequent hand washing reduces the risk of infection significantly.³²

Influenza A and B viruses are responsible for important morbidity and mortality in profoundly immunocompromised patients.^{33,34} In a study in immunosuppressed adults, out of all influenza infections pneumonia developed in approximately two-thirds of these patients with a case-fatality rate of up to 50 percent.³³ The severity of influenza in immunosuppressed patients appears to be related to the degree and duration of immunosuppression. Amantadine and Rimantadine are the effective treatment options for influenza-A infection. However, the benefit of the prophylactic or therapeutic use of these compounds in immunosuppressed individual is uncertain.

The neuraminidase inhibitors Zanamivir and Oseltamivir are active against both influenza A and B viruses. Several placebo-controlled trials have documented the efficacy and safety of neuraminidase inhibitors in the treatment of influenza in immunocompetent adults.³⁵ Studies are needed to assess the role of these antiviral agents in immunosuppressed patients. To reduce the risk of nosocomial transmission of influenza viruses, infection control measures and immunization with influenza virus vaccine of patients and hospital personnel are recommended.^{36,37}

Cytomegalovirus

Cytomegalovirus (CMV) has its origin from the Greek words, Cyto means- “cell”, and Megalo means, “large”. It is typically abbreviated as CMV. The species that infects humans is commonly known as human CMV (HCMV) or human herpesvirus-5 (HHV-5), and is the most studied of all cytomegaloviruses.³⁸ Human cytomegalovirus is a species of virus that belongs to the viral family known as Herpesviridae or herpesviruses. It is typically abbreviated as HCMV and is alternatively known as human herpesvirus-5 (HHV-5).³⁸ Within Herpesviridae, HCMV belongs to the Betaherpesvirinae subfamily, which also includes cytomegaloviruses from other mammals.³⁹ Although they may be found anywhere in the body, HCMV infections are frequently associated with the salivary glands.³⁹ In health individuals, HCMV infection is not clinically significant, but can be life-threatening for the immunocompromised persons and newborn infants.³⁸ After infection, HCMV has an ability to remain latent within the body over long periods and gets activated whenever body gets severely immunosuppressed.

CMV infection, is usually defined as the isolation of CMV in tissue culture or the identification of markers for CMV in tissue specimens or blood by histologic and histochemical means, or by specific antigen staining, by direct CMV DNA/RNA or CMV antigen detection, or by a four-fold or higher rise in CMV antibody titer.⁴⁰

CMV-associated interstitial pneumonia is defined as a progressive interstitial pulmonary process, as evidenced by chest X-ray findings and increased hypoxia, with evidence

of CMV infection in the lung and without evidence for other causes of pneumonitis. CMV enteritis is defined as an enteropathic syndrome with pain, nausea and vomiting, or diarrhea and evidence of CMV infection at the site of an inflammatory or ulcerative mucosal lesion. In general, other CMV-associated organ-related syndromes, such as hepatitis and encephalitis, are defined as syndromes with specific organ dysfunction and the concomitant presence of active CMV infection. With the exception of CMV retinitis, the diagnosis of CMV disease cannot be made without histologic evidence of CMV infection in the involved organ.

Immunosuppressed patients are at high risk for serious CMV disease following primary infection, reinfection, or reactivation of virus. Patients of allogeneic hematopoietic stem cell transplant (HSCT) are particularly at risk for CMV disease and the strongest predictor of CMV infection after allogeneic HSCT is the pretransplant CMV seropositivity of the patient. Failure to reconstitute a CMV-specific CD8+ cytotoxic T-cell response after HSCT contributes to the risk for CMV infection.^{41,42} CMV viremia is a major predisposing factor for CMV pneumonia and gastrointestinal CMV disease. In patients with acute leukemia, CMV pneumonia was reported to occur in 2.9 percent of patients with a case-fatality rate of 57 percent.⁴³ Even with the best possible therapy, CMV pneumonia after HSCT is associated with a mortality rate of 45 to 78 percent.^{44,45} Thus, in patients of HSCT and severe immunocompromised hosts, primary emphasis is given on the prevention of CMV disease.

It's well established now that even high-dose intravenous acyclovir as a prophylactic agent given only partial protection from CMV disease after allogeneic HSCT, and is absolutely ineffective in autograft recipients.⁴⁶ Prophylaxis with IV ganciclovir results in less frequent CMV disease but overall no improved survival⁴⁷ but on the other hand, if pre-emptive ganciclovir therapy initiated promptly upon recognition of CMV infection, is associated with both decreased incidence of CMV disease and better survival also.⁴⁸ The pre-emptive IV foscarnet appears as efficacious as ganciclovir and is associated with less hematotoxicity.⁴⁹ Results of a retrospective study, showed that IV cidofovir may be used in the treatment of CMV infection in HSCT recipients.⁴⁵

Valganciclovir is an oral prodrug of ganciclovir with a ten-fold greater bioavailability compared to oral ganciclovir.⁵⁰ Systemic ganciclovir exposure achieved with valganciclovir is comparable to that of intravenous ganciclovir.⁵⁰ The pharmacokinetics and safety of oral valganciclovir after allogeneic SCT are currently being investigated.

EBSTEIN-BARR VIRUS

Epstein-Barr virus (EBV), also known as human herpesvirus 4 (HHV-4), is a virus from the herpes family. It is best

known as the cause of infectious mononucleosis in immunocompetent individuals. It has been also associated with particular forms of cancer, particularly Hodgkin's lymphoma, Burkitt's lymphoma, nasopharyngeal carcinoma, and central nervous system lymphomas in patients with human immunodeficiency virus.⁵¹

Primary infection in normal hosts results in infectious mononucleosis (transient lymphoproliferative disorder), that is restricted by cytotoxic and suppressive lymphocytes. However, in the immunocompromised hosts, EBV-induced lymphoproliferation behave in a biologically malignant fashion and ranges from fulminant mononucleosis and invasive polyclonal B cell hyperplasia to monoclonal B cell malignancies known as post-transplant lymphoproliferative disease (PTLD).⁵²

Severe infections by Epstein-Barr virus (EBV) are relatively uncommon following HSCT, but if they happen, the most serious one is EBV related PTLD. PTLD is the result of the uncontrolled proliferation of donor derived EBV+B cells due to the lack of T cell immunity. The most significant risk factors for developing PTLD include the use of unrelated donor grafts (hematopoietic or solid organ grafts), T cell depletion of hematopoietic donor grafts, the use of OKT-3 for prophylaxis against rejection, or the treatment of acute graft versus host disease (GVHD) leading to more immunosuppression, and having received antithymocyte globulin.^{53,54} This suggests that selective T-cell depletion results in depletion of immunoregulatory T cells while leaving behind EBV+B cells that are susceptible to uncontrolled proliferation. PTLD occurs in <2 percent of allogeneic-HSCT⁵³ and typically occurs during the first six months after transplant. PTLD occurring after the first year post HSCT have been reported and occur mainly in patients with chronic GVHD where more immunosuppression is used.⁵³

Clinical manifestations of PTLD include fever, anorexia, lymphadenopathy, lethargy or confusion, hepatitis, or hepatosplenomegaly.⁵⁵ The diagnosis of PTLD is made by biopsy of affected organs. EBV serology is not helpful in establishing a diagnosis of PTLD, but monitoring changes in viral load may be useful. EBV DNA can be detected in >60 percent of allogeneic BMT recipients but isolated increase in the EBV DNA doesn't mean PTLD.⁵⁶ The difference in the load and the clinical picture holds the key to diagnosis. Patients with PTLD have a significantly higher viral load compared to patients without PTLD.⁵⁶ Even in patients with sustained increases in EBV viral load, only approximately 50 percent will develop PTLD.⁵⁷ In addition, the predictive value of threshold viral load may vary from center to center,^{56,57} and the patients' individual risk for PTLD must be taken into account when acting on PCR results. The interval between first demonstrating a rise in viral load and clinical signs of PTLD is often short.

Regional and node-based polyclonal proliferations may respond to prompt reduction of immunosuppressive

therapy and efforts to interrupt the replicative cycle with antiviral agents. Systemic cytotoxic therapy often leads to further immunosuppression and should be reserved for patients with progressive disease, advanced visceral involvement, and monoclonal lymphoid malignancies.

Successful treatments for PTLD have included donor leukocyte infusions,⁵⁸ EBV specific cytotoxic T lymphocytes,⁵⁹ chemotherapy,⁶⁰ and anti-CD20 monoclonal antibodies.^{56,61,62} Anti-CD20 antibodies (rituximab) are commercially available, thus making them attractive choices for therapy. Pre-emptive treatment with rituximab based on rising EBV DNA titers has prevented the development of PTLD in one series.⁶¹ Both pre-emptive rituximab treatment based on viral load and treatment at the first clinical signs of PTLD can be effective therapy, although initiating treatment only when patients demonstrate a high viral load may result in the unnecessary treatment of some patients.

HERPES SIMPLEX VIRUS

Herpes simplex virus (HSV) 1 and 2 (HSV-1 and HSV-2), also known as human herpes virus 1 and 2 (HHV-1 and -2), are two members of the herpes virus family, Herpesviridae, that infect humans.⁶³ Both HSV-1 (which produces most cold sores) and HSV-2 (which produces most genital herpes) are ubiquitous and contagious. They can be spread when an infected person is producing and shedding the virus. HSV types 1 and 2 are a common cause of mucocutaneous lesions in immunosuppressed patients.⁶⁴

Symptoms of herpes simplex virus infection include watery blisters in the skin or mucous membranes of the mouth, lips or genitals.⁶³ Lesions heal with a scab characteristic of herpetic disease. Sometimes, the viruses cause very mild or atypical symptoms during outbreaks. However, as neurotropic and neuroinvasive viruses, HSV-1 and -2 persist in the body by becoming latent and hiding from the immune system in the cell bodies of nerves. After the initial or primary infection, some infected people experience sporadic episodes of viral reactivation or outbreaks. In an outbreak, the virus in a nerve cell becomes active and is transported via the nerve's axon to the skin, where virus replication and shedding occur and cause new sores.⁶⁵

HSV encephalitis is a rare complication even in immunosuppressed individuals. It occurs in the general population with a frequency of 1 in 250,000 to 500,000 persons per year, and does not appear to be more common even in HSCT patients which are severely immunocompromised.⁶⁶ In the "normal" host, the clinical presentation consists of acute onset of fevers and focal, primarily temporal lobe, neurologic signs and symptoms. However, in the immunocompromised host, the presentation is atypical, with a subacute but progressively deteriorating course.

Diagnosis of HSV infection relies upon both clinical and laboratory criteria. Sometimes, clinically it might

be difficult differentiating between HSV and VZV. In the past, rapid diagnosis of cutaneous lesions was made with adequate scrapings of fresh, early lesions examined microscopically after Giemsa (Tzanck preparation), Wright or Papanicolaou staining. The demonstration of intranuclear inclusions and/or giant cells confirmed a diagnosis of herpesvirus infection. However, these staining techniques do not differentiate between HSV and VZV, and therefore the preferred test is for HSV (and VZV) antigens or DNA. These scrapings can be submitted for antigen detection by direct fluorescent antibody, peroxidase or enzyme-linked methods. These are highly specific and sensitive tests if the specimens are obtained early in newly erupted lesions. Polymerase chain reaction (PCR) can be used to detect HSV DNA in swabs or scrapings from mucocutaneous lesions, is more sensitive than culture, and many centers now use it as the standard of practice.⁶⁷ The gold standard of diagnosis of HSV infection is virus isolation. The positive culture will also provide the laboratory with an isolate that can subsequently be tested for antiviral resistance. Culture for HSV is particularly important when acyclovir resistance is suspected. A cytopathic effect may develop within 24 to 48 hours, but definitive identification may take from 48 to 96 hours. A tissue biopsy is usually required to make a diagnosis of visceral HSV infection. The diagnosis for HSV encephalitis made through isolation of the virus from brain tissue. However, the current method of choice is the much less invasive test of HSV DNA determination by PCR of cerebrospinal fluid.⁶⁸

Herpes simplex virus (HSV) infection results in most cases from reactivation of latent virus, thus antiviral drug prophylaxis is primarily given to HSV seropositive patients. Antiviral drug treatment including, acyclovir, valaciclovir and famciclovir is aimed both at shortening the duration of HSV disease and at preventing the dissemination of HSV to visceral sites which can lead to life-threatening disease.^{64,69,70} Prophylactic intravenous or oral acyclovir has become a standard of care for HSV seropositive cancer patients during periods of profound immunosuppression.⁶⁴ Valaciclovir and famciclovir have an oral bioavailability 3-5 times superior to that of oral acyclovir.

In HSCT patients, it has been proved that the risk of HSV reactivation is proportional to the pretransplant HSV immunoglobulin G titer.⁷¹ The allogeneic HSCT recipients who develop acute graft-versus-host disease are on prolonged immunosuppression and usually require a prolonged HSV prophylaxis.

Although not systematically studied, Oral valaciclovir is commonly used in the prevention of HSV reactivation after HSCT. Intravenous acyclovir remains the therapy of choice for severe mucocutaneous or visceral HSV disease in immunocompromised hosts.^{64,69-70} Oral acyclovir, valaciclovir, or famciclovir may be considered as alternative therapies for less serious manifestations of HSV disease.⁷⁰

Varicella-Zoster Virus

Varicella zoster virus (VZV) is one of pathogenic herpes viruses known to infect humans. VZV is also known as chickenpox virus, varicella virus, zoster virus, and human herpes virus type 3 (HHV-3). Primary VZV infection results in chickenpox (varicella), which may rarely result in complications including encephalitis or pneumonia. Even when clinical symptoms of chickenpox have resolved, VZV remains dormant in the nervous system of the infected person (virus latency), in the trigeminal and dorsal root ganglia.⁷² In about 10 to 20 percent of cases, VZV reactivates later in life producing a disease known as shingles. Shingles leads to potential complications like postherpetic neuralgia, zoster multiplex, myelitis, herpes ophthalmicus, or zoster sine herpette.

The clinical manifestations of VZV infection are chickenpox (varicella) and herpes zoster. Chickenpox results from primary VZV infection and occurs in most cases in children under 10 years of age. Immunocompromised children who develop varicella have VZV pneumonia in up to one-third of patients with a fatality rate of about 10 percent.⁷³ Herpes zoster is due to reactivation of latent VZV and is most frequently observed in immunocompromised hosts like, patients with malignancy and on chemotherapy or in recipients of autologous or allogeneic HSCT.^{74, 75}

The diagnosis of VZV infection can be made by a variety of techniques, including viral culture, viral antigen detection, and viral DNA detection. Serologic testing is useful to demonstrate that the patient has had prior primary VZV infection and is therefore harboring the virus in sensory ganglia, but serologic tests are not useful for diagnosis of active VZV infection. PCR technology has revolutionized the diagnosis of VZV, because it is sensitive and rapid. Sometimes, clinical specimen contains inhibitors that may cause false-negative results in PCR assays, signifying the importance of high degree of clinical suspicion and early intervention.

Prevention of chickenpox in immunodeficient patients requires strict isolation from infectious individuals. Following contact with an infected VZV person, the seronegative immunocompromised patients should be given the infusions of VZV hyperimmune globulins within 96 hours of exposure.⁷⁶ Immunization with a VZV vaccine, an additional preventive measure is discussed in the chapter “vaccination of the immunocompromised hosts”.

The drug that changed the clinical scenario for immunosuppressed patients running chickenpox or zoster was acyclovir and is the treatment of choice for these patients.^{77,78}

Localized zoster, seen in patients with mild to moderate immunosuppression, can be treated with high-dose oral acyclovir, valaciclovir or famciclovir with a good efficacy as good as the intravenous therapy. In a randomized study, famciclovir and acyclovir were found to be equally

efficacious and the time to heal the lesions and the rates of secondary zoster dissemination were similar in the two groups.⁷⁹

Following allogeneic HSCT, VZV reactivation may occur for a prolonged period of time. However, long-term antiviral drug prophylaxis is not advisable in allograft recipients, since it only delays the occurrence of zoster and carries the potential for induction of VZV resistance.⁷⁷

The use of a live attenuated VZV vaccine in seronegative immunosuppressed children results in high seroconversion rates and in a reduction of break through varicella and of subsequent herpes zoster.^{80,81} This practice is usually practiced after 12 months in patients with HSCT. In a series of 15 children after HSCT, a VZV vaccine was effective in preventing VZV disease for up to 2 years after immunization.⁸² Among 75 VZV seropositive HSCT recipients randomized to receive an inactivated VZV vaccine or no intervention, immunization was further associated with a better reconstitution of the specific cellular immunity and markedly reduced the severity of zoster.⁸³

FUNGAL INFECTIONS

Fungal infections are one of the very important causes of the mortality and morbidity in the immunocompromised hosts. To discuss each and every fungal infection in detail is beyond the scope of this chapter, so the discussion will involve the epidemiological data and the diagnosis of invasive fungal infection. Only PCP will be discussed here in brief and the Tables 7 and 8 will give the basic management strategies of the common fungal infections and the important facts about the commonly used antifungal agents.

Historically, systemic *Candida* infections have been primarily responsible for invasive fungal infections (IFI) in the immunocompromised hosts but over the last decade mold infections have increased.⁸⁴⁻⁸⁹ The change may be secondary to either the introduction of more accurate diagnostic procedures for diagnosis of IFI or the widespread use of fluconazole prophylaxis. Fluconazole therapy targets many *Candida* spp., but not *Aspergillus* spp. or other molds as given in Table 7.⁸⁷ Yeast infections are less common than mold infections, and *Candida* is still the predominant yeast pathogen. Recently, the emergence of other opportunistic mold pathogens (e.g. *Fusarium* spp. and *Zygomycetes*) has been reported, while infections due to other fungal pathogens remain rare.⁹⁰⁻⁹⁴ In general, the patient's immune status, degree of organ damage (i.e. mucositis or GVHD), microbial exposure (i.e. colonization, journal homepage: environment, and prior infection), older age, type of chemotherapy agent received (i.e. cytarabine) and the use of new drugs (such as monoclonal antibodies) are major factors influencing the likelihood of IFI.⁹⁵⁻⁹⁷ However, deep and prolonged granulocytopenia is the greatest risk factor for IFI. Another key risk

Table 7: Common fungal infections and their management strategies¹¹⁷

<i>Fungal infections</i>	<i>First-line options</i>	<i>Second-line options</i>	<i>Supportive management</i>
Systemic Candidiasis	Voriconazole (PO or IV): 4 mg/kg twice daily in children ≥ 12 yrs Caspofungin (IV): Day 1st—70 mg/m ² Day 2 onwards—50 mg/m ² /day Fluconazole: 8-12 mg/kg daily PO/IV (some authors consider it as an 2nd line)	Amphotericin B lipid complex (IV): 5 mg/kg daily Liposomal amphotericin- B (IV): 3 mg/kg daily IV	Consider the use of G-CSF in neutropenic Steroids to be decreased if possible Remove CVC immediately if possible Do the fundoscopy before the treatment ends in every invasive candidiasis Treatment duration: Uncomplicated candidemia—14 days once blood culture is sterile. Switch over to oral once blood is sterile. Complicated candidemia—duration of treat- ment usually is 4-6 weeks depending upon the condition.
Invasive Aspergillosis	Voriconazole (PO or IV): Age 2-12 yrs: 7 mg/kg twice daily PO or IV Age ≥ 12 yrs: 4 mg/kg twice daily Liposomal amphotericin-B (IV): 3 mg/kg daily (dose escalation to 10 mg/kg not helpful in randomized trials)	Amphotericin B lipid complex (IV): 5 mg/kg daily IV Caspofungin (IV): Day 1st—70 mg/m ² Day 2 onwards—50 mg/ m ² /day	Consider surgery if accessible in skin, sinus, lungs, CNS and soft tissue infections. Consider the use of G-CSF in neutropenic Steroids to be decreased if possible In a unit where we see more of zygomycosis, starting voriconazole might not be the first line. Duration is highly individual based on clinical and culture response. Once clinical response is achieved, IV can be switched over to oral voriconazole.
Antifungal agents as an empirical therapy:			
<i>Indication</i>			
<ul style="list-style-type: none"> • Patient on antibiotics and day 5th of fever <ul style="list-style-type: none"> – Start with liposomal amphotericin-B, dose 1-3 mg/kg daily IV or caspofungin IV, 70 mg/m²/day on day 1 and then 50 mg/m²/daily once 			
Antifungal agents as prophylaxis therapy:			
<i>Indication</i>			
<ul style="list-style-type: none"> • Any patient who is undergoing hematopoietic stem cell transplant or high dose chemotherapy <ul style="list-style-type: none"> – Fluconazole @ dose of 8-12 mg/kg daily, is usually the first agent, or – Voriconazole @ dose of 1 mg/kg daily or – Micafungin @ dose of 1 mg/kg daily or 			
Posaconazole is recommended in patients with HSCT and graft versus host disease @ doses 200 mg three times a day and helps invasive fungal infections. Posaconazole has also shown the overall survival benefit in patients undergoing chemotherapy for AML or MDS.			
Patient on azoles prophylaxis should be given polyene or echinocandin group drugs as these patients usually will be colonized with <i>Glabrata</i> or <i>Krusei</i> species.			

factor for IFI is steroid use; such use modifies phagocyte migration, decreases the antifungal activity of monocytes and macrophages, and enhances the growth of *Aspergillus* spp.⁹⁸ Some reported risk factors are related to specific pathogens. For example, indwelling catheters, prior exposure to broad-spectrum antimicrobial agents, and prior surgery have been well-recognized to facilitate yeast access to the bloodstream and cause invasive candidiasis.⁹⁹

The clinical signs and symptoms of IFI strictly depend on the patient's immune status and the etiological agent and range (i.e. from focal localization to hematogenous dissemination in which almost all organs are involved).¹⁰⁰ During the earliest phase of infection, IFI may be asymptomatic, or fever may be the only clinical symptom

observed. This lack of symptoms may be related in part to the masking of clinical symptoms by treatments (i.e. steroids) administered for the underlying malignancy. The lungs are most frequently affected by *Aspergillus* or other mold infections, and cough, dyspnea, and chest pain is often reported during the early course of pulmonary infections; in advanced stages, severe manifestations (including hemoptysis or pneumothorax) may also occur. *Pneumonia* due to *Zygomycetes* or other molds is clinically indistinguishable from that caused by *Aspergillus*, except for a higher frequency of rhinosinusal localization.⁹⁰ Dissemination to secondary sites of infection (i.e. skin or the central nervous system) may cause additional clinical symptoms.

Table 8: The commonly used antifungal agents ^{118-122*}

Antifungal agents and their mechanism of action:

Drugs acting on cell membrane

Polyenes: Amphotericin-B deoxycholate, amphotericin-B lipid complex, liposomal amphotericin-B and amphotericin-B colloidal dispersion

Triazoles: Fluconazole, itraconazole*, voriconazole and posaconazole

Drugs acting on cell wall

Echinocandins: Caspofungin, micafungin and anidulafungin*

Nucleic acid synthesis inhibitors

Flucytosine

<i>Antifungal agents</i>	<i>Spectrum</i>	<i>Half-life (t_{1/2})</i>	<i>CSF penetration</i>	<i>Significant side effects</i>	<i>Renal adjustment when Cr clearance < 30 ml/mt</i>
Fluconazole	Active Active against most <i>Candida</i> (including <i>Albicans</i> and parapsilosis) but not against <i>C. Krusei</i> and <i>C. Glabrata</i> Active against <i>Cryptococcus neoformans</i> , <i>Coccidioides</i> species and <i>Histoplasma</i> Not active Not active against <i>Aspergillus</i> , <i>Fusarium</i> species, <i>Zygomycetes</i> , <i>Scedosporium</i> and <i>Trichosporon</i>	24 hr	Excellent	Hepatotoxicity Rash + Nausea and vomiting	Not a contraindication but doses should be adjusted
Voriconazole	Active Active against most <i>Candida</i> (including <i>Albicans</i> and parapsilosis) but not against <i>C. Krusei</i> and <i>C. Glabrata</i> Active against <i>Cryptococcus neoformans</i> , <i>Coccidioides</i> species, <i>Histoplasma</i> and <i>Scedosporium apiospermum</i> Active but not a great agent <i>Candida glabrata</i> and <i>Fusarium</i> species Not active <i>Zygomycetes</i> , <i>Scedosporium prolificans</i>	6-24 hr	Excellent	Hepatotoxicity Rash ++ Nausea and vomiting Transient visual disturbances	Oral—can be given IV—contraindicated
Posaconazole	Absolutely same as voriconazole +active against <i>Zygomycetes</i> also	8-24 hr	Poor	Rash ++ Nausea and vomiting Hepatotoxicity very minimal	Oral—can be given No IV preparation available
Amphotericin-B deoxycholate	Active against almost everything except <i>Scedosporium prolificans</i> Active but not a great agent: <i>Aspergillus terreus</i> <i>Candida krusei</i> <i>Fusarium</i> species and <i>Scedosporium apiospermum</i>	Biphasic: Initial phase—24-48 hr; Terminal phase—15 days	Poor in CSF but reaches brain tissue	Common: General— Chills, fever, and headache, pruritus, rash, urticaria, bronchospasm and anaphylaxis Thrombophlebitis Metabolic— Hypokalemia, hypomagnesemia Renal— Renal tubular dysfunction and renal failure Uncommon: CVS— Arrhythmias, flushing, hyper-/hypotension CNS— Delirium, malaise, seizures Hepatotoxicity Hematologic: Anemia, leukopenia, thrombocytopenia (Side effects are minimal with lipid and liposomal preparations)	Contraindicated but the lipid and liposomal preparations can be given with close monitoring

Contd...

<i>Echinocandins</i>	Active	Caspo—	No CSF	Fever	Caspo—no adjustment
Caspo-fungin	All <i>Candida</i> and <i>Aspergillus</i> species	12 hrs	concentration	Rash, thrombophlebitis	needed
Micafungin	Active against <i>Pneumocystis</i>	Mica—18 hrs	but	Hepatotoxicity (doses need to be adjusted)	Mica—no adjustment needed
and Anidulafungin	<i>Carinii</i> but can't be used as a single agent	Anidula-24 hrs	reaches brain	Nausea, vomiting and diarrhea	Anidula—no adjustment needed
	Not Active:			Hypokalemia	
	<i>Cryptococcus neoformans</i> , <i>Coccidioides species</i> , <i>Blastomycosis</i> and <i>Histoplasma</i>			Allergic reactions to infusion	
	<i>Fusarium species</i> , <i>Zygomycetes</i> , <i>Scedosporium</i> and <i>Trichosporon</i>				

* Drugs not approved in pediatric patients

DIAGNOSIS OF INVASIVE FUNGAL INFECTIONS

Laboratory diagnosis of IFI is based on the direct microscopic detection of the etiologic agent in clinical specimens, isolation and identification of the pathogen in culture, or nonculture-based methods involving detection of a serologic response to the pathogen or other markers of its presence (i.e. fungal antigens or metabolites). Microbiological cultures are often insensitive or of limited use. To facilitate the early diagnosis of IFI, the newer fungal markers are galactomannan [GM] and 1,3-beta-D-glucan [BG] assays. GM in a recently published meta-analysis showed an overall sensitivity of 71 percent and specificity of 89 percent for proven cases of IA (invasive aspergillosis) when used for surveillance.¹⁰¹ The measurement of serum BG has also been shown to aid in the diagnosis of fungemia and deep-seated mycoses, including IA. One of the non-culture-based methods for the diagnosis of candidiasis is platelia *Candida*, an ELISA that combines the detection of mannan antigen and antimannan antibodies in serum, allows the earlier diagnosis of *Candida* infection than do blood cultures.¹⁰² A range of polymerase chain reaction (PCR)-based methods has been developed with the goal of offering a highly specific, sensitive, and rapid method of fungal detection and identification. Most of these methods have focused on *Aspergillus* and *Candida* species in various specimen types (i.e. serum, plasma, or BAL fluid), even though pan-fungal PCR amplification technology may be able to detect a broad range of fungal targets.¹⁰³ A recent prospective evaluation of serial PCR assays against or along with GM and chest-computed tomography was carried out in immunocompromised hosts; the PCR method showed acceptable sensitivity and specificity.¹⁰⁴ Recent studies have focused attention on the role of adaptive immunity in the host defense against *Aspergillus* species.¹⁰⁵ In particular, a preliminary report on ELISPOT, *Aspergillus*-specific IFN γ -TH₁, and *Aspergillus*-specific IL-10-producing T-cells (IL-10-TH₂) through an *ex vivo* enzyme-linked immunospot assay showed promising results in the diagnosis and follow-up of IA.¹⁰⁶

Radiological exams are one of the most important diagnostic tools, particularly for pulmonary-localized mold infections.¹⁰⁷ A standard chest X-ray is the first-line

approach, even if it is often not diagnostic. A chest CT-scan is better particularly a high resolution CT-scan (HRCT-scan); with a sensitivity and specificity approaching 100 percent.¹⁰⁸ These scans can demonstrate the presence of the “halo sign,” or the presence of the “air crescent sign,” which usually becomes more prevalent later in the course of the disease.¹⁰⁹ The radiological scans do not allow us to diagnose a specific aspergillosis because of their similarity to other angioinvasive fungi such as *Zygomycetes*, *Fusarium* spp., or *Scedosporium* spp., and this issue makes biopsy necessary to clarify the diagnosis. A study evaluated the utility of CT-guided lung biopsy for the diagnosis of IFI; this study combined Calcolfluor white staining, GM, and PCR on biopsy specimens. This combination resulted in the fast and reliable identification of the fungus with a specificity and sensitivity of 100 percent. However, performing such a detailed and invasive diagnostic study is very critical, because of the many contraindications for the performance of an invasive procedure in these immunocompromised hosts (i.e. thrombocytopenia and hemodynamical instability).¹¹⁰

PNEUMOCYSTIS JIROVECI PNEUMONIA

Historically, *pneumocystis jiroveci* pneumonia is (PCP) known to be associated with HIV but this in one of the significant cause of morbidity and mortality in immunocompromised children with hematological malignancies, brain tumors, and those undergoing HSCT. A recent Cochrane review recommended PCP prophylaxis as an important management strategy in these immunocompromised children¹¹¹ and three times a week is now the acceptable protocol for the prophylaxis.

P. jiroveci infection commonly presents with tachypnea, nonproductive cough and fever, but the severity can vary. There is usually a subacute diffuse pneumonitis and chest X-ray changes can be subtle. These often take the form of bilateral diffuse interstitial changes, although lobar, miliary or nodular changes can be seen. HRCT may show ground glass attenuation, consolidation, nodules, thickening of interlobular septa and thin walled cysts. Mortality ranges between 5 and 40 percent, if treated, but can reach

nearly 100 percent if left untreated. Identification of PCP can be difficult. Definitive diagnosis depends on identifying the organism in respiratory tract secretions or lung tissue, usually from tracheal secretions, bronchial secretions or from lung biopsy. More recently, PCR technology has been developed for identifying PCP from secretions. In a review of children diagnosed with severe combined immune deficiency (SCID) treated at a supraregional center, 10 out of 50 were identified as having PCP. One was diagnosed on BAL prior to transfer to the supraregional center, one was diagnosed on nasopharyngeal secretions and BAL, seven were diagnosed on BAL alone, and in one diagnosis was not made until lung biopsy was performed.¹¹²

Recommended first line PCP treatment is high dose cotrimoxazole. This can, however cause a number of adverse effects, for example, neutropenia, anemia, renal dysfunction, rash, vomiting and diarrhea. Those that cannot tolerate cotrimoxazole or those that have not improved after 5 to 7 days of treatment should be changed to a different agent. Choices include pentamidine, atovaquone, clindamycin/ primaquine or dapsone, but experience with these agents in children is limited.

In children that cannot tolerate cotrimoxazole, either dapsone or aerosolized pentamidine can be used. Corticosteroids should be given as an adjunctive therapy in moderate and severe PCP. A number of studies have shown a reduction in acute respiratory failure, decreased need for ventilation and decreased mortality.¹¹³⁻¹¹⁵ A recent Cochrane review supports the use of corticosteroids in HIV-infected patients with PCP, especially in those with substantial hypoxaemia.¹¹⁶

SUMMARY

Infections in immunocompromised children are difficult both in diagnosis and management. Organisms which are usually mild in an immunocompetent host can have devastating effects in an immunocompromised child. Clinical diagnosis is often very difficult and establishing a microbiological diagnosis is rather difficult. Clinical suspicion holds the key for early and appropriate management. Negative tests should not be taken to be reassuring if there is clinical suspicion and it may be necessary to look further and more closely. Once an infection is identified, it must be acted upon quickly as delay may be disastrous. Treatment of any infection in an immunocompromised child is likely to be more intense and prolonged than in a child with a fully functioning immune system. It is also important to consider prophylaxis for specific patient groups in specific situations (e.g. post-HSCT) and each unit should have defined policies and guidelines to follow for these patients. To conclude, when dealing with an immunocompromised child, for whatever reason, if there is any suspicion of infection, think about early intervention.

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Health Care-Associated Infections in Pediatric Intensive Care Unit

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INTRODUCTION

Pediatric Intensive Care Unit (PICU) related health care associated infection (HAI) is defined as any infection that was not present or incubating at the time of PICU admission but occurred at 48 hours or more after admission to the PICU.¹ As a better reflection of the diverse health care settings currently available to patients, the term health care-associated infections replaced old ones such as nosocomial, hospital-acquired or hospital-onset infections. Most infections that become clinically evident after 48 hours of hospitalization are considered hospital-acquired. Infections that occur after the patient is discharged from the hospital can be considered health care-associated if the organisms were acquired during the hospital stay.

Pediatric intensive care units (PICUs) differ from adult intensive care units (ICUs) in a number of ways, apart from the age of their patients. First, they are usually multidisciplinary.² Second; they frequently lack the physical barriers between patients now commonly present in adult ICUs. Third, fewer children than adults in ICUs have chronic or degenerative organ system disorders;³ and probably the majority of children in PICUs will, if successfully treated, return to a normal productive life. Nosocomial infections represent an important cause of morbidity and mortality in this population.⁴

Health care associated infection (HAI) rates vary widely between different patient populations, with the highest rates usually occurring in pediatric intensive care units (PICUs) and neonatal intensive care units (NICUs). These infections often lead to increased morbidity and mortality. Furthermore, prolonged need of hospitalization due to HAIs may give rise to substantial additional costs.

Patients in the pediatric intensive care unit (PICU) are particularly susceptible to HAI in part due to the use of invasive devices and procedures in this critically ill

population.⁵ Incidence of nosocomial infections due to antibiotic-resistant organisms is increasing, with specific examples in the pediatric intensive care unit (PICU).⁶⁻⁹ The prevalence of hospital-acquired or nosocomial infections in pediatric patients ranges from 6 to 12 percent in the PICU and 10 to 25 percent in the NICU.¹⁰⁻¹⁵

SOURCES AND MODES OF TRANSMISSION

Health care associated infections can be caused by endogenous or exogenous organisms. Endogenous infections usually occur as a result of health care-associated interventions (e.g. surgical procedures or the insertion of vascular catheters or other indwelling devices) by colonization and subsequent infection with microorganisms from the hospital environment due to immunosuppression, or by normal flora altered through antimicrobial therapy. Exogenous infections result from the transmission of organisms from the hospital environment.

Pathogens-associated with HAIs in hospitalized children differ from those in adults. Gram-negative bacilli, including ESBL and other multidrug-resistant isolates, may be more frequent than MRSA and VRE in many PICUs and NICUs. Patients who are transferred from chronic care facilities may be colonized with resistant gram-negative bacilli at the time of admission to the PICU.

RISK FACTORS FOR HEALTH CARE-ASSOCIATED INFECTIONS

The identification of risk factors enables the development of preventive strategies. Most PICUs care for a heterogeneous population of children of varying age, diagnosis, and underlying illness, ranging from infants with congenital anomalies to adolescents with multiple traumas. Consequently, even patients admitted to the same PICU may differ substantially in their risk for HAI.

A systematic review of observational studies on risk factors for health care-associated infection in pediatric intensive care units,¹⁶ revealed the risk factors for a first episode of health care-associated infection included: post-operative period, greater severity upon admission based on the PRISM or PRISM III, invasive procedures, the use of antimicrobial agents, parenteral nutrition, remaining more days or more than seven days in the pediatric ICU. Reducing health care associated infections requires best practice in clinical care, consistently and reliably. However, reducing HAI also requires that other issues, beyond best practice at the point of care, be addressed, e.g. isolation practice, bed occupancy, hospital policies, compliance, monitoring, surveillance, screening, antibiotic stewardship, bed management, patient pathways, bed moves, staffing levels, training, expertise, leadership, information management, environment and design, management systems, laboratory service, equipment, devices, cleaning standards and contracts, decontamination, procurement, accountability, risk management, resource allocation, etc. The prevention of infection is a core component of patient safety, and achieving patient safety in acute health care requires more than individual carefulness.¹⁷

TYPES OF HEALTH CARE-ASSOCIATED INFECTIONS

Catheter-Related Bloodstream Infections

Stable vascular access is essential to the management of the critically ill patient. Central venous access devices (CVADs) provide reliable venous access for short-term and extended infusion of intravenous chemotherapy, bi-therapy, and supportive therapies during the diagnostic phase, treatment phase, or the palliative phase of their disease course. Most patients will have at least one central venous catheter, and many may have an arterial catheter as well. An increasing number of patients will have some type of tunneled, cuffed central venous catheter or some type of subcutaneous central venous port.

The relative risk of bloodstream infection caused by various intravascular devices ranges widely, depending on the length of the device, the type of device, the patient population, the techniques used in insertion, the frequency of manipulation, and the time they have been in place.^{18,19}

The highest risk is with short-term, noncuffed central venous catheters, in the range of 2 to 5 per 1,000 catheter days, and is especially high with temporary hemodialysis catheters. Arterial catheters used for hemodynamic monitoring and peripherally inserted central venous catheters used in hospitalized patients seem to have a risk of catheter-related bloodstream infection (2–3 per 1,000 catheter days) similar to conventional subclavian, internal jugular, or femoral short-term, noncuffed central venous

catheters. In contrast, the risk of bloodstream infection with small, peripheral intravenous catheters is 0.1 cases per 1,000 catheter days. With good care, surgically implanted ports are associated with a much lower risk of bacteremia/fungemia than temporary percutaneous catheters, approximating 0.2–1 per 1,000 catheter days.¹⁸

Risk factors for development of CR-BSI have been recognized in PICU patients includes; Extracorporeal life support, presence of multiple intravascular devices, and longer duration of intravascular device use were associated with an increase in rate and risk of developing CR-BSI in PICU patients. Use of arterial catheter and packed red blood cell transfusion, as well as the presence of a genetic syndrome, were identified by multivariate analysis as risk factors for nosocomial primary blood stream infection (BSI) in PICU patients.²⁰

Published guidelines from the CDC have set criteria²¹ for diagnosing bloodstream infections that involve intravascular catheters. A catheter-related bloodstream infection is either a bacteremia or fungemia documented with at least one peripherally obtained blood culture that is obtained from a vein and not a catheter. Clinical evidence of an infection, including a host response, must be present that cannot be attributed to any source other than the catheter.

The growth of an organism in the bloodstream must be documented by (a) positive semiquantitative or quantitative cultures of a catheter segment with an organism identical in species and antibiogram as isolated from a peripheral blood culture, (b) simultaneously drawn peripheral and line quantitative blood cultures with greater than a 5:1 ratio in catheter blood versus peripheral blood colony counts, or (c) a differential in timing of culture positivity of >2 hrs between the catheter and peripheral blood culture, where the catheter culture is positive first.

A catheter-associated bloodstream infection has less rigorous criteria and requires the presence of a central line being in place during the 48 hrs prior to the drawing of the positive culture and compelling evidence that the infection is related to the line. This definition is helpful for surveillance but can overestimate the true incidence of bloodstream infections.²¹

Coagulase-negative staphylococci are the most common cause of pediatric health care related bloodstream infections, accounting for 20 percent to nearly 50 percent of isolates. Gram negative bacteria account for 25 percent of PICU health care related bloodstream infections. *S. aureus* and *Candida* spp. are responsible for ~10 percent each throughout the pediatric age range. Other organisms that cause health care related bloodstream infections are dependent upon the age of the child and other clinical factors. Hemolytic streptococci are more prevalent in the neonatal population, causing 8.5 percent of the hospital-acquired infections in this age group. Bimodal peak is reported for enterococcal infections seen in infants and

patients 13 to 65 years of age, with 9.4 percent and 8.5 percent of isolates, respectively. At 7.3 percent, *Klebsiella* spp. are the third most common isolates behind coagulase-negative staphylococci and *S. aureus* in the pediatric oncology population.²²⁻²⁴

Empiric therapy for CR-BSI should consist of an agent to cover gram-positive and an agent to cover gram-negative organisms, based on local antimicrobial resistance patterns. The 2009 IDSA guidelines for intravascular catheter-related infection provides an extensive review of the management of CR-BSIs in adult and pediatric populations. Vancomycin is recommended for empiric gram-positive therapy in health care settings with known high rates of MRSA.

Empiric coverage for gram-negative bacilli should be based on local susceptibility patterns and the severity of disease. Fourth-generation cephalosporins, carbapenems, or β -lactam/ β -lactamase combinations are recommended because of their coverage of *Pseudomonas* sp. An aminoglycoside may also be added empirically, and is specifically recommended for neutropenic patients, those who are severely ill and those with sepsis, in addition to patients known to be colonized with multi-drug resistant gram-negative organisms. Patient with femoral lines are recommended to have gram-positive, gram-negative coverage and well as coverage for *Candida* sp. Culture results should be used to de-escalate antimicrobial therapy when known.²⁵

The duration of antimicrobial therapy for CR-BSI vary by host and pathogen. In most cases, it is recommended that catheters that are infected be removed and that the patient receive intravenous antimicrobial therapy for 7 to 14 days, depending on the isolated pathogen. Duration of therapy is based on the day of the first negative blood culture result. A longer duration of therapy is recommended for CR-BSI caused by *S. aureus*. Even longer durations of antimicrobial therapy are recommended for patients with persistent bacteremia or fungemia due to supportive thrombophlebitis, endocarditis, osteomyelitis or other severe infections. Coagulase-negative *Staphylococcus* sp. (CONS) may be treated from 5 to 7 days after catheter removal.²⁵

VENTILATOR-ASSOCIATED PNEUMONIA

Pneumonia is the second most common cause of infection acquired in the ICU and a ubiquitous cause.^{26,27} In an ICU, it can be difficult to determine whether fever is due to pneumonia when patients commonly have other noninfectious processes producing abnormal chest radiographs and gas exchange (i.e. congestive heart failure, atelectasis, acute respiratory distress syndrome).

Many patients in an ICU are intubated and sedated, cannot cough, and have other reasons for abnormal secretions. In addition, immunocompromised patients, such as solid organ transplant recipients, may have severe

pneumonia without fever, cough, sputum production, or leukocytosis.^{28,29}

Ventilator-associated pneumonia (VAP) is diagnosed based on criteria from the US Centers for Disease Control and prevention (CDC).²⁹ However, there is no gold standard for the diagnosis of VAP in children or adults. In general, VAP criteria include a new or progressive radiographic infiltrate, consolidation, cavitations or pneumatocoles (in infants under 12 months of age) that has persisted for at least 2 days as well as two of the following: a temperature above 38.5°C or below 35.0°C, a leukocyte count above 10,000/mm³ or less than 5,000/mm³, purulent sputum, or isolation of pathogenic bacteria for endotracheal tube (ETT) aspirates.²⁹

Age criteria for those infants under 1 year and children greater than 1 year but less than 12 years of age have also been created.^{30,31} Specimens obtained from the lower airway for respiratory culture are preferred. The use of bronchoalveolar lavage (BAL), nonbronchoscopic-BAL or protected specimen brush samples are safe and aid in the acquisition of an adequate of sample for respiratory culture in suspected pediatric VAP patients.

Although the main contributing factor for VAP development is mechanical ventilation, risk factors for the development of VAP have been studied and include the presence of a genetic syndrome, reintubation, transport out of the PICU, use of neuromuscular blockade agents, and immunosuppression.^{32,33} Other risk factors for the development of VAP include female gender, postsurgical, the presence of enteral feedings, and the use of narcotic medications.³⁴

The use of H2-blocking agents may allow for enteric bacteria to colonize the upper gastrointestinal tract and may predispose pediatric patients to VAP.³² Other medications that may contribute to the development of VAP include steroids and total parenteral nutrition (TPN).³³ Narcotic agents have also been associated with VAP.³⁴

Single agents that may be efficacious for VAP include carbapenems, cefepime, or piperacillin-tazobactam. Fluoroquinolones may also be used for monotherapy for VAP in certain situations. There is no specific recommendation for VAP treatment duration of therapy. Short treatment courses of 5 to 7 days may be appropriate in those patients with uncomplicated disease,³⁵ but longer treatment courses may be warranted for critically ill children infected with MDR organisms (MDROs).

Ventilator Bundles in the Management of VAP

The prevention of VAP bundle of care, was developed for adult patients, but has been applied to pediatric practice as well. Following are the interventions for, prevention of VAP bundle of care:

- Conduction of active surveillance for VAP
- Adherence to hand hygiene guidelines

- Maintenance of patients in a semirecumbent position (30-45 degree head of bed elevation)
- Daily sedation vacation and assessment of readiness to extubate with use of weaning protocols
- Regular oral care with an antiseptic solution
- Use of noninvasive ventilation whenever possible, minimizing the duration of ventilation
- Preference for orotracheal intubation over nasotracheal intubation
- Maintenance of endotracheal cuff pressure of at least 20 cm H₂O
- Removal of condensate from ventilator circuits, keeping the ventilator circuit closed during condensate removal
- Changing of the ventilator circuit only when visibly soiled or malfunctioning
- Avoidance of gastric overdistention
- Avoidance of histamine receptor 2 blocking agents and proton pump inhibitors
- Use of sterile water to rinse reusable respiratory equipment.

There are some limitations in pediatric age group which limits the generalization of bundle care applicable in adult age group:

- *Head end elevation* >30° is challenging in the infant due to neck bending.
- *Daily sedation vacation*: Difficult in pediatrics due to high risk of unplanned extubation.
- *Use of cuffed endotracheal tubes* may not be possible in all cases.

Chlorhexadine mouthwash has been shown to significantly reduce the incidence of VAP.³⁶ Early enteral feeding, a favored practice in pediatric, is recognized as contributing to improved patient outcomes and morbidity as well as providing some protection against the development of stress ulcers.

Urinary Tract Infections

Urinary catheterization is a routine procedure in an intensive care unit for monitoring urine output of critically ill patients. Catheter-associated bacteriuria or candiduria usually represents colonization, is rarely symptomatic, and is rarely the cause of fever or secondary bloodstream infection,³⁷ even in immunocompromised patients,³⁸ unless there is urinary tract obstruction, the patient has had recent urologic manipulation or surgery, or is granulocytopenic.^{39,40}

The traditional clinical signs and symptoms (dysuria, urgency, pelvic or flank pain, fever or chills), that correlate well with significant bacteriuria in noncatheterized patients are rarely reported in ICU patients with documented catheter-associated bacteriuria or candiduria of >10⁵ colony-forming units (cfu)/ml.

The most common complication of the use of bladder catheterization is infection. Cystitis, pyelonephritis and secondary BSI can occur from catheter-associated urinary tract infection (UTI). The most commonly isolated pathogens are enteric gram-negative organisms as well as other perineal flora including *Enterococcus* sp. and *Candida* sp. Patients may or may not have pyuria.

The basic management of catheter-associated UTI is the removal of the catheter, when possible. Patients with complications of UTI such as pyelonephritis or BSI require systemic antimicrobial therapy. Currently, there is no consensus on duration of therapy for urinary catheter-associated UTI.⁴¹

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Childhood Tuberculosis

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INTRODUCTION

Not long ago tuberculosis used to be a major public health problem practically all over the world. In recent years it has been brought under control in the affluent countries of the west to an extent that it has ceased to be a health hazard. However, it continues to be a major public health problem and a killer in developing countries like India.

By itself, tuberculosis is one of the major infections affecting children worldwide. Young children carry the greatest burden of disease. They are not only most likely to develop disease after infection but also more prone to develop extra pulmonary and severe disseminated disease. Also those with latent infection become the reservoir for future transmission following disease reactivation in adulthood. Tuberculosis, on the whole, has better prognosis in children than the young adults and children with this disease are far less frequently infectious than older individuals, but the relevance of childhood tuberculosis lies in the fact that the most serious manifestation of tuberculosis in older people has its beginning in childhood when most infections take place in the developing countries. Childhood tuberculosis has been relatively neglected and there is very little information about the burden of disease in children worldwide. According to estimates, in industrialized countries childhood TB constitutes about 7 percent of all TB cases and the disease is much more prevalent in resource poor developing countries (15-40% of all TB). In India, 1.5 percent of about 2,45,000 new smear-positive cases on DOTS were aged 0 to 14 years and pediatric cases made up 3 percent of total load of new cases registered. However, these figures are likely to be substantially lower than the true burden of disease. It has been estimated that 10 percent of the actual total TB caseload in India is amongst children.¹

The rate of infection does not seem to be dependent *per se* on race, religion and socioeconomic conditions. It

depends entirely on opportunities of infection. Since poor people live ordinarily in congested localities, the higher infection among them are not so much due to poverty than overcrowding resulting in increased opportunities of infection.

ETIOPATHOGENESIS

Tuberculosis is a chronic infectious disease caused by *Mycobacterium tuberculosis*. Primary infection can occur when a previously uninfected child inhales even a single infectious aerosol droplet (containing as little as five bacilli) that penetrates into a terminal airway. The risk of a person developing disease once infected is determined by various factors including age, recently acquired infection, the nutritional and immune status of the child, genetic factors, the virulence of the organism and the size of infecting dose and inter current infections such as measles, pertussis. It has been estimated to be 5 to 10 percent in adults, 15 percent in adolescents, 24 percent in children 1 to 5 years of age and as high as 43 percent in infants. Primary infection before 2 years of age frequently progresses to serious disease within the first 12 months without significant prior symptoms. However, for infants the time span may be as short as 6 to 8 weeks. Also about 25 to 30 percent of children with tuberculosis have extra-pulmonary presentation in comparison to adults in whom about 15 percent have extrapulmonary presentation.² HIV coinfection can further increase the risk of developing the disease across all age groups.

PRIMARY PULMONARY DISEASE

Entry and establishment of bacilli in human body constitutes infection. It usually takes 6 to 8 weeks for the establishment and manifestation of infection. Infection is indicated by a positive reaction to a tuberculin skin test

(Mantoux test). Primary infection is an infection occurring for the first time in susceptible individuals who are exposed to tubercle bacilli. Droplet nuclei that are inhaled into the lungs, are so small ($<5\ \mu\text{m}$) that they avoid the muco-ciliary defences of the bronchi and lodge in the terminal bronchiole or alveoli of the lungs. Subsequently, the bacilli multiply and invade the hilar lymph nodes through the lymphatics. The subpleural lung lesion, lymphangitis and hilar adenopathy together constitute a *primary complex*. In most cases, the host's immune defences overcome the primary infection, which generally passes unnoticed. The initial parenchymal inflammation usually is not visible on chest radiograph, but a localized, nonspecific infiltrate may be seen before the development of tissue hypersensitivity. About 70 percent of lung foci are subpleural, and all lobar segments are at equal risk for initial infection. The hallmark of primary tuberculosis in the lung is the relatively large size of the regional lymphadenitis compared with the relatively small size of the initial lung focus. The hilar lymph nodes can continue to enlarge compressing the regional bronchus and causing obstruction. The usual sequence is hilar lymphadenopathy, focal hyperinflation, and then atelectasis. Endobronchial TB occurs when the infected lymph nodes erode into a bronchus. Enlargement of lymph nodes may result in signs suggestive of bronchial obstruction (partial or complete bronchial obstruction). Usually, it is the result of deposition of caseous material within the lumen.³

The symptoms and physical signs of primary pulmonary TB are comparatively less considering the degree of radiographic changes often seen. Up to 50 percent of infants and children with radiographically moderate to severe pulmonary TB have no physical findings. Infants are more likely to experience signs and symptoms. Nonproductive cough and mild dyspnea are the most common symptoms. Systemic complaints such as fever, night sweats, anorexia, and decreased activity occur less often. Some infants and young children with bronchial obstruction have localized wheezing or decreased breath sounds.

PROGRESSIVE PRIMARY PULMONARY DISEASE

As tuberculosis progresses, infected material may be spread via the airways into other parts of the lungs, causing a patchy bronchopneumonia. Erosion of a parenchymal focus of tuberculosis into a blood or lymph vessel may lead to dissemination of the organism and a "miliary" (evenly distributed small nodules) pattern on the chest film. Disseminated tuberculosis can occur in primary disease and may be an early complication of tuberculosis in children (both immunocompetent and immunocompromised).

A rare but serious complication of tuberculosis in a child occurs when the primary focus enlarges steadily and develops a large caseous center. Liquefaction can cause

formation of a primary cavity associated with large numbers of tubercle bacilli. The enlarging focus can slough necrotic debris into the adjacent bronchus, leading to further intrapulmonary dissemination. Significant signs or symptoms are common in locally progressive disease in children. High fever, severe cough with sputum production, weight loss, and night sweats are common.

REACTIVATION TUBERCULOSIS

Tuberculosis that develops as a result of endogenous reactivation of latent infection usually causes abnormalities in the upper lobes of one or both lungs. Cavitation is common in this form of tuberculosis. The most frequent sites are the apical and posterior segments of the right upper lobe and the apical-posterior segment of the left upper lobe (*Simon foci*). This form of tuberculosis is rare in childhood but can occur in adolescence. This form of disease usually remains localized to the lungs, because the established immune response prevents further extrapulmonary spread.

Older children and adolescents with reactivation tuberculosis are more likely to experience fever, anorexia, malaise, weight loss, night sweats, productive cough, hemoptysis, and chest pain than children with primary pulmonary tuberculosis. However, physical examination findings usually are minor or absent, even when cavities or large infiltrates are present. Most signs and symptoms improve within several weeks of starting effective treatment, although the cough can last for several months.

PLEURAL TUBERCULOSIS

There are two mechanisms by which the pleural space becomes involved in tuberculosis. The difference in pathogenesis results in different clinical presentations, approaches to diagnosis, treatment, and sequel. Early in the course of a TB infection a few organisms may gain access to the pleural space (from a subpleural pulmonary focus or caseated lymph node) and, in the presence of cell-mediated immunity, cause a hypersensitivity response. Tuberculous pleural effusion is uncommon in children <6 yr of age and rare in children <2 yr of age. Effusions are usually unilateral but can be bilateral. Commonly, this form of tuberculous pleuritis goes unnoticed, and the process resolves spontaneously. In some patients, however, tuberculous involvement of the pleura is manifested as an acute illness with fever and pleuritic pain. If the effusion is large enough, dyspnea may occur, although the effusions generally are small and rarely are bilateral. In approximately 30 percent of patients there is no radiographic evidence of involvement of the lung parenchyma; however, parenchymal disease is nearly always present. Often the radiographic abnormality is more extensive than would be suggested by physical findings or symptoms. The TST is positive in only 70 to 80 percent of cases.

The second variety of tuberculous involvement of the pleura is empyema. This is much less common than tuberculous pleurisy with effusion and results from a large number of organisms spilling into the pleural space, usually from rupture of a cavity or an adjacent parenchymal focus via a bronchopleural fistula. A tuberculous empyema is usually associated with evident pulmonary parenchymal disease on chest films and air may be seen in the pleural space. In the absence of concurrent pulmonary tuberculosis, diagnosis of pleural tuberculosis requires thoracentesis and, usually, pleural biopsy.

Diagnostic thoracentesis usually reveals yellow fluid and only occasionally tinged with blood. The typical fluid shows a exudative lymphocytosis although in the early part polymorphonuclear cells might predominate. The glucose concentration may be low or in the low-normal range (20-40 mg/ dl). AFB is usually negative. Cultures of the fluid are positive in <30 percent of cases. Pleural biopsy using a Cope's or Abraham's pleural biopsy needle is useful in doubtful cases and usually would show caseating granulomas (sometimes positive AFB stain or culture).

EXTRAPULMONARY TUBERCULOSIS

Lymphadenitis

Superficial lymphadenitis (responsible for 44 to 67 percent of cases): It is the most common site of extrapulmonary TB followed by pleural, meningeal, osteoarticular and miliary TB in varying frequency depending on the patient population. It usually affects the anterior cervical and submandibular nodes. Firm, nontender or minimally tender enlarged lymph nodes, without generalized symptoms is the most common presentation. In advanced disease, matting, adherence to the overlying skin with dark discoloration of the skin, and subsequent sinus formation may occur.

Tubercular Meningitis

Tubercular meningitis (TBM) is the most feared complication of tuberculosis and is most common in the younger children— 0 to 4 years of age accounting for 80 percent of meningitis cases. The clinical presentation is usually indolent, with symptoms present 1 to 4 weeks before diagnosis. The most common presenting symptoms are fever, vomiting, lethargy, headache, and seizures. Seizures are especially common in children less than 2 years of age. Physical findings include nuchal rigidity, cranial nerve palsies and hemiparesis. The clinical course is divided into stages that have prognostic significance: Stage I (nonspecific symptoms such as fever, irritability, headache, sleepiness, or malaise with no focal neurologic findings), Stage II (nonspecific symptoms with neurologic findings), and Stage III (marked decrease in mental status with neurologic findings). Most cases with stage I will have intact

recovery while stage III cases have a significant mortality and morbidity.

Miliary TB

Miliary TB occurs following hematogenous dissemination with spread to two or more organs. It may occasionally present acutely, but, in most cases, weeks of fever, cough, weight loss, anorexia and malaise are present before diagnosis. Hepatosplenomegaly and generalized lymphadenopathy develop in 50 to 70 percent of cases. Bilateral diffuse micronodular pulmonary consolidations develop in 90 percent of cases and manifest as respiratory distress, diffuse rales, or wheezing. Military and meningeal tuberculosis frequently present together, especially in children less than 5 years of age.

Osteoarticular TB

Osteoarticular TB accounts for 1.4 percent of all cases of pediatric TB and 5.9 percent of cases of extrapulmonary TB in children. The vertebrae, followed by knee, hip, and elbow are the bones most commonly affected. Presenting signs and symptoms may include localized inflammation, pain, swelling, fever, decreased movement and limited range of motion of the affected bone or joint. Radiographic evidence of spondylitis, arthritis, and osteomyelitis may occur and chest radiograph abnormalities may be seen in up to 50 percent of cases.

Abdominal Tuberculosis

Abdominal tuberculosis may present as localized disease such as mesenteric lymphadenopathy, intestinal disease, peritoneal involvement or systemic disseminated disease presenting as hepatosplenomegaly.

Additional presentations, such as tuberculosis of the gastrointestinal tract, eyes, genitourinary tract, pericardium, skin, larynx or middle ear rarely occur in children.

DIAGNOSIS

Diagnostic difficulties pose the greatest challenge to childhood tuberculosis management. Main impediments to the accurate diagnosis of active tuberculosis are the paucibacillary nature of the disease, nonspecific clinical presentation and the fact that young children seldom produce sputum. Thus bacteriological diagnosis, which is gold standard for diagnosing TB, is difficult in children. The diagnosis of TB is, therefore, dependent on combination of clinical history and presentation, history of contact with a known TB case and result of TST and radiology. The two basic approaches to the diagnosis of TB: the direct approach including detection of *Mycobacteria* or its products and the indirect approach including measurements of humoral and cellular responses of the host against TB are discussed further.

Direct Approach in Diagnosis

Mycobacterial Detection and Isolation

Despite the difficulties of bacteriological diagnosis, a sincere and active effort must be made in all suspects. The sensitivity of smears for identification of *M. tuberculosis* is low (in the range of 25-30%) but specificity is very high (in the range of 90-99%). Pediatric TB is usually paucibacillary, unless there are visible cavities in the lung and further there is a difficulty with specimen collection as children do not expectorate or bring up sputum and also because they may have extrapulmonary TB, where access to appropriate body specimen may not be easy or feasible.

Specimens to be used:

- *Sputum and induced sputum:* Unless endobronchial tuberculosis is present, children <6 years of age usually do not have a cough deep enough to produce sputum for analysis. However, where feasible, sputum analysis should be done. Sputum induction by nebulized hypertonic saline has been reported to induce a higher yield of *M. tuberculosis* than gastric washings. However, feasibility of this technique has not been tested outside hospital settings and the infection control procedures must be strictly adhered to.
- *Gastric aspirates:* First morning gastric aspirates have traditionally been the best clinical specimens to obtain in young children. These aspirates may be positive for *M. tuberculosis* in 30 to 50 percent of all cases and in as many as 75 percent of infants. Hospitalization is not necessary to obtain gastric aspirate specimens from children with suspected TB as it can be done after 4 to 6 hours of fasting on an OPD basis. Traditionally 3 consecutive gastric aspirates/lavages have been used. Reports now suggest that two or even one gastric aspirate may yield optimal results. According to the revised WHO and RNTCP policies, 2 instead of 3 sputum samples are now considered sufficient to screen possible pulmonary tuberculosis in adults. Following suit, the same is being suggested for gastric aspirates.
- *Bronchoalveolar lavage (BAL):* The evidence so far is balanced between simple GAs and BAL while the ease would certainly tilt the balance in favor of GAs. Bronchoscopy, however, can provide direct visual clues to diagnosis in form of caseation, etc.
- *Others:* Depending on the location of the disease lymph node tissue, pleural/ascitic fluid, cerebrospinal fluid, bone marrow, liver, urine may be undertaken.

Direct Smear and AFB Staining of Specimens

Microscopy: Smear examination remains the simplest and the most rapid test currently available for the diagnosis of AFB by Ziehl-Neelsen stain or its modifications. The advantages are that it is rapid, cheap, simple, no infrastructure required, can be made available in field

setting. The major limitation is that it requires at least 5×10^3 bacilli per ml of sputum and it requires trained staff (observer dependent). As a significant proportion of childhood TB is paucibacillary, the utility of this test is further limited in children. Fluorescence microscopy has several advantages over light microscopy using ZN staining and is widely used in most developed nations. Fluorochrome staining procedure used with FM is not only simpler than that of ZN staining but is also has about 10 percent greater sensitivity for detecting AFB in patient specimens.⁴ As FM can be examined at a lower magnification than ZN (20-40 vs 100 \times), slides are read more quickly and efficiently with FM. It has been estimated that using FM may take up to 75 percent less time than ZN.⁴ Unfortunately, FM was not so popular so far in resource poor settings due to its high capital and maintenance costs, limited lamp life, and need to keep away from dusty environments. User acceptance was also poor due to production of UV light and heat and the requirement to work in a dark room for long hours. Recently, the low-cost, ultra-bright light-emitting diodes (LEDs) have replaced the mercury vapor lamps in the FM and made it possible to use as side laboratory equipment.

Mycobacterial Culture

Mycobacterial culture remains the gold standard for detection and drug susceptibility testing (DST). Traditionally, culture on an egg-based solid media, known as Lowenstein-Jensen medium, may take as long as 4 to 6 weeks because of the slow growth and additional 4 weeks for drug susceptibility testing. Liquid culture systems (BACTEC and MGIT) offer a more sensitive and rapid alternative to conventional solid culture and may detect growth in 1 to 3 weeks.^{5,6}

BACTEC system: This radiometric technique is specific for *Mycobacterium* growth, where in ^{14}C labeled palmitic acid in 7H12 medium is used. This system detects the presence of mycobacteria based on their metabolism rather than their visible growth. When the ^{14}C labeled substrate present in the medium is metabolized, $^{14}\text{CO}_2$ is produced and measured by the growth index value (GI). This method can detect growth as early as in 5 to 10 days though a sample is considered negative if only there is no growth even after 6 weeks of incubation.

Compared to the conventional culture and drug susceptibility testing methods BACTEC method is faster (87% of the positives being obtained by 7 days and 96 percent by 14 days) and it showed a good correlation in drug susceptibility tests with conventional Solid LJ media. However studies have failed to show an increased efficiency in detecting smear negative cases.

MGIT 960 Mycobacteria detection system: It is a nonradiometric automated system for the growth and detection of

mycobacteria with a capacity to incubate and continuously monitor 960 mycobacteria growth indicator tubes (MGIT) every 60 minutes for increase in fluorescence. Growth detection is based on the AFB metabolic O₂ utilization and subsequent intensification of an O₂ quenched fluorescent dye contained in a tube of modified MGIT. Using paired specimens, BACTEC 460 and MGIT 960 systems took about 13.4 versus 15.5 days for *M. tuberculosis* isolation respectively. MGIT 960 system exhibits greater potential as a rapid, accurate and environment friendly method.⁶

The yield of mycobacteria is high when the samples are repeated, in extensive pulmonary disease and in infants, where it can be up to 70 percent. Availability of LED fluorescent microscope now is expected to make Auromine staining and smear examination simpler, faster with an improved yield. While neutralization of the aspirate has generally been recommended before transporting the sample to the laboratory for culture, the experience with newer liquid culture methods has shown a higher risk of contamination due to this.

Genotypic Methods

Genotypic methods are available with newer modifications for the diagnosis of TB as an alternative for smear microscopy. *Polymerase chain reaction (PCR)* methodology is rapid; results are available within a day of DNA extraction from the sample. The most common target used in the PCR is IS6110. A variety of PCR methods have been described in the search for a sensitive and reliable screening test for TB in clinical specimens. Species-specific and genus-specific PCR methods are being used with various targets and modifications of PCR.

Real time PCR: Realtime PCR is a significant advance which can detect the presence of amplified nucleic acid target in a closed system without having to resort to cumbersome gel—or ELISA-based detection. Thus the risk of cross-contamination of samples by amplified DNA from previous positive samples is precluded.

GeneXpert® MTB/RIF system developed by Cepheid (CA, USA) together with the Foundation for Innovative New Diagnostics uses a closed real time PCR system packaged inside a cartridge. This system is one of the first point-of-care PCR test which requires minimal manipulation of sample and operator training. The test not only identifies *M. Tb* but can also simultaneously identify rifampin resistance using a region of the *rpoB* gene of MTB that is responsible for 95 percent of rifampicin resistance. Preliminary studies in adult patients have been promising demonstrating a sensitivity of 100 percent for smear-positive patients and 71.7 percent for smear-negative, culture-positive patients. The system is currently under evaluation for the diagnosis of TB in children. Given the relatively good performance of GeneXpert in smear-negative case this may prove to be a useful tool for rapid diagnosis of TB in children.⁷

Other modifications of the PCR include strand displacement amplification (SDA), nucleic acid sequence based amplification (NASBA), branched DNA (b-DNA) and line probe assay (LiPA). One of the promising LiPA is GenoType MTBDRplus, (Hain Lifesciences, Nehren, Germany) wherein amplified DNA from regions of the genome involved INH and rifampicin resistance is hybridized onto a strip containing probes for the wild type (sensitive) as well as the most common drug resistance mutations.⁸ However, limited data exist on the performance of this test in smear-negative samples and these tests have not been specifically evaluated in childhood TB.

Indirect Approach in Diagnosis

Tuberculin Skin Test or Mantoux Test

It is one of the important tools used for supporting diagnosis of TB among children. 5 TU or lower dose is given intradermally and read after 48 to 72 hours (1 TU RT23 is the preferred dose). Induration ≥10 mm is considered positive for diagnostic purposes—suggestive of MTB infection, but is neither very specific or sensitive test. Ulceration, higher size of induration have little predictable relation with active disease. BCG vaccination can interfere with its interpretation.

Interferon γ Assays (IGRAs)

These tests use antigens which do not cross react with BCG and therefore these are more specific and sophisticated tests now available to detect TB infection. They provide the same information as TST but do not need a second patient visit for measurement and the results are available by 24 hours. Two commercially available IGRAs are ELISPOT-TB which uses *in vitro* stimulation of PBMCs with ESAT-6 and CFP-10 antigens and Quantiferon-Gold in tube test which uses *in vitro* stimulation of whole blood with these antigens, in addition to TB 7.7 antigen. However, none of these can detect active disease or make a distinction between infected, diseased and treated cases. These new tests thus offer limited incremental value compared to TST. The data on their role in immunocompromised (HIV), young children (<3 years) and malnourished children remain limited.⁹

The latest innovation has been combining the virtues of TST with IGRAs and preparing a *Lactococcus* fermented, recombinant skin test reagent which contains 1:1 wt/wt of rdESAT-6 and CFP-10. This investigational skin test reagent rdESAT-6 and CFP-10 appeared safe and non-sensitising in this first-in-man clinical trial in human volunteers and may form the future TST.¹⁰

Adenosine Deaminase

Adenosine deaminase is an enzyme required for the conversion of adenosine to inosine and is found in many

tissues, particularly in T-lymphocytes from the lymphoid tissue. High ADA levels in tuberculosis appear to be related to the subset of activated T-lymphocytes in response to tuberculous antigens. The use of ADA is increasing because it is simple and affordable. Consequently, many studies have been published that have evaluated the performance of ADA. A recent systematic review and meta-analysis of 13 studies including 380 patients with TBM calculated the sensitivity, specificity and diagnostic odds ratios (DOR) on arbitrary ADA cut-off values from 1 to 10 U/l. None of the cut-off values could be used to discriminate between TBM and bacterial meningitis. The different methods used to measure ADA and the heterogeneity of data does not allow standardization of this test as a routine.¹¹ Another recent Meta analysis including 5 studies confirms the clinical value of ADA activity as adjunctive diagnostic marker of TP among other causes of pericardial effusion with a sensitivity and specificity of 88 percent and 83 percent, respectively with an optimal cut-off point of 40U/ L.¹² Meta analysis of 4 studies showed high sensitivity (100%) and specificity (97%) of ADA in peritoneal TB with an optimal cut-off value of 39 IU/ L.¹³ The test performance of ADA in tuberculous pleural effusion is also reasonably good with a summary measure of test characteristics was 92.2 percent for both sensitivity and specificity with an optimal cut-off point of 40 IU/L.¹⁴ Most of the studies included have compared cases of tuberculosis with untreated pyogenic infections. However, the utility of ADA in distinguishing cases of partially treated pyogenic with tubercular disease is unclear since most studies have not included such patients. Hence, ADA should be used cautiously in such cases.

Body Fluid Assessment

Body fluids like pleural, pericardial, ascetic or cerebrospinal fluids when involved, typically show a predominantly lymphocytic cytology with exudative biochemistry. The fluid may show cobweb formation on standing due to its high protein content.

Radiology in Diagnosis

Diagnosis of TB still remains difficult since no microbiological test is highly sensitive or specific. Sputum microscopy (and culture) is specific for diagnosis and may be widely available, however, a large proportion of children are smear-negative. Imaging remains useful for diagnosis, detection of complications, monitoring response to therapy, and for evaluating outcome. Conventionally radiological TB has been divided into primary and reactivation TB.

Recent evidence suggests that TB infection may not be a single event. Also, exogenous reinfections in endemic areas are common. It has been seen that >50 percent of recurrent disease occurring in endemic settings results from reinfection. Primary infection can occur at any age

(especially in countries with low TB incidence). Primary TB accounts for 23 to 34 percent of all adult cases. Hence the conventional classification of primary and reactivation TB may not be appropriate. Radiologically, TB can be classified as lymph node TB (gangliopulmonary TB), air-space parenchymal TB (consolidation), tuberculoma, miliary TB, cavities, pleural TB or fibrosis and destruction.¹⁵

Radiology although is helpful radiographic signs are nonspecific. Also there is subjective interpretation with inter- and intraobserver variability of readers, difficulty in distinguishing active from inactive disease and infection from disease. With emergence of HIV coinfection and emergence of drug resistance (MDR, XDR TB) the radiology is also changing. Radiology of TB in other organ systems is very diverse and beyond the scope of this chapter.

The diagnosis of TB in children relies on careful and thorough assessment of all the evidence derived from a careful history, clinical examination and relevant investigations, e.g. TST, chest X-ray (CXR) and sputum smear microscopy. Although bacteriological confirmation of TB is not always feasible, it should be sought whenever possible, e.g. by sputum microscopy for children with suspected pulmonary TB who are old enough to produce a sputum sample.

TREATMENT

The appropriate management of tuberculosis requires assessment of the patient correctly with respect to the site of disease, bacteriological status, treatment type of patient and the severity of disease. After appropriately defining the disease, the patient is then classified to receive appropriate anti-TB therapy (Table 1).¹¹ Currently WHO guidance and RNTCP strategy is to classify TB patients as either New or Previously treated cases. While all new cases (never treated in the past or received total TB treatment of <4 weeks duration) are given a 4 drug regime (erstwhile Category 1), the previously treated cases receive the erstwhile category 2 treatment. The drug dosages are given in Table 2 and management of interruptions of treatment in Table 3.

The treatment of TB in children and adults has been revised by the RNTCP and WHO. The major changes from the previous guidelines are:

- Child with cough for 2 weeks becomes a TB suspect (previously 3 weeks).
- Two sputum samples are required (previously 3 were required).
- For diagnosis of smear-positive TB even one positive sample is considered diagnostic.^{16,17}

Recent WHO 2010 guidance for children have suggested some changes. Now the recommended doses of anti-TB drugs have been increased keeping in mind the data on pharmacokinetics of these drugs in children. The children with HIV/ AIDS should only be treated with

Table 1: Old RNTCP treatment regimens

Category of treatment	Type of patient	Treatment regimens ***	
		IP	CP
Category I	New sputum smear-positive PTB	2H3R3Z3E3	4H3R3
	New sputum smear-negative PTB, seriously ill*		
	New extra-PTB, seriously ill*		
Category II	Sputum smear-positive relapse	2S ₃ H3R3Z3E3+ 1H3R3Z3E3+	4H3R3
	Sputum smear-positive treatment failure		
	Sputum smear-positive treatment after default		
Category III	New sputum smear-negative, not seriously ill**	2H3R3Z3	4H3R3
	New extra-PTB, not seriously ill**		
	Now withdrawn All these types of patients are also treated as Category I		

* In children, seriously ill sputum smear negative PTB includes all forms of sputum smear negative PTB other than primary complex. Seriously ill EPTB includes TB meningitis (TBM), disseminated TB, TB pericarditis, TB peritonitis and intestinal TB, bilateral extensive pleurisy, spinal TB with or without neurological complications, genitourinary TB, and bone and joint TB.

** Excluding the ones in the category of seriously ill.

Table 2: Antituberculous drug and their dosages

Drug (symbol)	Daily dosages per kg body weight	Maximum per day dose (daily regime)	Intermittent dosage as under RNTCP per kg body weight	Maximum per day dose (intermittent regime)	Major side effects
Streptomycin (S)	15-20 mg	1000 mg	20 mg	1000 mg	Tinnitus
Rifampicin (R)	10-15 mg	600 mg	15 mg	600 mg	Hepatotoxicity, gastritis, flu-like illness
Isoniazid (H)	10-15 mg	300 mg	15 mg	600 mg	Peripheral neuropathy, Hepatotoxicity,
Pyrazinamide (Z)	25-30 mg	2000 mg	35 mg	2000 mg	Arthralgia, hepatotoxicity,
Ethambutol (E)	20-25 mg	1000 mg	30 mg	1200 mg	Oculotoxicity

daily treatment in the intensive phase, while children with Tubercular meningitis and osteoarticular tuberculosis should be treated for total of 12 months.¹⁷

STEROID THERAPY

Definite indications for concomitant steroid therapy include TBM and pericarditis. Steroids are routinely not indicated in lymphadenitis and pleural effusion. They may be used in endobronchial tuberculosis or mediastinal compression syndrome due to tuberculosis, pleurisy with severe distress and miliary disease with alveolocapillary block. Prednisolone 2 to 4 mg/ kg/ d or its equivalent is used for 2 to 4 weeks and then tapered over next 2 weeks.¹⁷

MONITORING OF PATIENT ON TREATMENT

It is important to monitor the patient for:

- Response to treatment
- Treatment adherence
- Occurrence of side effects

Monitoring for Response to Therapy

Clinical

The clinical improvement in a patient on ATT is the mainstay of assessing the response to therapy. Symptomatic improvement should be assessed on each clinic visit especially at the end of the initial phase and in subsequent follow up, by judging the improvement of fever, decrease in cough, weight gain, improved appetite and subjective well-being, and decrease in lymph node size. Majority of the patients shows clinical improvement in symptoms and signs within a few weeks time. In the presence of poor response or worsening of clinical condition, it should be ensured that the diagnosis of TB was correct and tenable; the patient should be evaluated for compliance to therapy, other co morbid conditions or secondary infection should be ruled out and then only the possibility of drug resistant tuberculosis considered. Follow-up should be continued every 4 weeks for the duration of treatment and subsequently every 3 to 6 months for next 2 years particularly in

Table 3: Managing patients with interruptions in treatment

<i>Duration of therapy</i>	<i>Duration of interruption</i>	<i>Decision</i>
Up to 4 weeks	<2 weeks	Resume original regime
	> 2 weeks	Reassess and start treatment again
4-8 weeks	<2 weeks	Resume original regime
	2-8 weeks	Extend intensive phase by 1 month more
	>8 weeks	Category II if diagnosis is still TB
>8 weeks	<2 weeks	Resume original regime
	>2 weeks	Review activity Continue same treatment if no active disease Category II therapy for active diseases

children with serious disease such as congenital tuberculosis or meningitis, or those with extensive residual chest radiographic findings at the end of chemotherapy.

Radiological

The patients should be assessed for resolution of the radiological abnormalities at the end of initial phase. If it shows improvement in combination with clinical response, no further X-ray film may be required. In patients, who show increase or little change in radiological shadows coupled with inadequate clinical response, we suggest prolongation of intensive phase by 4 more weeks. Further roentgenogram should be done at end of this period and if it shows features of resolution than the continuation phase is started else the patient is investigated for treatment failure and drug resistant tuberculosis. Normal chest radiograph appearance is not a necessary criterion for discontinuation of therapy in children treated for primary pulmonary disease. After completion of therapy, hilar adenopathy may be present for 2 to 3 years.

Microbiological

To monitor treatment outcome, it is recommended by WHO that all patients with pulmonary tuberculosis should have repeat sputum/gastric aspirate smears performed at the end of initial phase of treatment to detect conversion to negative status among those who were initially positive and to detect early failures in those who were AFB negative. To verify treatment success, additional sputum examinations should be done at least once before stopping treatment. Where culture facilities are available, sputum cultures should be obtained at the start of treatment. Sensitivity tests for all available drugs if possible should be performed for a new patient whose sputum is still positive

at the end of the intensive phase of treatment, and for any patient suspected to be at risk of being drug resistant e.g., relapsed cases, defaulters.

Treatment Adherence

This must always be checked along with response to treatment. It could be undertaken by asking the patient directly, by a pill count or prescription check and by asking for the color of the urine. Patients should be evaluated monthly and should be given only enough medicine for the interval between evaluations. As far as possible, all patients must be on Directly Observed Treatment, Short course (DOTS). Local arrangements for supervision must be arranged either at the nearby health facilities, family practitioner or by a responsible person/relative. Patients not on directly observed therapy should be followed up more regularly. The patient must be made aware of his follow-up appointments to ensure compliance with treatment. To strengthen patient adherence, the patient and the caregiver should be educated about the illness and treatment, and regularly motivated during the course of treatment. Efforts should be made for prompt defaulter tracing. Often the complete treatment of a patient may entail socioeconomic assistance and advice for the family. It must be emphasized that routine hospitalization of tuberculosis patients is not required to ensure completion of treatment while those with serious sickness and complications may need to be admitted.

Drug Toxicity Monitoring and Management

The common side effects of Anti TB drugs are given in see Table 2. Rates of adverse reactions to antituberculous drugs among children are low. The important side effects, which have clinical implications, include hepatotoxicity, ocular toxicity, and skin hypersensitivity reactions. All patients should be monitored clinically for adverse reactions during the period of chemotherapy. They should be informed about symptoms of common adverse reactions to the medications they are receiving. Children taking ethambutol require regular monitoring of visual acuity and color discrimination. Routine biochemical monitoring is usually not required.

Minor Side Effects

Minor side effects, such as gastrointestinal intolerance, mild skin rash, pruritus or flushing are best managed by reassurance and symptomatic treatment and the patient should be encouraged to continue anti tuberculosis treatment. Nonsteroidal anti-inflammatory drugs (NSAIDs) provide symptomatic relief for pyrazinamide related arthralgia. Skin rashes can usually be managed by withholding the causative drug and if it is really necessary to reintroduce the drug, the patient should undergo desensitization.

Major Side Effects

Physicians must manage severe skin reaction and Steven-Johnson syndrome. Other common serious drug toxicity is hepatitis. The factors that may decide hepatotoxicity include acetylator phenotype, doses and combination of ATDs, malnutrition, and severity of disease. As the anti-TB drugs are hepatic enzyme inducers, asymptomatic biochemical derangement without increase in bilirubin level may be tolerated till the enzymes remain up to 5 times the normal range. However, if patient develops jaundice or other signs of liver dysfunction during therapy, it's prudent to stop ATT immediately irrespective of enzyme levels. The drugs are withheld till the serum bilirubin becomes normal and the enzymes also start touching the normal range. Although many patients with drug-induced hepatotoxicity can be successfully rechallenged, this is best done in a place where liver function can be carefully monitored. The drugs should be re introduced in the order of rifampicin, followed by isoniazid and then pyrazinamide. If the period without drugs is likely to be prolonged, and the patient is sick and requires treatment, at least two other drugs (e.g. streptomycin, ethambutol, fluoroquinolones) should be given until it is determined whether the offending drug can be resumed. Drugs causing severe intolerance are best avoided and substituted with other drugs. All patients who require alteration from the standard regimen should be referred to experienced physicians

Clinical manifest neuritis in children on INH therapy due to pyridoxine deficiency is very rare. If at all it occurs, it manifest as pins and needles sensation in hands and feet. It is treated with pyridoxine 25 to 50 mg/day. Ocular toxicity due to ethambutol may occur in up to 5 percent of patients if doses are between 25 and 50 mg/kg/day. However, it is rare in doses of 15 and 20 mg/kg/day. The toxicity results in reversible optic neuritis, blurred vision, and alteration in colour vision. In young children if ethambutol toxicity is suspected they should be monitored by electroretinogram (ERG) in consultation with an eye specialist. However, in older patient regular monitoring of color vision is sufficient.

The development of the following conditions contraindicates further use of the offending drug:

- Thrombocytopenia, shock and/or renal failure due to rifampicin.
- Visual impairment due to ethambutol
- Eighth nerve damage from streptomycin.
- Stevens-Johnson syndrome.

Interruption of Treatment

Patient compliance is crucial factor in treatment failure and the development of acquired drug resistance. It is very important to realize that the emergence of MDR TB

is always a man made problem and failure of the patient to complete the prescribed course completely and adequately is one of the reasons. In general, if it is certain that the patient was taking all medications correctly prior to interruption, then (s)he can be managed as per the guidelines for treatment after interruption shown in Table 3. Whenever treatment is interrupted for more than 2 wks, the child should be reassessed clinically and radiologically, with bacteriological examination, wherever possible. In all such cases the resumption of treatment must be preceded by evaluation for activity and investigating the causes for nonadherence. The pediatrician should not merely restart the treatment but also enable the completion of treatment by addressing issues related to nonadherence in the first instance. Addressing issues like side effects of the therapy (real or perceived), cost involved as well as educating about the need for a complete treatment even after the symptoms abate may help adherence. Both the child as well as the caregivers must be involved in decision-making for reinitiating treatment.

Chemoprophylaxis

Six months of INH chemoprophylaxis is recommended for all children under 6 years of age who are a contact of any infectious case, irrespective of their BCG or nutritional status.¹⁷ PPD positive children over 6 years of age and who do not have any evidence of active disease but are planned for immunosuppressive therapy (e.g. children with nephrotic syndrome, acute leukemias, etc.) may also be given the benefit of chemoprophylaxis.

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Revised National Tuberculosis Control Programme (RNTCP) and Guidelines for Pediatric Tuberculosis

Vasant Chinabhavdar, SP Yadav, Anupam Sachdeva

Of the estimated global annual incidence of 9.4 million TB cases in 2009, 2 million were estimated to have occurred in India, contributing to 20 percent of the global burden of TB.

DIAGNOSING PEDIATRIC TUBERCULOSIS (TB) IN CLINICAL PRACTICE

No specific scoring system has yet shown proven utility in diagnosing (TB) in pediatric practice. Diagnosing TB in children presents a unique set of challenges due to the lower bacterial load (paucibacillary disease), nonspecific radiologic changes and relative difficulty in obtaining suitable sputum samples for analysis. In general, clinicians should suspect TB when a child presents with:

- Fever and/or cough for more than three weeks, with or without;
- Loss of weight/ no weight gain; and
- History of contact with a suspected or diagnosed case of active TB disease within the last two years.

In children who fulfill these criteria further screening may include:

- **Bacteriology:** Consists of sputum (or gastric aspirate) analysis by smear and culture.
- **Mantoux test:** Performed using 1 TU PPD RT 23 Tween 80 by intradermal route. Test is interpreted after 48 to 72 hours.
- **Radiography:** A chest X-ray, preferably in an upright position (PA view) should be obtained.
- **Serology and PCR:** The role of these modalities is yet to be properly defined for diagnosis in the pediatric population on a large-scale. Hence, their routine use is not recommended by the RNTCP.

Referral to a qualified pediatrician is recommended for children who need detailed evaluation even if they do not fulfill the above criteria. Also, a low threshold for initiating

investigations should be maintained for children with history of steroid therapy, immunocompromised states, measles, pertussis and for those below one year of age.

PEDIATRIC TB—TREATMENT

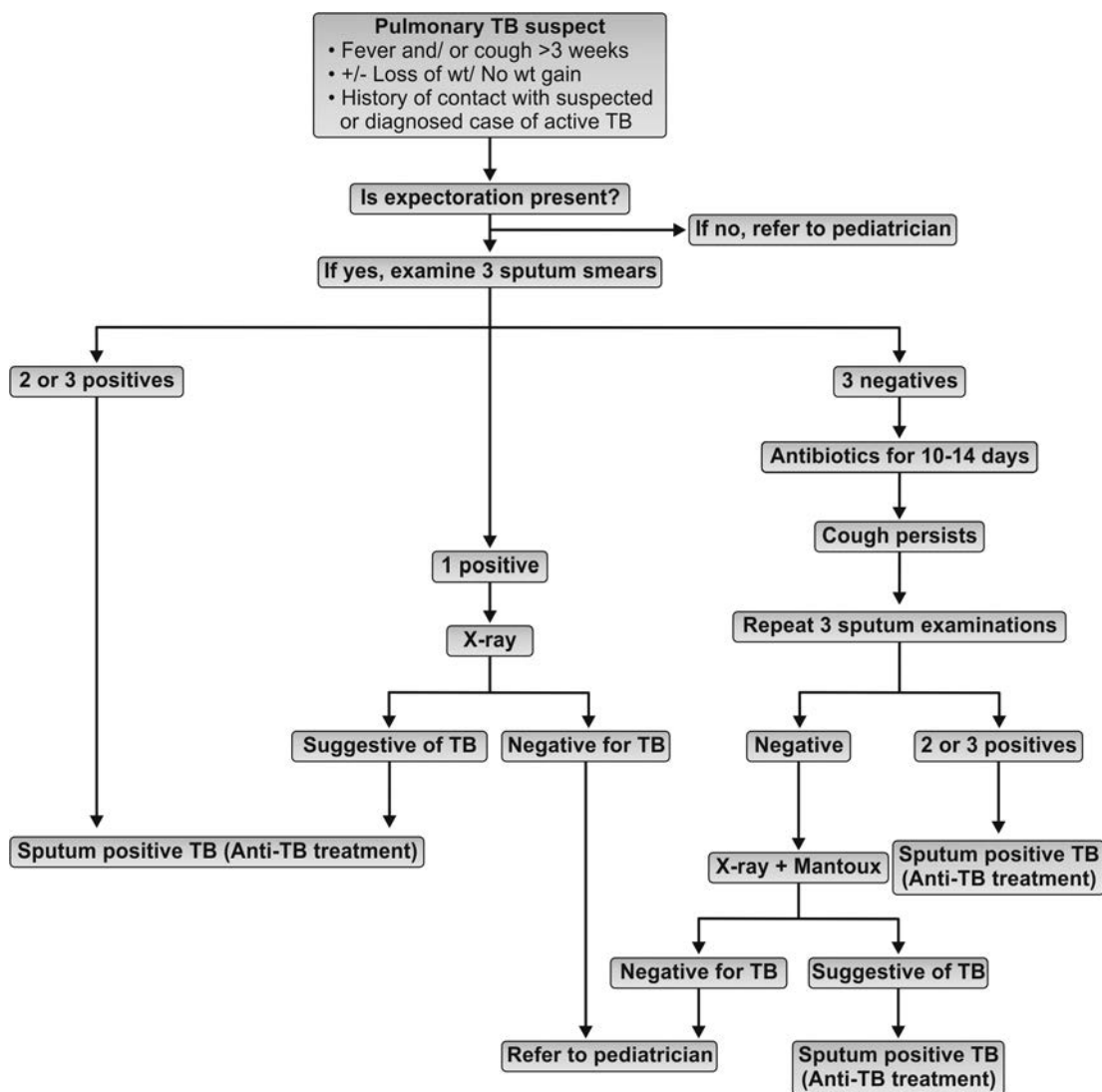
The Revised National TB Control Programme (RNTCP), based on the internationally recommended Directly Observed Treatment Short-course (DOTS) strategy, was launched in 1997. The program is active in the entire nation since March 2006, reaching over a billion people (1164 million) in 632 districts/reporting units. It had originally recommended treatment of pediatric cases of tuberculosis (TB) with drug doses based on body weight. The guidelines proposed that children below the age of six years receive treatment based on the $2R_3H_3Z_3/4R_3H_3$ regimen (Flow chart 1).

WHO estimated TB mortality in India at about 280,000 (23/100,000 population) in 2009. Deaths due to TB have been reduced by almost half since the implementation of the RNTCP. A total of 6.3 million patients have been treated under the RNTCP during 1997 to 2006. This has averted an estimated 1.3 million deaths.

The RNTCP recommends short course chemotherapy (SCC) for the treatment of pediatric TB. SCC is based on the following principles:

- A combination of at least three to four drugs should be used in the initial intensive phase (two months). The drugs are isoniazid (H), Rifampicin (R), Pyrazinamide (Z), and either Streptomycin (S) or Ethambutol (E). This ensures rapid killing of all populations of bacilli.
- Drugs can be given either daily or intermittently (twice or thrice weekly).
- The minimum duration of treatment is six months when Rifampicin is used throughout and Pyrazinamide is used in the initial intensive phase. If only two drugs are used, the duration of treatment has to be at least nine months.

Flow chart 1: RNTCP diagnostic algorithm for pediatric pulmonary TB



- The drugs should preferably be given together and administered as a single dose.

The advantages of SCC:

- Faster and more powerful bactericidal and sterilising action so that even if the patient defaults after the first few months of therapy, cure is more likely.
- The patient is exposed to potentially toxic drugs for shorter periods of time.
- The regimens are less expensive and more cost-effective than traditional therapy.
- More time and resources can be allotted to ensuring adherence.

In 2004, following a consensus meeting between the RNTCP and the Indian Academy of Pediatrics (IAPS), these recommendations were revised to include Ethambutol in the treatment of children even below the age of six years. Also, to overcome the problem of administering appropriate doses in younger children the required

drugs were made available in specific patientwise boxes (PWBs) as had already been done for adult patients. The pediatric population was divided into four discrete weight bands for treatment purposes. Specific color-coded boxes containing appropriate doses of the drugs were packaged to ensure adequate dosing of medication.

The new formulations to be used in RNTCP:

- Rifampicin – 75/ 150 mg
- Isoniazid – 75/ 150 mg
- Ethambutol – 200/ 400 mg
- Pyrazinamide – 250/ 500 mg

For the purpose of treatment, the pediatric population has been divided into four weight bands:

- 6–10 kg
- 11–17 kg
- 18–25 kg
- 26–30 kg

Eligibility to Category I treatment category widened as:

- RNTCP included all new cases who were HIV infected irrespective of type of TB, site or severity
- All new cases of TB in pediatric cases except primary complex and minor forms of EPTB.

In view of these changes, a meeting of national experts of the RNTCP 2009 decided to have only two firstline TB treatment regimens in future and discontinue the 3-drug Cat-III regimen from the guidelines. Further, it was decided that these regimens would be called regimen for new (Category I) and previously treated (Category II) cases (Table 1).

The 2004 consensus meeting had already recommended that some modifications in the type of patients under each treatment category be made, keeping in mind the different diagnostic criteria used in children, namely:

- In patients with TB meningitis on Category I treatment, the usual four-drug regimen used during the intensive phase—HRZE—should be replaced by HRZS as Ethambutol does not penetrate the CSF well
- The continuation phase of treatment in TB meningitis (TBM) and spinal TB with neurological complications should be given for six to seven months, extending the total duration of treatment to eight to nine months
- Steroids should be used initially to reduce inflammation in hospitalized cases of TBM and TB pericarditis and reduced gradually over six to eight weeks.

TB Chemoprophylaxis

Current RNTCP recommendations advise six months of daily Isoniazid (5 mg/kg) chemoprophylaxis for asymptomatic children under six years of age, if exposed to an adult with infectious (smear positive) TB.

The overall algorithm proposed is reproduced in flow chart 2.

Drug Resistant Tuberculosis

A large scale population based survey in Gujarat and Maharashtra indicated multidrug resistance levels of 3

percent among new TB cases and 12 to 17 percent among previously treated TB patients. Though the rate of MDR-TB is relatively low in India, this translates into a large absolute number of cases, with an estimated annual incidence of 99,000 cases of MDR-TB in the country.

Poor adherence by patients to treatment and poor patient management by physicians are the two main causes for drug resistance demonstrated by TB. Drug resistance patterns are similar in the pediatric and adult populations. Initial drug resistance to Isoniazid is reported to be around 10 to 15 percent and for Rifampicin, the range is 2-3 percent. These rates are much higher in patients who have taken prior, irregular treatment.

Drug resistance should be suspected when:

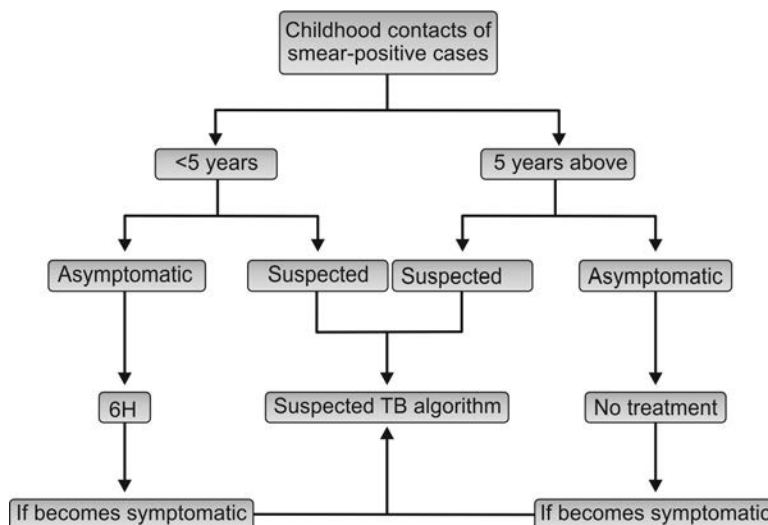
- The child is in contact with a known case of drug-resistant tuberculosis
- The child's adult contact has been on chronic irregular treatment and continues to be sputum positive
- The adult contact died after taking irregular treatment
- The child shows initial improvement to antituberculosis treatment but then deteriorates (clinically and radiologically).

Successful therapy for drug resistant TB requires treatment with at least two bactericidal drugs to the infecting strain of *M. tuberculosis* is susceptible. If specific pattern of drug resistance is known exact treatment regimens can be tailored. When these patterns are unknown, at least three drugs to which the patient has not been exposed earlier should be given. Resistance to Isoniazid or Streptomycin alone can usually be managed with any of the standard four drug regimens with good results. However, when resistance to both Isoniazid and Rifampicin is present (i.e. multidrug resistant TB), the management is more complicated and requires the use of second line drugs. The duration of therapy is usually extended to 12 months, if either Isoniazid or Rifampicin can be used, and to at least 18 to 24 months if resistance to both drugs is present. Occasionally, surgical resection of a diseased lung or lobe is required.

Table 1: Revised RNTCP patient categories

Treatment groups	Type of patient	Regimen	
		Intensive phase	Continuation phase
New (Cat I)	<ul style="list-style-type: none"> • New sputum smear-positive • New sputum smear-negative • New extrapulmonary • New others 	2H ₃ R ₃ Z ₃ E ₃	4H ₃ R ₃
Previously treated (Cat II)	<ul style="list-style-type: none"> • Smear-positive relapse • Smear-positive failure • Smear-positive treatment after default • Others 	2H ₃ R ₃ Z ₃ E ₃ S ₃ / 1H ₃ R ₃ Z ₃ E ₃	5H ₃ R ₃ E ₃

Flow chart 2: Chemoprophylaxis guidelines RNTCP recommendations



Overall, the RNTCP uses a Standardized Treatment Regimen (*Cat IV*) for the treatment of MDR-TB cases (and those with rifampicin resistance) under the program. Cat IV regimen comprises of six drugs- kanamycin (Km), ofloxacin (Ofx) (replaced by levofloxacin in this regimen in 2009-2010), ethionamide (Eto), pyrazinamide (Z), ethambutol (E) and cycloserine (Cs) during 6-9 months of the intensive phase and four drugs ofloxacin (or levofloxacin), ethionamide, ethambutol and cycloserine during the 18 months of the continuation phase. Para-aminosalicylic acid (PAS) is included in the regimen as a substitute drug if any bactericidal drug (K, Ofx, Z and Eto) or two bacteriostatic (E and Cs) drugs are not tolerated.

RNTCP CATEGORY IV REGIMEN: 6 (9) Km Ofx (Lv_x) Eto Cs Z E /18 Ofx (Lv_x) Eto Cs E

The treatment consists of two phases—the *Intensive phase (IP)* and the *continuation phase (CP)*. IP is recommended to be given for at least six months. After 6 months of treatment, the patient should be reviewed and the treatment changed to CP if the 4th month culture result is negative.

If the 4th month culture result remains positive, the treatment must be extended by 1 month. Extension of IP beyond 1 month would be decided on the results of sputum culture of 5th and 6th months. If the result of the 4th month culture is still awaited after 6 months of treatment, the IP would be extended until the result is available, with further treatment being decided according to the culture result. The IP can be extended up to a maximum of 3 months after which the patient should be initiated on the CP irrespective of the culture result. The recommended duration for CP is 18 months.

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Multidrug Resistant Childhood Tuberculosis

Varinder Singh, Satnam Kaur

INTRODUCTION

Emergence of drug resistant tuberculosis—multidrug resistant tuberculosis (MDR-TB) followed by extensively drug resistant tuberculosis (XDR-TB) and most recently pan drug resistant tuberculosis has ensured that the disease remains one of the major health problems especially in developing countries, despite all the advances made in treatment and management. Drug resistance severely threatens tuberculosis control since it raises the possibility of return to an era where no effective drugs are available for treatment of TB even though progress is being made in global control of drug susceptible tuberculosis *viz.* falling incidence of TB since 2004, achievement of 87 percent success rate of antituberculosis treatment in 2007.¹

Till date because of difficulty of establishing an accurate diagnosis and lower priority given to children by tuberculosis control programs, the research and surveillance data in the field of childhood tuberculosis have been limited. Relatively, far less is known about the diagnosis and management of childhood MDR-TB. Clinical management as well as outcome of treatment of MDR-TB in children is not well documented.

DRUG RESISTANCE—DEFINITIONS

Drug resistance in mycobacteria is defined as decrease in sensitivity to a sufficient degree to be reasonably certain that the strain concerned is different from a sample of wild strains of human type that have never come in contact with the drugs.²

Multidrug resistant tuberculosis (MDR-TB): MDR-TB is caused by strains of *Mycobacterium tuberculosis* that are resistant to at least isoniazid (INH) and rifampicin (RMP) with or without resistance to other first line drugs.

Extensively resistant tuberculosis (XDR-TB): XDR-TB is caused by strains of *Mycobacterium tuberculosis* that are MDR

with additional resistance to any fluoroquinolone and one of the three second line injectable drugs—amikacin, kanamycin or capreomycin.

Polyresistance: Strains of *Mycobacterium tuberculosis* that are resistant to combination of drugs other than both INH and RMP is called polyresistant.

Pan drug resistant tuberculosis: Pan drug resistant tuberculosis is caused by strains of mycobacteria resistant to all known antituberculosis drugs and has been recently reported.³⁻⁴

Monodrug resistant tuberculosis: It is also well documented and monoresistance to INH and RMP is of particular relevance as these are the two pivotal drugs in the treatment of tuberculosis. Once the *mycobacterium* is no longer susceptible to INH or RMP, management of disease becomes complicated because the remaining drugs are less effective, more toxic, have far longer duration, expensive and lack pediatric formulations.

TYPES OF DRUG RESISTANCE

Drug resistance may be broadly classified as primary or acquired. When drug resistance is demonstrated in a patient who has never received anti-TB treatment previously, it is termed primary drug resistance. The resistance that develops in a patient who has received prior chemotherapy is acquired drug resistance. WHO has now replaced the term primary resistance by the term “drug resistance among new cases” and acquired resistance by the term “drug resistance among previously treated cases”.⁵ When one is not sure whether the resistance is primary or acquired due to concealed history of previous treatment or unawareness of treatment taken before, it is known as initial drug resistance. Combined resistance is sum of primary and acquired resistance. The level of primary resistance in the community is considered to reflect

the efficiency of control measures in the past while the level of acquired resistance is a measure of on-going TB control measures.

DISEASE BURDEN

WHO estimates that 4,40,000 cases of MDR tuberculosis occurred in 2008 (3.6% of the estimated total incident tuberculosis episodes).⁶ Of these 3,60,000 were new and relapse cases and 94,000 were in individuals previously treated for disease. However, only about 30,000 cases of MDR-TB were notified to WHO (11% of total number of estimated cases). India and China together carry nearly 50% of the global burden followed by Russia (7%). An estimated 1,50,000 deaths were caused due to MDR-TB in 2008.⁶

According to the Fourth WHO/Union Global Project on Anti-Tuberculosis Drug Resistance Surveillance Report, any drug resistance was seen among 17 percent of new case, 35 percent of retreatment cases and 20 percent of all TB cases in the specimens analyzed till 2005. Corresponding figures for INH resistance and multidrug resistance among the three groups were 10.3 percent, 27.7 percent, 13.3 percent and 2.9 percent, 15.3 percent, 5.3 percent, respectively. As expected, drug resistance was higher in retreatment than in untreated cases; moreover, rates of INH resistance are high, and there is not much data on RMP monoresistance, but it appears to be rare, with rates as low as 0.02 percent being reported.⁷

High rates of MDR transmission (>3% of all new tuberculosis) have been reported for at least one country in all six WHO regions. Of particular note are several countries of former Soviet Union, where more than 12 percent of new cases and 50 percent of previously treated cases are MDR tuberculosis. Nearly, all cases of MDR in these countries are also resistant to other first line drugs.⁶ This level of high drug resistance translates into not only a higher failure of the initial drug therapy but also emergence of further resistance due to inadequate initial regimes. Drug resistance surveillance (DRS) surveys have been ongoing since 2005 in Andhra Pradesh, Gujarat, Maharashtra, Orissa and Uttar Pradesh in India. The prevalence of multidrug-resistant TB (MDR-TB) in new smear-positive pulmonary TB cases ranges from 1 percent to 3 percent in some districts. In the state of Gujarat, the prevalence of MDR-TB in new TB cases was 2.4 percent (95% CI 1.6–3.1) and in previously treated cases, 17.4 percent (15.0–19.7). It is estimated that 5.4 percent of all TB patients in India have MDR-TB.⁷

Comprehensive studies on resistance to anti-TB drugs in children are limited and the prevalence of drug resistant tuberculosis in children is not well defined, given the difficulties of culture confirmation in this age group. But the pattern of drug resistance among children reflects that found among adults in the same population as most resistance in children is caused by primary transmission of a resistant organism. A recent study from India documented

INH resistance in 12.6 percent and MDR-TB in 4 percent of culture positive pediatric cases; similar to drug resistance rate in adult population in the area.⁸ Similar experience has been reported from Western Cape province of South Africa as well as Peru.^{9–11}

XDR-TB is far more difficult to evaluate as drug susceptibility testing against second line drugs is unavailable in most resource limited settings. However, XDR-TB is widespread with 58 mainly low burden countries reporting at least one case.⁶ There appears to be high proportion of XDR-TB cases among MDR-TB cases in countries such as Japan, Korea and countries of former Soviet Union. A review of South Africa's laboratory database found that 5.6 percent of MDR-TB cases were XDR-TB. In India, second line testing of MDR-TB isolates in Gujarat showed 4 percent XDR-TB among MDR-TB cases detected in the smear-positive retreatment adult cases.⁶

RISK FACTORS FOR DRUG RESISTANCE

The clinician has few tools with which to gauge drug resistance when evaluating a child presenting with symptoms of TB and the only definite way of diagnosing drug resistance is by isolating *M. tuberculosis* from sputum or tissues and assessing its susceptibility pattern. However, several studies have identified risk factors, such as: residence in regions with known high MDR/XDR-TB prevalence, contact with a case of drug resistant TB or if the contact has been on irregular treatment and continues to be sputum positive or died after irregular treatment, presence of a comorbidity like HIV/AIDS/other immunocompromised state, previous TB therapy-especially within the past year, relapse after previous successful treatment, nonadherence to treatment, and if the child shows initial improvement on anti-TB treatment and then deteriorates.

MECHANISM AND CAUSES OF DRUG RESISTANCE

Spontaneous mutations in the genome of *M. tuberculosis* at predictable rates for each antituberculosis drug (e.g. isoniazid 10^{-6} , rifampicin 10^{-8}) and not a horizontal gene transfer lead to development of resistance to antituberculosis drugs.^{12,13} Thus, in patients with active tuberculosis subpopulations of resistant mycobacteria arise spontaneously and can emerge as the dominant strain in the presence of drug selection pressure. For example, INH monotherapy selects INH resistant mutants and allows them to multiply. Resistance to additional tuberculosis drugs can be added in a stepwise manner to create polyresistant strains. This is the process of acquired resistance and is the rationale behind not adding a single drug to a failing regimen. However, for patients not responding to first line tuberculosis treatment in high burden settings, current practice is to replace standard first line treatment with an extended regimen that adds streptomycin as the only

additional drug (Category 2 regimen) without doing any drug susceptibility testing due to lack of resources. While this practice has worked in most parts of our country but it has led to acquisition of further drug resistance especially in areas with high level of drug resistance to first line drugs as in east European region.^{14,15}

Once created, drug resistant strains can be transmitted giving rise to drug resistant tuberculosis in individuals never previously exposed to antituberculosis drugs (primary or transmitted resistance). Thus, the global epidemic of drug resistant tuberculosis is due to a combination of acquired and primary resistance.

Drug resistant tuberculosis is essentially a man made problem and its causes are multifactorial. Poor functioning national tuberculosis programs, unnecessary administrative control on purchase and distribution of drugs with no proper mechanism on quality control; inappropriate drug combinations/fixed dose combination, poor storage condition of drugs; lack of knowledge of physicians regarding dosage, duration of treatment, standard regimens and frequent change of brand names; use of anti-TB drugs (antibiotics) for indications other than TB; noncompliant patients due to monetary problems, lack of information, side effect of drugs and social myths and misconceptions; the epidemic of HIV infection; lab delays in identification and susceptibility testing of *M. tuberculosis* isolates; improper infection control measures all are contributory.¹⁶

CLINICAL FEATURES

The spectrum of disease caused by multidrug resistant bacilli is not any different from that caused by drug sensitive bacilli. Children and adolescents with drug resistant tuberculosis tend to have features of primary tuberculosis as hilar and/or mediastinal lymphadenopathy, segmental lesions or pleural involvement. The incidence of extrapulmonary tuberculosis appears to be similar among drug sensitive and resistant infections. Thus, it may not be possible to differentiate between the two on the basis of clinical and radiological features.^{11,17-19} Though in three of these studies^{11,17,19} around one-third to one-half of patients had cavitory disease on chest X-ray and a very high proportion were smear/culture positive (44–94%), the authors had concluded that this was probably due to delay in starting appropriate treatment and advanced stage of disease. Furthermore, the patients who acquire MDR-TB due to noncompliance with antituberculous therapy often have cavitory consolidations (50%) and generally demonstrate a postprimary radiographic pattern. Nevertheless, approximately one-third of adult patients in one of the study did not show the “expected” radiographic pattern. The adult patients who developed primary MDR-TB during an outbreak showed noncavitory consolidations, pleural effusions, and a primary radiographic pattern (70%).²⁰

A high index of suspicion is therefore required to diagnose drug resistant tuberculosis early and the presence of risk factors as mentioned in the earlier section should be sought in every case, especially history of contact with a known case of multidrug resistant tuberculosis. In such cases the drug susceptibility tests (rapid tests if possible) should be ordered and results obtained at the earliest for starting appropriate treatment thus avoiding delay and its serious consequences.

This process is not only very time consuming but also has limitation as the AFB isolation rates among children with active pulmonary tuberculosis is low (25–50%) even in most well equipped centers. Yet when there is a possibility of drug-resistant disease, the bacillary isolation should be pursued aggressively. All attempts using early morning gastric aspirates, bronchoalveolar lavage, and/or tissue diagnosis (FNAC or open biopsy) should be made to isolate the bacilli as this not only is the surest method of identifying drug resistant cases also the information derived from isolates can guide selection of appropriate therapy. Drug resistant tuberculosis ultimately is a laboratory diagnosis.

However, sometimes it may be difficult to have access to correct body specimen or the facilities for mycobacterial isolation and sensitivity may not be there. In such situations, the diagnosis is sometimes based on certain indirect clues. History of prior antitubercular therapy with persistent AFB positivity even after months of treatment is used as proxy indicator to suggest that the patient by now may be harboring resistant bacteria. This may be true for the patients with multibacillary disease but it cannot be said with certainty without drug sensitivity in all cases.

Certain peculiarities of tuberculosis disease further tend to confound the diagnosis of drug resistance, if this is inferred solely from clinical and/or radiological failure to treatment as persistent symptoms are a poor proxy for activity. Intercurrent pneumonia can cause a radiological as well as clinical deterioration in patients with tuberculosis. The persistence of clinical symptoms like cough and sputum production can also be due to post-tubercular sequel like bronchiectasis and bronchial hyper-reactivity. The resolution of radiological findings can be delayed for months after a successful therapy and chest skiagrams can sometimes show progression in the absence of a bacillary failure.²¹ Tuberculomas of brain are known to increase in size and number despite successful therapy in a proportion of cases. About 15 to 20 percent of the patients with susceptible organisms continue to have lymph nodes of considerable size even after successful completion of therapy. In some cases these may fluctuate intermittently. Thus clinical definition has limitation in application. Demonstration or isolation of AFB is the only sure way to differentiate such situations from a true failure. Suffice to say that the diagnosis of drug resistant tuberculosis in

the absence of demonstration of AFB may be more often untenable than correct.

For places where the facilities for reliable susceptibility testing may not be available, WHO has given certain clinical criteria to suspect drug resistance based on failure of therapy. The definition of failure of the WHO retreatment regimen (category II) is a tuberculosis patient excreting bacilli either after 5 months of chemotherapy given under direct observation. Some later studies suggest that most of the patients who respond to retreatment regime do so within first 3 months and therefore suggest that persistent positivity after 3 month of treatment with a supervised five drug regime should alarm for a change in treatment to second line drugs.²² For the patients who have received more than two courses of chemotherapy, the WHO suggests the term—chronic patients. Chronic patients are usually, but not always, excretors of resistant bacilli and often excretors of multidrug resistant bacilli.

DIAGNOSIS

In today's era of drug resistant tuberculosis, early and timely identification of drug resistance is one of the core needs for tuberculosis control. As treatment of MDR/XDR TB is expensive, longer lasting, much less effective and carries more risk of adverse events compared to treatment of drug susceptible TB, it is crucial that drug resistant TB is detected and treated as soon as possible to control further spread. Globally smear microscopy has been the cornerstone of tuberculosis diagnosis but with growing threat of drug resistant TB efforts are on to develop newer rapid diagnostic tools for establishing drug resistance.

Diagnosis of drug resistant tuberculosis relies on establishment of drug susceptibility of *M. tuberculosis* which is assessed either phenotypically (culture growth in the presence of drug) or genotypically (identification of resistance conferring mutations). Various tests for diagnosis of drug resistance (either well established or available though role not well established or experimental) are detailed below:²³⁻²⁵

- Microscopy (vital staining) to predict drug resistance: Vital staining with fluorescein diacetate (FDA) and fluorescence microscopy can determine the viability of *M. tuberculosis*. FDA is hydrolyzed intracellularly and fluorescein, which rapidly accumulates, is detected under ultraviolet (UV) illumination. Serial sputum examination can be used to follow the response of a patient to treatment; persistent *M. tuberculosis* viability may predict treatment failure due-to-drug resistance.
- Conventional indirect drug susceptibility testing: Conventional methods for detection of MDR-TB involve primary culture of specimens and isolation of *M. tuberculosis* (MTB), followed by drug susceptibility testing (DST). This process, referred to as indirect susceptibility testing has a long turnaround time (TAT) of around 6 to 8 weeks.

- Automated liquid culture platforms: Radiometric liquid culture system (Bactec460 automated liquid culture system)—Radioactive palmitic acid in $^7\text{H}_{12}$ media is taken up by growing mycobacteria; $^{14}\text{CO}_2$ is released as a metabolic by-product and measured. It is widely used and regarded as the first and second-line DST reference standard.

Nonradiometric platforms have superseded Bactec460 over the past decade, including Bactec MGIT960, MB Redox, BacT/Alert3D and the VersaTrek. Automated mycobacteria growth indicator tube (MGIT) detects *M. tuberculosis* growth using a nonradiometric ruthenium salt colorimetric method in which the unquenched salt fluoresces under UV light as oxygen in the tube is consumed by tuberculosis growth.

Even though liquid-based indirect susceptibility tests have improved the TAT (2-3 weeks), they are still not rapid enough to allow timely decisions on patient management in case of MDR TB. More rapid TB susceptibility tests are needed, particularly in TB high burden countries. Recently, the focus has shifted to rapid direct tests in which decontaminated respiratory samples are directly inoculated in drug-free and drug-containing medium or amplified for detection of MDR TB.

- Thin layer agar for tuberculosis detection: Detection of *M. tuberculosis* microcolonies on selective thin layer $^7\text{H}_{12}$ agar (TLA) compares favorably with Lowenstein-Jensen media and time to detection is significantly shorter at 7 to 11 days. TLA is one of the cheapest diagnostic tests available, and use of a conventional microscope facilitates implementation in low-resourced settings. Drawbacks include the training required to recognize colony formation and the lack of performance data supporting TLA use for direct DST.
- Microscopic observation drug susceptibility assay: Microscopic observation drug susceptibility assay (MODS) depends upon observation of characteristic cord formation of *M. tuberculosis* in liquid media (Middlebrook $^7\text{H}_9$ broth). The “cording” growth appearance of MTB in liquid medium is characteristic, preventing confusion bacteria or fungi. *M. avium-intracellulare* complex and *M. kansasii* are readily differentiated from MTB using MODS on the basis of their characteristic noncorded appearance. It is one of the cheapest diagnostics available. Principal limitations are the need for an inverted microscope and training to recognize cord formation.
- Colorimetric redox indicator assay: Colorimetric methods are low-tech, low-cost methods which make use of an oxidation-reduction indicator that changes color in response to the metabolic products associated with *M. tuberculosis* growth. When isolates are cultured in a range of concentrations of anti-TB drugs, an MIC may be determined by noting at what concentration color change is inhibited.

- Nitrate reductase assay (NRA or Griess assay): KNO_3 incorporated into conventional LJ media is a significant advantage as laboratories already doing LJ should be able to move to the NRA relatively easily. Nitrate in LJ media is reduced to nitrite by MTB growth and is detected by addition of a colorimetric reagent after 28 days. Currently, its use is limited to smear-positive sputa and for first line drugs only.
- Genotypic testing: The validity of genotypic testing hinges on the observation that 90 to 95 percent of isolates phenotypically resistant to isoniazid or rifampicin demonstrate common resistance mutations. Theoretically, it is possible for laboratories to detect such resistance in over 90 percent of isolates within 2 days. Line probe assays (LiPAs) use multiplex polymerase chain reaction (PCR) amplification and reverse hybridization to identify *M. tuberculosis* complex and mutations to genes associated with rifampicin and isoniazid resistance. The genotype MTBDR plus assay detects rifampicin and isoniazid resistance; MTBDRsl detects resistance to fluoroquinolones, aminoglycosides, capreomycin and ethambutol. Recently, the World Health Organization (WHO) recommended the use of molecular line probe assays (LPAs) for rapid screening of MDR-TB in low and middle income settings. Frequent barriers to use of molecular tools include specimen processing and DNA extraction. The GeneXpert[®] assay is a promising technology that automates the process completely requiring little input from laboratory workers and modest infrastructure making it more accessible to resource limited settings. It has very good specificity and its sensitivity can be improved by multiple sampling. This innovative tool packs real time PCR technology into a cartridge as a point of care test and the results from a direct specimen can be got in a matter of hours.²⁶

While every effort should be made to establish a bacteriological diagnosis (and obtain DST) in a child with suspected MDR-TB, in practice pediatric cases may not always be confirmed bacteriologically.

Symptomatic pediatric household contacts should receive an evaluation by a physician, including history and physical examination and then be investigated for TB. Tuberculin skin testing with purified protein derivative (PPD), chest X-ray examination, sputum/gastric aspirate smear—culture and DST. Every effort should be made to establish a bacteriological diagnosis (and obtain DST) in a child with suspected DR-TB. Bacteriological confirmation may include more aggressive measures such as induced sputum, gastric aspirate, lymph node aspirate or other relevant sample, plus culture and DST. Human immunodeficiency virus (HIV) counseling and testing (in areas of high HIV prevalence or if parent(s) are known, or suspected to be, HIV-infected) should also be done. When the tuberculin (PPD) skin test result is >5 mm but the

chest radiograph and gastric aspirate or sputum smear are negative, the symptomatic child can be treated with a broad-spectrum antibiotic that is not active against TB. The child should be followed closely, with evaluations including smear test and culture on samples from induced sputum or gastric aspirates, or sputum samples whenever possible, as well as chest X-rays. The optimal frequency of these evaluations has not yet been determined.

MANAGEMENT

Typically, the clinician faces two types of cases for management as MDR tuberculosis namely (a) those diagnosed with microbiologically confirmed or (b) presumed MDR-TB. Confirmed disease occurs when an organism is isolated from the child and is shown to be either genotypically or phenotypically resistant to isoniazid and rifampicin. Presumed disease occurs when TB is diagnosed in combination with either known contact with an MDR-TB source case or after the failure of appropriate first-line therapy where adherence has been verified.

When confirmed, the treatment should be tailored to the drug susceptibility test (DST) pattern of the child's strain. When diagnosed presumptively, treatment should be directed by the DST of the source case, where available. If no DST is available, and the child's clinical condition is highly suggestive of TB, or progressively deteriorates and (s)he has been a close contact of a known MDR infectious case, empirical therapy designed according to the DST pattern of the strain from the index case can be started. Children with MDR-TB who are incorrectly treated with usual short-course chemotherapy (SCC) may suffer significant and protracted morbidity as a result of ongoing active disease, with the possibility of lifelong disability or even death.

Uncertainties surrounding the activity and safety of the available drugs make the treatment of MDR-TB in children particularly challenging. The second-line drugs are not only expensive but are also rarely available as pediatric formulations or appropriate tablet sizes, necessitating breaking, splitting, crushing or grinding. This can lead to dosing errors, inaccuracies leading to a possibility of sub-therapeutic or toxic levels. The taste of the medications is often unpalatable. A number of the drugs cause vomiting and diarrhea which may affect the amount absorbed and causes further uncertainty about the dosing. The daily pill burden can be vast as the child may require multiple TB medications, ART, other antibiotics as well as supplements of vitamins and calories.

Although management of MDR/XDR-TB is difficult, proper use of existing technologies and management strategies can make it fruitful. Further, no randomized control trials are available to guide optimum treatment strategies for MDR/XDR-TB though observational studies have shown effectiveness of treatment if properly planned and

tailored. Treatment success rates as high as 83 percent for MDR TB and 60 percent for XDR-TB have been reported in adults in the absence of HIV infection.^{27,28} However, outcomes are substantially worsened with HIV coinfection. Treatment outcome for children with drug resistant tuberculosis are based on case reports and cohort studies.^{17,29-31} In one study, cure rates of 95 percent were documented in 38 children in Peru, showing that drug resistant tuberculosis in children can be managed effectively, even in resource limited settings.¹¹ The choice of drugs largely depends on results of DST or standardized regimens based on knowledge of the DST profile of the specific geographic region.

Despite scarcity of evidence, some guiding principles have been developed for treatment of MDR/XDR-TB, based on expert consensus and data from observational studies.¹⁸

- Regimens should be based on the history of drugs taken by the patient and the prevalence of resistance to first-line and second-line drugs in the area.
- In the treatment of MDR-TB any first-line drugs to which the organism is still susceptible are used.
- Regimens should consist of at least four drugs with either certain, or almost certain, effectiveness. If the evidence about the effectiveness of a drug is unclear, the drug can be included in the regimen but it should not be depended upon for success. Often, more than four drugs may be started if the susceptibility pattern is unknown, if effectiveness is questionable for an agent or if extensive, bilateral pulmonary disease is present.
- Drugs are administered at least six days a week. When possible, pyrazinamide, ethambutol and fluoroquinolones should be given once per day because the high serum levels attained in once-a-day dosing may be more efficacious. Once-a-day dosing is permitted for other second-line drugs, depending on patient tolerance. PAS should be given in two split doses during the day as it has no postantibiotic effect. Intermittent therapy with the injectable agent (three times weekly after an initial period of 2 to 3 months of daily therapy) can be considered for patients in whom the injectable agent has been used for a prolonged period and when the risk of toxicity increases.
- The drug dosage should be determined by body weight.
- An injectable agent (an aminoglycoside or capreomycin) is used for a minimum of 6 months and at least four months after the patient first becomes and remains sputum smear or culture negative.
- Treatment is for a minimum duration of 18 months beyond conversion, particularly in cases with extensive lung involvement, severe forms of extrapulmonary disease or disseminated (meningitis or miliary TB) disease. However in children with paucibacillary disease, shorter duration of treatment (12 months) may be sufficient for early, nonextensive disease.

- If a patient fails to get bacillary quiescence (culture negative) by 6 months of therapy then the probability of success of the current regime is very poor. Because XDR TB is still quite a new phenomenon, data on treatment duration required for cure are limited.
- Adherence can be challenging in children either too young to understand or not old enough to cooperate or those with improper or sick caregivers. Treatment for MDR-TB in children should therefore always be given under directly observed therapy (DOT) but in reality, in many settings, responsibility is often given to the caregiver who is given a week or a month's supply of drugs. Each dose should preferably be given as DOT throughout the treatment.
- DST, when available and from a reliable laboratory, can be used to guide therapy. Regimens should include at least four drugs that are highly likely to be susceptible, based on DST and/or the drug history of the patient.
- Pyrazinamide can be used for the entire treatment if it is judged to be effective. Many MDR-TB patients have chronically inflamed lungs, which theoretically produce the acidic environment in which pyrazinamide is active.
- If pulmonary disease is sufficiently localized and residual lung function is adequate, resective surgery should be considered as an adjunct to chemotherapy.

Classes of antituberculosis drugs available for treatment of a drug resistant case:

Antituberculosis drugs have traditionally been divided into first and second-line drugs, with isoniazid, rifampicin, pyrazinamide, ethambutol and streptomycin being the primary first-line drugs. A group system based on efficacy, experience of use and drug class is also being used for ease of design of treatment regimens.

Group 1: (First-line oral antituberculosis drugs—Isoniazid, Rifampicin, Ethambutol, Pyrazinamide)—Most potent and best tolerated antituberculosis drugs but should be used only where there is laboratory evidence or clinical history to suggest their efficacy.

Group 2: (Injectable antituberculosis agents—Streptomycin, Kanamycin, Amikacin, Capreomycin, Viomycin)—A Group 2 injectable agent should be given to all patients in whom susceptibility is documented or suspected. If the strain is susceptible, streptomycin is the usual agent of choice. Kanamycin or amikacin is the logical second choice and have close to 100 percent cross resistance. The ease of pediatric formulation may make Amikacin a more attractive choice as compared to Kanamycin where no pediatric formulations are available leading to wastage and unnecessary expense.

Group 3: (Fluoroquinolones—Ciprofloxacin, Ofloxacin, Levofloxacin, Moxifloxacin, Gatifloxacin)—A group 3 drug should be used if the strain is susceptible. Currently, the most potent available fluoroquinolones in descending

order based on *in vitro* activity and animal studies are: moxifloxacin = gatifloxacin > levofloxacin > ofloxacin = ciprofloxacin.³²

Group 4: (Oral bacteriostatic second-line antituberculosis drugs—Ethionamide, Prothionamide, Cycloserine, Terizidone, *P*-aminosalicylic acid, Thioacetazone)—Group 4 drugs are added on the basis of estimated susceptibility, drug history, efficacy, adverse effects profile and cost. If only one of these agents is needed, ethionamide/prothionamide is often added because of its proven efficacy and low cost. If cost is not a constraint, PAS may be added first because the enteric-coated formulas are relatively well tolerated. If two agents are needed, cycloserine is commonly used in conjunction with ethionamide/prothionamide or PAS. Since the combination of ethionamide/prothionamide and PAS has a high incidence of gastrointestinal adverse effects, these two agents are commonly used together only when all three group 4 agents are needed. Terizidone contains two molecules of cycloserine and can be used instead of cycloserine because its efficacy is assumed to be similar but has less side effects. The use of thioacetazone is limited by the development of rashes that are more prevalent in HIV-positive individuals and can result in Stevens-Johnson syndrome and death.

Group 5: (Clofazimine, Amoxicillin/Clavulanate, Clarithromycin, Linezolid). The group 5 drugs are not recommended by WHO for routine use in MDR-TB treatment because of uncertain efficacy. However, they can be used in cases where adequate regimens are impossible to form with the medicines from other four groups.

Monitoring Therapy

Patients should be monitored (clinical monitoring supplemented with objective laboratory evaluation) closely for signs of treatment failure and adverse effect of drugs. A pediatrician should examine the child monthly till bacillary conversion and 2 to 3 monthly thereafter. DOT worker should screen the patient regularly for adverse events—rashes, gastrointestinal symptoms, psychiatric symptoms (psychosis, depression, anxiety, suicidal tendencies), jaundice, ototoxicity, peripheral neuropathy and symptoms of electrolyte wasting (muscle cramps, palpitations). At each visit to the pediatrician, height and weight of child should be measured and enquiry made regarding symptomatology. A normal growth rate should resume after few months of successful treatment. Lab tests to be done at baseline include sputum smear and culture along with DST, chest X-ray, complete blood count (CBC), renal function test (RFT), liver function test (LFT), electrolytes, Thyroid function test, HIV screening. Sputum smear and culture should be done monthly till smear and culture conversion (conversion is defined as two consecutive negative smear and culture taken 30 days apart). After conversion, smears should be done monthly and culture at least quarterly. For patients who remain smear and culture

positive during treatment, DST can be repeated but not earlier than three months as sputum conversion is slower in MDR-TB than drug susceptible TB. Chest X-ray should be done six monthly or earlier if there is clinical worsening or surgery is being planned. RFT and electrolytes monitoring should be monthly till patient is on injectable drugs. LFT should be done 3 to 6 monthly and CBC 6 to 12 monthly. In addition, TSH should be monitored 6 monthly if patient is on ethionamide/prothionamide and/or PAS.¹⁸

CHEMOPROPHYLAXIS

Though the role of chemoprophylaxis in children exposed to drug susceptible TB is well established, little information is available regarding optimal chemoprophylaxis for children with MDR-TB contacts. Current WHO guidelines recommend close follow-up of contacts of patients with MDR TB for a period of two years and prompt initiation of treatment with a regimen to treat MDR TB if active disease develops.¹⁶ Use of second line drugs for routine chemoprophylaxis of MDR-TB contacts is not recommended despite ineffectiveness of INH and rifampicin in this setting. In 2005, the CDC published guidelines proposing 2 years of clinical follow-up and individual decision-making about appropriate LTBI treatment.³³ A Cochrane review in 2006, found no randomized control studies assessing the efficacy of treating latent tuberculosis infection in people exposed to MDR-TB.³⁴ A prospective cohort study of childhood contacts of MDR-TB cases in the Western Cape included 105 contacts without active disease at study entry who were followed-up for 30 months. Forty-one received chemoprophylaxis tailored to the susceptibility profile of the index case. Of the 41 children who received chemoprophylaxis, 68 percent were infected (defined as Mantoux test ≥ 15 mm induration) at baseline, as were 52 percent of the untreated contacts. Active disease resulted in only 5 percent of contacts who received chemoprophylaxis and in 20 percent of contacts who did not. This suggests that a chemoprophylactic regimen customized to the susceptibility pattern of the adult contact's isolate may be effective in preventing disease.³⁵ Kritski et al conducted a retrospective cohort study of household contacts of drug resistant TB cases. Among infected contacts (defined as Mantoux test ≥ 10 mm induration), active disease developed in 4 percent of treated contacts compared with 9 percent who did not receive INH. Although the study results were not statistically significant, the trend was toward a lower incidence of TB disease with INH chemoprophylaxis.³⁶

In TB endemic areas, exposure to multiple source cases, both drug-susceptible and drug-resistant TB, is not uncommon. Some clinicians therefore prefer a 3-drug combination of high-dose (15-20 mg/kg) isoniazid and two drugs to which the source case's isolate is susceptible or naïve, usually a fluoroquinolone (ofloxacin) and ethambutol (or ethionamide).³⁷

More studies are needed to identify the right agent and to support use of chemoprophylaxis in MDR contacts.

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Childhood Tuberculosis: Newer Diagnostic Tools

Renu Dutta

Tuberculosis is prevalent in one-third of world's population and from this reservoir 8 million new cases of tuberculosis develop worldwide each year that carry a death toll of 3 million. Ninety-five percent of the 8 million newly infected cases occur in developing countries and 75% of these are in the age group of 15 to 50 years. Ninety-eight percent of TB deaths are in developing countries (WHO). A direct consequence of increasing number of adults with tuberculosis is an increase in childhood tuberculosis. Neonatal BCG immunization has had little effect in preventing childhood tuberculosis in developing countries. Infants and young children (less than 5 years, commonest age being 1-4 years) are at particular risk for infection and disease.

The most common presentation in childhood tuberculosis is smear negative pulmonary tuberculosis (PTB), as cavitating TB is infrequent in children. The next most common type is extrapulmonary tuberculosis (EPTB), which includes miliary tuberculosis and tuberculous meningitis (usually in children <3 years of age); tuberculous lymphadenopathy (all ages); tuberculous effusions (pleural, pericardial and peritoneal) and spinal tuberculosis (often school-aged children). Smear positive PTB is usually diagnosed in children older than 6 years. The prevalence of PTB is normally low between 5 and 12 years and then increases in adolescents, which is like adult PTB, often with cavitation.

Thus, rapid and accurate diagnosis of symptomatic patients is a cornerstone of global tuberculosis control strategies. Early confirmation of diagnosis of tuberculosis is a challenging problem, especially in case of paucibacillary and extrapulmonary tuberculosis and even pulmonary tuberculosis in the pediatric population. The quotation by Carl Sagan "Absence of evidence is not evidence of absence", aptly defines the current scenario of tuberculosis.

The mycobacteriology diagnostic services have been remarkably upgraded during last two decades in terms of

speed and quality, especially in the developed countries. But in disease endemic countries these gains are still unrealized thus leaving many patients still undiagnosed.

The role of microbiology laboratory is to confirm the diagnosis of clinically suspected case of tuberculosis by:

- Detection and isolation of *Mycobacterium*
- Identification of species of the isolate
- Antibiotic susceptibility testing of isolate.

COLLECTION AND TRANSPORT OF SPECIMENS

Pulmonary Tuberculosis

Gastric Lavage: A 5-10 ml fluid to be collected in infants and young children, on 3 consecutive days. Fasting, early morning specimens are recommended to obtain sputum swallowed during sleep. A 20 to 30 ml of warm sterile saline should be pushed with a sterile syringe attached to nasogastric tube passed into the stomach. This fluid should be aspirated back into syringe and transferred to a sterile container from the syringe. The pH of this lavage fluid should be adjusted to neutral with 100 mg sodium carbonate or (10%) immediately following collection or maximum within 4 hours. This may be provided by the laboratory in container. Un-neutralized specimens are not acceptable as acid is detrimental to mycobacteria.

BAL: 5 ml of BAL to be sent. Material obtained on bronchial brushings should be placed in sterile tube containing 10 ml of MB7H9 broth, 1-2% BSA and Tween 80.

Sputum: Clean, sterile, wax free wide mouth container should be used.

Transtracheal aspirate: Rarely.

Fine needed aspiration material: Rarely.

Open lung biopsy: It may be obtained in difficult cases.

EPTB

Body fluids: Cerebrospinal fluid (CSF), pleural peritoneal, pericardial fluids. Ideally 10-15 ml of fluids should be sent. Small volume fluids may be directly inoculated into liquid culture medium bottles. For CSF, at least 1-2 ml of CSF should be sent. Bloody specimens should be anticoagulated with sodium polyanethol sulfonate (SPS).

Tissues: Approximately one gram of biopsy material from lymph node, skin or other sites without fixative/ preservatives should be sent in a sterile container. Neither saline or any other fluid should be added, nor should it be wrapped in gauze piece.

Abscess: Aspirated, small volume material may be transported in MB7H9 broth.

Urine: Preferably complete first morning voiding of urine should be sent on 3 consecutive days to laboratory but at least 40 ml must be sent. It may be collected by clean catch technique, or by catheterization or suprapubic tap. A 24 hour pooled urine, or urine collected from catheter bag or volume less than 40 ml are not acceptable.

Blood: To be collected in immunocompromised (e.g. AIDS) patients with disseminated tuberculosis. For its collection, Isolator Lysis centrifugation system or Radiometric BACTEC 13A blood culture bottle is recommended. Heparin or SPS may be added as anticoagulant, if it needs to be transported before inoculation into systems mentioned above. Coagulated blood or blood with EDTA is not acceptable.

Stool: More than one gram should be collected, in sterile wax free, disposable container. Its processing is recommended only for detection of MAC involvement in gastrointestinal tract of patients with AIDS.

GENERAL PRECAUTIONS TO BE OBSERVED FOR COLLECTION OF SPECIMENS

- Containers should be sterile, leak proof, disposable and properly labeled
- Waxed containers should be used as they may give false positive results
- Contamination with tap water and other fluids should be avoided as they may carry viable/nonviable environmental mycobacteria or indigenous flora
- Swabs are not recommended for isolation
- No fixatives or preservatives should be added
- The specimens should be transported to laboratory in as short time as possible to avoid overgrowth by contaminating bacteria and fungi. If delay of more than one hour is expected, then refrigerate the specimen (except blood). Once received in lab, refrigerate until processing.

DETECTION AND ISOLATION OF MYCOBACTERIUM**Microscopy**

Although relatively insensitive (46-78%), the ZN stain retains its primary role in case detection, as it is inexpensive to perform and is very specific in high prevalence settings. It detects the most infectious subsets of patients. Smear microscopy requires at least 10,000 bacteria/ ml of sputum. The time to examine a specimen by microscopy was shortened with the introduction of fluorescent microscopy and staining with auramine-phenol.

Proficiently performed microscopy can detect AFBs in 60 to 70 percent of culture positive respiratory specimens. Microscopy on material from solid and often liquid cultures can be used to make a presumptive diagnosis of TB, although it is not possible to distinguish between *M. tuberculosis* and Non-tuberculous Mycobacteria (NTM) in clinical specimens. However, a more accurate method is needed for identification at the species level.

The ability, simultaneously to assess the smear status and distinguish between *M. tuberculosis* and NTM in respiratory specimens, has important implications for patient treatment and hospital infection control. A potential advance in microscopy that might facilitate this is the use of peptide nucleic acids (PNAs) in a fluorescent stain format. Peptide nucleic acids (PNAs) are DNA like molecules, in which the sugar phosphate backbone is replaced with a peptide like structure. The binding of PNA to DNA or RNA is sequence specific and the interaction is stronger than that of a DNA-DNA interaction. Because of their hydrophobic nature, PNAs can pass more easily across cell walls, and with suitable treatment can bind to specific intracellular nucleic acid sequences. Labeling the PNA with a fluorescent dye enables visualization with a suitable microscope. Peptide nucleic acids (PNAs) specific for *M. tuberculosis* complex and NTM have been formulated and tested against a panel of cultured mycobacterial species with some success.

ISOLATION OF MYCOBACTERIA IN CULTURE

Traditional culture is performed on solid and liquid media such as Lowenstein- Jensen, or Kirchner or the various Middle Brook formulations (7H9, 7H10, 7H11). Accurate identification of *M. tuberculosis* through culture is presently the yardstick for diagnosis, but the time required (6-8 weeks) and frequent negative results in paucibacillary specimens are important limitations. During the last two decades, several methods for achieving early growth of *M. tuberculosis* have been developed. These are automated or semiautomated liquid culture systems, that can detect growth much earlier than the naked eye. They may be either radiometric or nonradiometric systems.

Radiometric Liquid Culture System

In recognition of their superior speed and sensitivity, these have been in common use in level III mycobacteriology laboratories. The first such system to be used in the laboratory was BACTEC 460 TB instrument. Developed by BD, it uses a broth with radio-labeled ^{14}C -Palmitate as its sole carbon source; the metabolizing organism converts it to radio-labeled $^{14}\text{CO}_2$ which can be detected by BACTEC instrument within 5 to 10 days. Addition of NAP (p-nitro-alpha-acetylamino-beta-hydroxypropylphenone) helps in distinguishing *M. tuberculosis* (inhibited) from other mycobacteria. It can detect 10 to 100 organisms/ml of specimen.

Nonradiometric Liquid Culture Systems

New systems that rely on nonradioactive means for detection of growth in liquid media, have been developed commercially. These are:

MB/BacT (Organon Teknika): Fully automated system, adapted from strategy of colorimetric detection, earlier tried for detection of growth in blood cultures.

MGIT (Mycobacterial Growth Indicator Tube, BD): Growth is detected by using Fluorochromes which leads to increased O_2 consumption, visualized as bright orange color at the bottom of tube. The system helps in early detection of growth (7-12 days) and is reported to be useful but experience is limited.

Septichek (Roche): This is a biphasic medium consisting of enriched selective broth and a three sided paddle carrying solid media- Middle Brook Agar, NAP and egg containing medium and chocolate agar. Found to be useful for rapid growth of Mycobacteria.

BACTEC 9000 MB (BD): It monitors O_2 consumption by fluorescent sensor and utilizes modified MB7H9 medium.

Phage based assays (Biotec/ Mediaspan): These use mycobacteriophages to infect live *M. tuberculosis* bacilli which are detected by using one of the two methods—either as

plaques on a lawn of mycobacteria or by detection of light (using luminometry or photographic films) produced by luciferase reporter phages (LRP), after their infection of live *M. tuberculosis*. These are phages with firefly luciferase genes inserted within their genome. In general phage assays have a turn around time of 48 hours and require a lab infrastructure similar to that needed for performing mycobacterial cultures. Phage based assays are available commercially as kits, FAST plaque –TB (Biotec labs Ltd Ipswich UK) and phage TEK-MB and as in house assays. (i.e. lab developed) They have high specificity (83-100%) but modest and variable sensitivity (21-88%) as reported by 13 studies. Overall accuracy is slightly higher than smear microscopy.

Many studies have compared the performance of the different culture systems available. The BACTEC 460 TB remains the fastest and the most sensitive, followed by continuous automated nonradiometric liquid culture systems, with the solid media systems being the slowest. The cost of these commercial systems is considered too high for most Disease Endemic Countries health systems. The average duration required for recovery of mycobacteria from automated/ semi-automated culture systems, is on an average 10 to 15 days, as compared to 25 to 30 days on solid media in sputum smear positive cases. In sputum smear negative cases, the recovery rate is slightly more, i.e. 15 to 20 days in automated/semiautomated systems, whereas the duration of recovery is same on solid media in these cases. The recovery rates of *M. tuberculosis* in various culture systems are summarized in Table 1 and their mean detection time Table 2.

RAPID IDENTIFICATION OF MYCOBACTERIAL SPECIES OF THE CULTURED ISOLATES (TABLE 3)

DNA probes: *Accuprobe (Gen Probe USA):* It includes test for identification of *M. tuberculosis complex* (MAC), *M. avium*, *M. intracellulare*, *M. kansasii* and *M. goodii* using DNA probe complementary to rRNA sequences of these mycobacteria. It is in-solution assay and uses the

Table 1: Recovery rates of mycobacteria in different culture systems

Culture system	Recovery rate (%)			
	Overall	<i>M. tuberculosis</i>	MAC	NTM
BACTEC 460 TB	86-95	90-100	71-94	76-85
MGIT	76-93	77-92	77-94	67.5
MB/BacT	89	96	86	–
Septichek	95	81.5-100	92	76.9
BACTEC 9000	75	84-97	–	60-80
Solid L-J	75-87	82-95	68.77	–
Stone brink	68-69	79-85	62-75	33-60

Table 2: Mean time detection in days of automated/semiautomated culture systems

<i>Mycobacteria</i>	<i>Smear</i>			
	<i>Positive cases</i>		<i>Negative cases</i>	
	<i>Rapid system</i>	<i>Solid media</i>	<i>Rapid system</i>	<i>Solid media</i>
<i>M.tuberculosis</i>	10-15 days	≥ 20 days	15-20 days	25-30 days
MAC	10 days	25 days	15-20 days	40 days
NTM	15-17 days	30-40 days	–	–

Table 3: Comparative sensitivity of DNA, rRNA targeting probes and gene amplification assays for *M. tuberculosis*

<i>Technique</i>	<i>Sensitivity</i>	<i>Application</i>
DNA targeting probes	10,000-100,000 copies	Identification of isolates
rRNA targeting probes	100-1,000 copies	Identification of isolates, limited application on clinical specimens
Gene amplification assay	1-10 copies	Directed application on clinical specimens. Identify isolates by PCR- RFLP/sequencing

principle of hybridization protection assay and chemiluminescent acridinium ester as the reporter molecule. It is highly specific but separate tests need to be performed for each species.

Deoxyribonucleic acid (DNA) probes when used along with newer methods of detection of early growth (e.g. BACTEC MB/BacT, Septichek, MGIT, etc.) are of great help in rapidly confirming the identity of isolates within 1 to 2 days.

Ribosomal RNA (rRNA) based probes: RNA gene region has been extensively explored for designing systems for ribosomal DNA fingerprinting, development of probes and gene amplifications assays for various mycobacterial species, i.e. *M. tuberculosis*, *M. leprae*, *M. avium*, etc. These probes target rRNA, ribosomal DNA, spacer and flanking sequences. Commercially available probes are reported to be useful for quick identification of mycobacterial isolates. Earlier radiolabeled and now chemiluminescent labeled probes are in use. These rRNA probes are 10-100 fold more sensitive than DNA targeting. Disadvantage is the high cost capital equipment which makes them beyond the reach of most clinical labs.

HPLC analysis of mycolic acid: Very costly.

Gene amplification methods for identification: Specific gene regions, e.g. *hsp 65 kDa* gene, *kat G* and rRNA genes are amplified, amplification is followed either by sequencing at reference lab or by hybridization with species specific probes and subsequently RFLP analysis, which is easily practicable in clinical mycobacteriology labs—PCR restriction enzyme assay (PRA); LiPA Mycobacteria.

An extension of the solid phase detection of nucleic acids has been developed using high density DNA Probe arrays on a glass “microchip”, the system is theoretically capable of simultaneous strain identification, typing and detection of

drug resistance alleles in cultured isolates. This system has been commercially developed but the cost of specialized analytical equipment is prohibitive.

RAPID METHODS OF DETECTING MYCOBACTERIA IN CLINICAL SPECIMENS

(By NAATs: Nucleic Acid Amplification Tests)

The need for the rapid methods, for detection in clinical specimens was felt due to slow growth of most pathogenic Mycobacteria. The best known method is PCR, first developed in 1989. They may target DNA or rRNA. The specificity of a well developed conventional DNA based PCR is high, but sensitivity is less than that of a culture and more than that of smear. It can be improved by using nested PCR or RT-PCR; but the best way to improve sensitivity is to use high quality specimens. Typically microscopy detects AFB in 60 to 70 percent of culture positive respiratory material. Amongst culture positive respiratory material, the sensitivity of a good quality PCR is 90 to 100 percent in smear positive and 60 to 70 percent in smear negative specimens. A positive PCR result using *M. tuberculosis* specific primers on a smear positive result would indicate that AFB's present were *M. tuberculosis*; where as a negative PCR would suggest an NTM; as long as controls were performed to eliminate the possibility of reaction inhibition by sample components. With a smear negative specimen, however, a negative PCR does not exclude the presence of *M.tuberculosis*.

The tests that have been evaluated in clinical laboratory include:

PCR based amplicor (Roche): Amplifies part of 16s rRNA gene followed by colorimetric detection of PCR product.

Transcription mediated amplification-amplified *M. tuberculosis* direct (AMTD, Gen Probe): Rather than using DNA as the target uses rRNA of *M. tuberculosis* which is more

abundant than the corresponding DNA, making it theoretically more sensitive than PCR. The rRNA is transcribed by a reverse transcriptase forming a transcription complex from which isothermal amplification of the target sequence is catalyzed by RNA polymerase. The amplicon is detected with acridinium ester labeled DNA probe. Reports are encouraging.

Strand displacement amplification, BD Probe Tec-SDA: An isothermal amplification technique based upon the ability of Hinc II to nick the unmodified strand of hemiphosphorothioate form of its recognition. It uses the exonuclease deficient klenow fragment of DNA polymerase I to amplify DNA products from a DNA template. Exponential amplification results from coupling sense and anti-sense reactions.

Ligase chain reaction (LCR) – (LCx, Abbott system): It utilizes heat stable enzyme DNA ligase, to unite two strands of DNA to combine as double strand. It is possible only if the ends are complimentary and are an exact match. Therefore, by this method it is possible to detect mismatch of nucleotide which can occur in a mutation.

Q beta (QB) replicase based gene amplification: It involves production of RNA in the amplification reaction using QB replicase as the enzyme and reaction at fixed temperature (e.g. 37°C). Using a combination of suitable capture and detector probes, sensitivity up to 1 CFU has been reported for *M. tuberculosis*. Further, the inhibitions of PCR were observed to have no effect on this assay.

Indian laboratories have been active in development of PCR methods for detection of *M. tuberculosis*. Separate gene targets have been used by Indian investigators like *MPB64*, Repetitive sequences, GC Repeats, *devR*, *38KD*, *TRC4*, *IS 1081*. Some of them repeatedly have been found to be reproducible, highly sensitive and specific in double blind evaluations. IS 1081 based system has been further modified and a new nested PCR target of this gene has been developed at center for DNA fingerprinting and diagnostics (CDFD) Hyderabad, Andhra Pradesh, India.

SENSITIVITY, SPECIFICITY, PPV AND NPV OF MOLECULAR DIAGNOSTIC TECHNIQUES

In general NAATs have been found to be highly sensitive and specific for diagnosis of TB directly from clinical specimens. Depending upon bacteriological and copy number of target sequence, sensitivity has ranged from 70 to 100 percent, whereas specificity between 90 and 100 percent has been reported. The PPV ranging between 95 and 100 percent and NPV between 90 to 99 percent has been observed.

FALSE POSITIVE AND FALSE NEGATIVE RESULTS

There has been a genuine concern of false positivity, due to contamination occurring in clinics and laboratories.

It can be reduced by proper lab design, strict discipline about collection and processing of specimens, handling of reagents and use of certain blocking reagents. The strategies used to reduce the false negative results are, use of immunomagnetic beads and capture resins in addition to proper sample collection, extraction and assay. These specimens may contain very small number of organisms and/or inhibitors.

To sum up key to reliable results from NAATs, is submission of a high quality specimen, appropriate infrastructure, staff training and quality control procedures.

APPLICATION OF GENE AMPLIFICATION (NAATS) ASSAYS IN CLINICAL SPECIMENS

Pulmonary cases: PCR tried in sputum, BAL and gastric lavage. It is found to be useful. Gastric lavage is very useful in childhood PTB. Sensitivity is 95 to 100 percent in smear/culture positive specimens whereas in smear negative paucibacillary it ranges from 40 to 60 percent.

Pleural effusion: PCR helpful in confirming >60 percent of specimens which are negative for mycobacterial culture by conventional techniques.

Lymph gland: Cervical TB and other lymph glands involvement is common form of childhood TB. Using PCR, positivity rates varying from 40 to 90 percent have been reported.

Cutaneous TB: Many varieties of clinical presentations are observed. Positivity observed in the range of 50 to 60 percent of cases. PCR also used in unfixed biopsies as well as paraffin embedded section.

Ocular TB and chronic iridocyclitis: Difficult to diagnose by conventional techniques. Diagnosis confirmed by PCR in 50 to 70 percent of cases using aqueous/vitreous fluid as specimens.

Bone, kidney and genital TB: Bacillary load in these specimens is usually low. PCR found to be useful in substantial number of cases.

Neurotuberculosis: PCR tried in CSF and biopsy specimens in TBM and tuberculoma of brain. As compared to 5 to 20 percent positivity with AFB stain/culture, PCR has been found to be positive in 50 to 70 percent of specimens from cases with cardinal features and biochemical/cytological evidence of neurotuberculosis.

RAPID METHODS FOR DETECTION OF DRUG RESISTANCE

Since the diagnosis is aimed to enable the application of an appropriate treatment regimen, accurate drug susceptibility testing is an intrinsic part of the diagnostic process. Rapid methods can be either phenotypic or genotypic. Currently, the only drug which is screened for resistance

mutations clinically is rifampicin, because most mutations are confined to a short section of the gene *rpo B* encoding the beta subunit of bacterial RNA polymerase. The InnoLiPA (Line Probe Assay) rifampicin TB assay and an RNA-RNA mismatch assay have been used simultaneously for the identification of *M. tuberculosis* and screening for rifampicin resistant mutations directly in smear positive respiratory specimens and cultured isolates. They correlate with standard methods of detection of *M. tuberculosis* and rifampicin susceptibility testing in 94.7 percent and 100 percent of smear positive respiratory specimens.

Rapid phenotypic methods include luciferase reporter phage assay (LRP) with high specificity (83-100%) but modest and variable sensitivity (21-88%). The commercially available kits are: FAST plaque-TB-RIF, FAST plaque TB-MDR and now FAST plaque TB- Response is being developed for detection of drug resistance directly from sputum specimens.

The other tests used for DST are hybridization protection assay, BACTEC, MB/ BacT, MGIT, E-test, Flowcytometry, etc. and takes about 4 to 10 days time for interpretation of results.

Appropriate Use of New Technologies in the Diagnostic Procedure

Direct amplification tests (DATs) performed on primary specimens are a major improvement over standard techniques. It is recommended by ATS that DAT should always be performed in conjunction with microscopy and culture, and that the result should be interpreted alongside the clinical data. Local test performance and underlying TB prevalence are important variables that will have an impact on the decision analysis of result from DAT assays.

SEROLOGY

Serologic tests have not yet demonstrated sufficient performance to warrant routine use in national control program. Recently, there have been significant improvements in serological tests and in our understanding of humoral immune response, but the HIV epidemic and its impact on immunity threatens this progress. Existing commercialized tests for the most part use well described immunodominant antigens to detect IgG or other immunoglobulin classes in dipstick or ELISA format. The quality of clinical trial data is too poor to make firm statements about the performance of most of the serology tests on the market, though in general, they can be said to detect anywhere from 1/3rd to 3/4th of smear positive patients and a smaller portion of smear negative cases among HIV uninfected cohorts. In cases of HIV coinfection, most of these assays perform very poorly, detecting less than a third of these patients with active disease. Promising research developments in serology include: (1) The availability of highly purified and recombinant antigens; (2) Improved understanding of the heterotypic nature of the humoral response to TB and the development of multiantigen tests

that maintain high specificity; (3) Novel *M. tuberculosis* proteins identified and characterized with the assistance of the newly available genome sequence; (4) Characterization of a number of nonprotein antigens, some of which appear promising in HIV infected patients; (5) The development of improved and simplified test formats, including those accepting whole blood or noninvasively collected specimens.

TESTS TO DETECT LATENT INFECTION

Tuberculin skin testing (TST) is the only standard method for detecting latent active tuberculosis infection (LTBI) with *M. tuberculosis*. Unfortunately PPD shares a large number of antigens both with BCG and with environmental mycobacteria and hypersensitivity responses are relatively nonspecific. PPD skin testing is plagued by errors due to reader interpretation and by the need for return patient visits.

New *in vitro* tests have been developed, with the potential to avoid both of these problems. Among these is a commercial test that measures IFN-gamma produced by T-cells in whole blood after stimulation with PPDs obtained from *M. tuberculosis*; *M. avium* and *M. bovis* (1st Generation IFN-gamma assays, available in ELISA format as Quanti-FERON TB assay). Early studies have shown good correlation with TST results in patients and controls. Single specific antigens ESAT-6 (Early secretory antigenic target-6) and CFP-10 (Culture filtrate protein-10) have also been used in this assay to increase specificity. These low molecular weight proteins encoded within the region of difference 1 (RD1) of *M. tuberculosis* genomes are more specific to *M. tuberculosis* than PPD and they are not shared with BCG substrains and most NTM species (with the exception of *M. kansasii*, *M. marinum* and *M. szulgai*). Tests based on these TB specific antigens are called *RD 1 based IFN-gamma-assays*. Commercially available as Quanti FERON-TB Gold Test using ESAT-6 and CFP-10. It is available in Europe and approved by US-FDA in 2004.

Other assays using enzyme linked immunospot (ELISPOT) to detect IFN-gamma response have also been evaluated in different settings. The T-SPOT-TB (Oxford Immunotec Oxon UK) is the second assay to reach commercial development. This assay is performed using PBMC, employs ESAT-6 and CFP-10 and detects the number of IFN-gamma producing T-cells using a sensitive ELISPOT technology. In India both assays have been evaluated in research settings, in rural and urban populations. However, these assays are currently not used in clinical practice in India. Due to its higher specificity, IFN-gamma assays will be helpful in low endemic populations where cross reactivity due to BCG and NTM pose problems in TST interpretations. In high burden, resource limited settings such as India, where even access to simple technology such as sputum microscopy may be poor in some areas, TST might continue to serve a useful

purpose. In an Indian study from South, TST response is significantly associated with development of active TB. Specificity of IFN-gamma assays is higher as compared to TST whereas sensitivity is almost same.

CHALLENGES FOR FUTURE

Additional technical progress is still needed to refine, simplify and improve the performance of new TB diagnostics and to adapt them to laboratory conditions in developing countries where the burden of TB is greatest. Strategies need to be devised to put these new technologies to most appropriate use. In addition to technical innovation, further epidemiological and operational research is needed to optimize the use of alternative diagnostics which should be cost effective too.

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Biomedical Waste Management

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INTRODUCTION

'Hospitals' committed to patient care and community health paradoxically defy their own objectives. On one hand, they cure patients and on the other, they have emerged as a source of several diseases because surprisingly, until recent times, not enough attention has been paid to the disposal of hospital waste's. The waste that is generated from health care industry can be hazardous, toxic or even lethal as they have a high potential to transmit diseases. The hazardous and toxic components namely infectious sharps (hypodermic needles, knives, scalpels, etc.) and radioactive material if not properly treated or disposed off or if they are allowed to get mixed with other municipal waste, constitute a grave risk to the community. Further, its propensity to encourage growth of various pathogen and vectors and its ability to contaminate other nonhazardous/nontoxic municipal waste, jeopardizes the efforts undertaken for overall municipal waste management. Further, the illegal and unethical reuse of Biomedical waste (BMW) can be extremely dangerous and even fatal.

Judicious planning and management followed by a rigorous regime of segregation at source, is an effective measure to reduce the problem significantly. Similarly, overall expenditure on waste management can be controlled. Further proper training of health care establishment personnel at all levels coupled with sustained motivation can improve the situation considerably.

The last century has witnessed the rapid mushrooming of hospitals in the public and private sector dictated by the needs of an expanding population. The advent and acceptance of disposables has made the generation of hospital waste a significant factor in current scenario. Epidemiological studies reveal that a person who experiences one needle stick injury from a needle used on an infected source patient has risks of 30, 1.8 and 0.3 percent respectively to become infected with HBV, HBC

and HIV. It is estimated that approximately 3 million health care workers experience per cutaneous exposures to blood borne viruses each year.

In 2002, the results of a WHO assessment conducted in 22 developing countries showed that the population of health care facilities that do not use proper waste disposal methods range from 18 to 64 percent. In India, hospital waste management has been brought into focus, particularly with the notification of the BMW management and handling Rules (1998), which makes it mandatory for all health care establishments to segregate, disinfect and dispose their waste in an eco-friendly manner.

DEFINITION

As per the WHO norms, health-care waste includes all the waste generated by health care establishments, research facilities, and laboratories. In addition, it also includes the waste originating from minor or scattered sources such as that produced in the course of health care undertaken in the home (dialysis, insulin injections, etc.).

The BMW (Management and Handling) Rules, 1998, define it as any waste, which is generated during the diagnosis, treatment or immunization of human beings or animals or in research activities pertaining there to or in the production of testing of biological and including categories mentioned in schedule 1 of the Rule is the biomedical waste.

Historical Aspects of Biomedical Waste Management

Prior to the discovery of bacteria as cause of disease, the principle focus of preventive medicine and public health had been on sanitation. The improper disposal of sewage and refuse were considered the important factors in causing epidemics. The invention of water closet by John Harrington (1561-1612) facilitated flushing away human

waste and helped to keep some dwellings clean, but flow from those indoor privies ran into cesspools and ultimately into waterways and wells. In 1848, Edwin Chadwick, emphasized to the British Government the need for proper removal of sewage and the protection of water supply. This together with Rudolph Virchow's militant advocacy of public health measures in Germany set the impetus for public health hygiene in UK and Europe.

Biomedical waste management came to the forefront in the late 1980s, when large quantities of syringes and needles were observed on the beaches of the East Coast and Florida, USA. The public outcry that followed the discovery of the needles, led to the formulation of the US Medical Waste Tracking Act (MWTa), which came into force on November 1, 1988. In the early 1990, the United States Environment Protection Agency (USEPA) estimated that there were some 6,000 hospital incinerators operating in USA. Incineration was found to be seriously harming the health of people, as was observed by many studies which linked the emissions to contain cancer-causing dioxin and furan. This resulted in incinerators being gradually phased out and by 2002 only around 500 incinerators remained in the US.

In India, the medical waste was earlier considered as a part of municipal waste. It was only when the problems with mixing the two were realised that separate policies were framed for their treatment. The Ministry of Environment and Forest came out with the draft rules on biomedical waste in 1995. It was the first time that medical waste was addressed as a category separate from municipal waste. The problem with this draft was that it laid too much emphasis on incineration. All hospitals having 30 or more beds were asked to install on-site incinerators. In the public interest case of *Dr BL Wadhwa vs Union of India*, the Supreme Court of India, in March 1996, ordered that this rule be implemented in the city of Delhi. *Srishti*, a NGO intervened with a Public Interest Litigation (PIL) of its own in which it petitioned for a review of this dangerous order and the court was also requested to include alternative technologies and their standards into the rules, both of which were agreed to. The second draft rules were notified in 1997. The final rules were notified on July 20, 1998 and were called Biomedical Waste (Management and Handling) Rules, 1998. Since July 1998, three amendments have been made to the rules:

- The first amendment was notified on March 6, 2000 and is referred to as the Biomedical Waste (Management & Handling) (Amendment) Rules, 2000. The amendment extended the deadline for implementation of the rules, considering that when the first deadline for eight cities with a population of more than three million was over, these cities had not been able to achieve anything significant.
- The second amendment to the rules was notified on June 2, 2000 and was called Biomedical Waste

(Management and Handling) (Amendment) Rules, 2000. Some of the major changes made through this amendment included defining the role of the municipal body, nominating Pollution Control Boards/ Committees as prescribed authorities, addition of forms for seeking authorization to operate a facility and for filing an appeal against orders passed by the prescribed authority.

- The third amendment was notified in September 2003. It made DGAFMS (Director General Armed Forces Medical Services) the prescribed authority for medical waste management in all medical establishments under the Ministry of Defence.

Salient Features of Biomedical Waste Management Rules, 1998

Under the Environmental Protection Act, the Biomedical Waste Management Rules were introduced. These Rules are directly relevant to the health sector. The salient features of these Rules are as follows:

- Biomedical waste means waste that is generated during the diagnosis, treatment or immunization of human beings or animals or in research activities pertaining thereto or in the production or testing of biologicals.
- It is the duty of every occupier of an institution generating biomedical waste which includes a hospital, nursing home, clinic, dispensary, veterinary institution, animal house, pathological laboratory, blood bank by whatever name called to take all steps to ensure that such waste is handled without any adverse effect to human health and the environment.
- Biomedical waste shall not be mixed with other wastes.
- Biomedical waste shall be segregated into containers/bags at the point of generation in accordance with Schedule II of these Rules prior to its storage, transportation, treatment and disposal. The containers shall be labeled according to Schedule III of these Rules.
- Biomedical waste shall be treated and disposed of in accordance with Schedule I of these Rules, which gives the categories of waste and methods for treatment and disposal. The rules also require compliance with the standards prescribed in Schedule V, which gives standards for different treatment technologies.
- Every occupier of an institution generating, collecting, receiving, storing, transporting, treating, disposing and/or handling biomedical waste in any other manner shall make an application in Form 1 to the prescribed authority for grant of authorization. This is not required for clinics, dispensaries, pathological laboratories, blood banks that provide treatment/service to less than 1000 (one thousand) patients per month.

Each state or union territory in India is responsible for implementing the Biomedical Waste Management Rules and the State Pollution Control Boards in states or Pollution Control Committees in the union territories are designated as the prescribed authorities.

National Legislations Governing Waste Management

National legislation is the basis for biomedical waste management practices in the country. It establishes control and permits for the disposal. The regulatory framework which governs the management of waste is as under:

- The Water (Prevention and Control of Pollution) Act, 1974 (*for liquid waste*)
- The Air (Prevention and Control of Pollution) Act, 1981 (*for air quality*)
- The Environment (Protection) Act, 1986
- Hazardous Wastes (Management, Handling and Transboundary Movement) Rules, 2008 (*for hazardous waste*)
- The Biomedical Wastes (Management and Handling) Rules 1998 (*for hospital waste*)
- The Municipal Solid Wastes (Management and Handling) Rules, 2000 (*for domestic municipal waste*)
- Battery (Management and Handling) Rules, 2001 (*for used batteries waste*)
- Manufacture, Storage and Import of Hazardous Chemicals Rules, 1989
- Atomic Energy Act 1962
- E-Waste Rules 2010.

CATEGORIES OF HOSPITAL WASTE

- *General waste:* Domestic type of waste, packing material, waste water from laundries, etc.
- *Pathological waste:* Consists of tissues, organs, body parts, human fetuses and animal carcasses, blood and body fluids.
- *Radioactive waste:* Includes solid, liquid and gaseous wastes contaminated with radionuclide's generated *in vitro* or *in vivo* testing.
- *Chemical waste:* Comprises of discarded solid, liquid and gaseous chemicals, e.g. from diagnosis, experimental work, cleaning, housekeeping and disinfecting procedures.
- *Infectious waste:* Includes cultures and stocks of infectious agents from laboratories, waste from survey and autopsy on patients in isolation wards and dialysis from infected patients.
- *Sharps:* Includes items like needles, blades, broken glass, etc. i.e., any item that can cause a cut or puncture.
- *Pharmaceutical wastes:* Consists of pharmaceutical products, drug and chemicals that have been returned from the wards.
- *Pressurized containers:* Include those used for demonstration and instructional purpose.

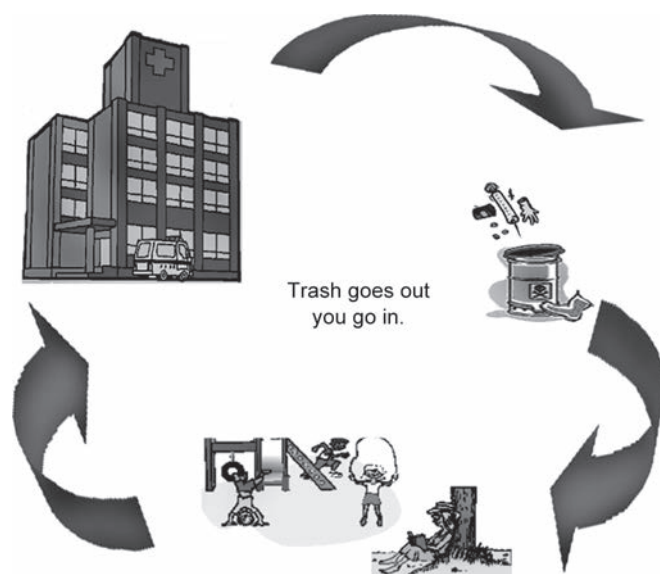


Fig. 1: Transmission pathway of biomedical waste

SOURCES OF BIOMEDICAL WASTE (FIG. 1)

The primary sources of biomedical waste are—Hospitals, diagnostic centers, laboratories, blood banks, nursing homes and clinics and veterinary hospitals and clinics. Noninfectious waste forms nearly 90 percent of the waste generated by a hospital. The remaining 10 percent comprises of infectious waste and is generated in all the wards, operation theaters, intensive care units, laboratories and blood banks. The waste generated in each of these areas can be categorized as under:

- *General ward (Outpatient department— OPD), wards of various departments, intensive care unit and emergency care:* Cotton, dressing, bandages, syringes, needles, IV sets and tubing, blood sets, urine bags—all contaminated with blood, pus or other body fluids and other waste material like packaging, paper waste and food waste.
- *Operation theaters:* Pathological waste, cotton, dressing, instruments, contaminated plastic waste like syringes, tubing, IV sets, blood sets, contaminated linen, contaminated gloves, disposable caps, masks, hospital gowns used by the patients as well as the staff and doctors.
- *Laboratories:* Contaminated samples, cultures, pipettes, petri dishes, tips, test tubes (both plastic and glass), slides.
- *Blood banks:* Contaminated samples, cultures, pipettes, petri dishes, tips, test tubes (both plastic and glass), slides, blood bags, unused blood bags (past the expiry date) and infected blood bags.
- *Nursing homes and clinics:* These generate the same kind of waste that hospitals generate but on a smaller scale depending on the facilities provided and the number of beds.

Classification of Biomedical Waste

Biomedical waste is classified into nonhazardous waste (75-90%) and hazardous waste (10-25%). Hazardous waste is further subdivided into:

- Infectious (15-18%) to include sharps, non sharps, plastic disposable and liquid waste
- Other hazardous waste (5-7%) like radioactive waste, discarded glass, pressurized containers, chemical waste, cytotoxic waste and incinerator ash.

The types of infection, pathogenic agents involved and the transmission pathway (Fig. 1) consequent to BMW generation are depicted in Table 1.

Quantum of Waste Generated in Hospitals (India)

It is estimated to be

- 1-2 kg per bed per day in a hospital, e.g. a 100 bedded hospital will generate 100 to 200 kg of hospital waste/day. It is estimated that only 5 to 10 percent of this comprises of hazardous/infectious waste (5 – 10 kg/day)
- 600 gm per day per bed in a general practitioner clinic.

TYPES OF BIOMEDICAL WASTES

Type A: Waste which does not require any special treatment. This is the waste produced by the hospital administration, the cleaning service, the kitchens, stores and workshops. It can be disposed off in the same way as household waste.

Type B: Waste with which special precautions must be taken to prevent infection in the hospital. This is usually taken to include all waste from in-patient and casualty wards and doctors' practices e.g. used dressings, disposable linen and

packaging materials. It only constitutes a risk for patients with weakened defenses while it is still inside the hospital. Once it has been removed from the wards it can be handled by the local domestic refuse collection service.

Type C: Waste which must be disposed off in a particular way to prevent infection. This is waste from isolation wards for patients with infectious diseases; from dialysis wards and laboratories, in particular those for microbiological investigations, which contains pathogens of dangerous infectious diseases, e.g. tuberculosis, hepatitis infectious diarrheal diseases and which constitutes a real risk of infection when disposing of this waste. It includes needles and sharp objects coated with blood, or disposable items contaminated with stool.

Type D: Parts of human bodies: limbs, organs, etc. This waste originates in pathology, surgical, gynecological and obstetric departments. It has to be disposed of separately, not to prevent infection but for ethical reasons.

Type E: Other waste—Hospitals provide a service, and hence have infrastructures which can also generate hazardous waste products, like chemical residues from laboratories, as well as inflammable, exposable, toxic or radioactive waste, which must be disposed off in accordance with statutory provisions.

Treatment and Disposal of biomedical waste: This should be done as per Schedule I (category wise treatment and disposal methodology) and in compliance with Schedule V (the standards for incinerators) of the BMW management and handling rules, 1998 (Fig. 3).

Schedules I, II and III are as under Tables 2, 3, and Fig. 2):

Table 1: Types of infections, pathogen agents and transmission path due to biomedical waste generation

	<i>Infection type</i>	<i>Pathogen agents</i>	<i>Transmission path</i>
1.	Gastrointestinal infections	<i>Enterobacteriaceae: Salmonella, Shigella</i> Spp, <i>Vibrio cholerae</i> helminths	Feces or/and vomiting liquid
2.	Respiratory infection	<i>Mycobacterium tuberculosis</i> , measles virus <i>Streptococcus pneumoniae</i> , herpes virus	Respiratory secretions, saliva
3.	Eye infections	Herpes virus	Eye secretions
4.	Genital infections	<i>Neisseria gonorrhoeae</i> , herpes virus	Genital secretions
5.	Skin infections	<i>Streptococcus</i> spp.	Purulent secretions
6.	Anthrax	<i>Bacillus anthracis</i>	Secretions of skin lesions
7.	Meningitis	<i>Neisseria meningitidis</i>	LCR
8.	AIDS	HIV	Blood, semen, vaginal secretions
9.	Hemorrhagic fevers	Iunin viruses, Lassa, Ebola Marburg	Biological fluids and secretions
10.	Septicemia	<i>Staphylococcus</i> ssp	Blood
11.	Viral hepatitis type A	VHA	Feces
12.	Viral hepatitis-B and C	VHB, VHC	Blood, biological fluids

Table 2: Schedule I: Categories of biomedical waste

<i>Waste Category</i>	<i>Waste Category Type</i>	<i>Treatment and Disposal Option +</i>
1.	Human anatomical waste (body parts, organs, human tissues, etc.).	Incineration @ /deep burial*
2.	Animal waste (animal tissues, organs, body part carcasses, bleeding parts, fluid, blood and experimental animals used in research, waste generated by veterinary hospitals, colleges, discharge from hospitals, animal houses).	Incineration @ /deep burial*
3.	Microbiology and Biotechnology waste (Wastes from laboratory cultures, stocks or microorganisms live or vaccines, human and animal cell culture used in research and infectious agents from research and industrial laboratories, wastes from production of biologicals, toxins, dishes and devices used for transfer of cultures)	Local autoclaving / microwaving / incineration @
4.	Waste sharps (needles, syringes, scalpels, blade, glass, etc. that may cause puncture and cuts. This includes both used and unused sharps)	Disinfection (chemical treatment@ @ /autoclaving /microwaving and mutilation/shredding ##
5.	Discarded medicines and cytotoxic drugs (Waste comprising of outdated, contaminated and discarded medicines)	Incineration @/destruction and drugs disposal in secured landfills
6.	Soiled waste (items contaminated with blood, and body fluids including cotton, dressings, soiled plaster casts, lines, bedding, other material contaminated with blood)	Local autoclaving/microwaving/incineration @
7.	Solid waste (Waste generated from disposal items other than the sharps such as tubings, catheters, intravenous sets, etc.).	Disinfection by chemical treatment@ @ autoclaving/microwaving and mutilation/shredding ##
8.	Liquid waste (Waste generated from laboratory and washing, cleaning, housekeeping and disinfecting activities)	Disinfection by chemical treatment @ @ and discharge into drains
9.	Incineration ash (Ash from incineration of any biomedical waste).	Disposal in municipal landfill
10.	Chemical waste (Chemicals used in production of biologicals, chemicals used in disinfection, as insecticides, etc.)	Disinfection by chemical treatment @ @ and discharge into drains for liquids and secured land fill for solids

Note:

@ There will be no chemical pretreatment before incineration. Chlorinated plastics shall not be incinerated.

*Deep burial shall be an option available only in towns with population less than five lakhs and in rural areas.

@@ Chemicals treatment using at least 1% hypochlorite solution or any other equivalent chemical reagent. It must be ensured that chemical treatment ensures disinfection.

Mutilation/shredding must be such so as to prevent unauthorized reuse.

+ Options given above are based on available technologies. Occupier/operator wishing to use other state of the art technologies shall approach the Central Pollution Control Board to get the standards laid down to enable the prescribed authority to consider grant of authorization.

Table 3: Schedule II: Color coding and type of container for disposal of bio-medical waste

<i>Color Coding</i>	<i>Type of Container</i>	<i>Waste Category</i>	<i>Treatment options as per Schedule I</i>
Yellow	Plastic bag	Cat. 1, Cat. 2, and Cat. 3, Cat. 6	Incineration/deep burial
Red	Disinfected container/plastic bag	Cat. 3, Cat.6, Cat.7.	Autoclaving/Microwaving/Chemical treatment
Blue/white translucent	Plastic bag /puncture proof container	Cat. 4, Cat. 7.	Autoclaving/Microwaving/ Chemical treatment and Destruction/Shredding
Black	Plastic bag	Cat. 5, Cat. 9 and Cat. 10 (Solid)	Disposal in secured landfill

Note:

1. Color coding of waste categories with multiple treatment options as defined in Schedule I, shall be selected depending on treatment option chosen, which shall be as specified in Schedule I.

2. Waste collection bags for waste types needing incineration shall not be made of chlorinated plastics.

3. Categories 8 and 10 (liquid) do not require containers/bags.

4. Category 3 if disinfected locally need not be put in containers/bags.



Fig. 2: Schedule III: Label for biomedical waste containers/bags



Biohazard



Cytotoxic

Fig. 3: Handle with care

Note: Label shall be non-washable and prominently visible.

POTENTIAL IMPLICATIONS OF BIOMEDICAL WASTE

- *Risk to health care workers:* Improperly contained contaminated sharps causing hepatitis B, C, E and HIV, etc. Occupational risk associated with hazardous chemicals, drugs, etc. Unauthorized repackaging and sale of disposable items and unused/date expired drugs pose greatest infectious risk associated with hospital waste.
- *Risk to waste handlers:* There is health risk to medical waste handlers from pathogens that may be aerosolized during the compacting, grinding or shredding process that is associated with certain medical waste management or treatment practices. Physical (injury) and health hazards are also associated with the high operating temperatures of incinerators and steam sterilizers and with toxic gases vented into the atmosphere after waste treatment.
- *Risk to the public:* Public impacts are confined to esthetic degradation of the environment from careless disposal and the environmental impact of improperly operated incinerators or other medical waste treatment equipment. There may be increased risk of nosocomial infections in patients due to poor waste management. Chances of vectors are high, like cats, rats, mosquitoes,

flies and stray dogs getting infected or becoming carriers which also spread diseases among the public.

- Inappropriate treatment and disposal contributes to environmental pollution (uncontrolled incineration causes air pollution, dumping in drains, tanks and along the river bed causes water pollution and unscientific land filling causes soil pollution) leading to change in microbial ecology and spread of antibiotic resistance.

STEPS IN WASTE MANAGEMENT

Medical waste should be managed according to its type and characteristics. For waste management to be effective, the waste should be managed at every step, from acquisition to disposal. The following are the elements of a comprehensive waste management system: waste survey, segregation, accumulation and storage, transportation, treatment, disposal and also waste minimization.

- *Waste audit/survey:* The survey should differentiate and quantify the waste generated. It should determine the points of generation, the type of waste at each point and the level of generation and disinfection within the hospital, deciding the type, size and placement of bins. A waste audit is the complete survey of a hospital's waste management practices. One can either do a survey by visiting each department and ward (to weigh and analyzed the composition of waste) or one can get all the waste bags labeled and analyze them at a central location. The first method gives an advantage of getting to know the hospital and its personnel better (for an external survey agency) while the second method offers the benefit of speed.
- *Waste segregation:* This consists of placing different kinds of wastes in different containers or coded bags at the point of generation. Segregation refers to the storing of waste in separate containers. It is the most important aspect of Bio-medical Waste (Management and Handling) Rules, 1998. The rules specify different categories of waste, the materials that comprise those categories, the prescribed color codes for them and the type of treatment technology for each of them. While there are ten categories of wastes specified in the rules, most of the waste commonly found in wards can be sorted into three categories. Some of the waste is very location specific and is not generated at all points. Segregation of waste is always done at the point of its generation and as soon as it is generated. Doing it elsewhere, or delaying the process, would result in mixing of waste (that is contaminating the entire waste stream) and will thus defeat the purpose of segregation. It helps to reduce the bulk of infectious waste as well as treatment costs. Segregation also helps to contain the spread of infection and reduces the chances of infecting other health care workers.

- *Waste collection and storage:* Waste collection and storage occurs between the point of waste generation and site of waste treatment and disposal. While accumulation refers to the temporary holding of small quantities of waste near the point of generation, storage of waste is characterized by longer holding periods and large waste quantity. Housekeeping staff should be trained to collect and transport waste. They should be warned against mixing, spilling or mishandling the waste and contingency measures in case of accidents/spills and the method of reporting these. Designating different people for different waste introduces some specialization into waste management. Collection of one particular hazardous waste from the entire hospital by one person, has the advantage of bringing in a system of accountability in that one man is answerable for that waste and its safety.

Different waste streams should be collected at different times. This reduces the chances of mixing. It also avoids wastage of bags, for example, general waste needs to be collected frequently, while the other bags do not. The time of collection for each type of waste would also depend on the time of its maximum use. In hospitals, mornings generally begin with dressings and other such activities, and the yellow bags meant for such waste are filled in the morning hours. Thus, noon can be fixed for collection of this waste. A similar 'timing' strategy can be adopted for all types of waste according to the hospital set up.

Closed containers not only offer an aesthetic advantage, but are also much safer in cases of accidents (to minimize spillage).

Storage time (the time lag between the generation of waste and its treatment) could differ as per the situation:

- Storage of waste within the hospital's wards/ departments
- Storage outside wards but within the hospital premises
- If the waste is taken to a treatment site, then storage in a vehicle
- Storage at the central facility.

According to the BMW Indian rules, waste should not be kept untreated for more than 48 hours. The WHO on the other hand recommends a refrigerated storage room; storage times for health care waste should not exceed 72 hours in winter and 48 hours in summer for temperate climate zones. In the case of warm climate the recommendation is 48 hours during the cool season and 24 hours during the hot season.

Storage within the hospital should be done in labeled, color-coded bins and bags in secured, balanced, easily washable containers that do not have any sharp edges.

The main storage site of the hospital should be accessible to vehicles. Storage areas are usually located near

where the waste is treated. Any offsite holding of waste is also considered storage.

To contain spills, storage areas should not have floor drains and should be recessed to hold liquids. Floor and walls should be impervious to liquid and easy to clean. They should be disinfected regularly. Refrigeration may be required for prolonged storage of putrifiable and other wastes.

- *Waste transportation:* When medical waste is not treated on site, untreated waste must be transported from the generation facility to another site for treatment and disposal.
- *Waste treatment:* Refers to the process that modifies the waste in some way before it is taken to its final resting place. Treatment is mainly required to disinfect or decontaminate the waste, right at source so that it is no longer the source of pathogenic organisms. After such treatment, the residue can be handled safely, transported and stored.
 - Needles and syringe nozzle - shredded in needle destroyer and syringe cutters
 - Scalpel blades/lancet/broken glass should be put in separate containers with bleach, transferred to plastic/cardboard boxes; sealed to prevent spillage and transported to incubators
 - Glassware should be disinfected, cleaned and sterilized
 - Culture plates with viable culture should be autoclaved; media are placed in appropriate bags and disposed off. The plates can be reused after sterilization
 - Gloves should be shredded/cut/mutilated before disposal
 - Swabs should be chemically disinfected followed by incineration. If they contain only a small amount of blood that does not drip, they can be placed in the garbage
 - Disposable items are often recycled and have the risk of being used illegally. Dipping in freshly prepared one percent sodium hypochlorite for 30 minute – one hour, followed by mutilation before disposal should be the policy adopted for such items
 - Under no circumstances, should heat be used for disposal of amalgam. The heat will cause mercury to volatilize and be released to the environment. So teeth with amalgam restoration should be treated by immersion in high-level disinfectant (e.g. Glutaraldehyde) for 30 minute. Treated teeth can then be rinsed.
 - Liquid waste generated by the laboratory is either pathological or chemical in nature. Noninfectious waste should be neutralized with reagents
 - Liquid infectious waste should be treated with a chemical disinfectant for contamination and then neutralized.

Methods of Waste Treatment

Biosafety is essentially a preventive concept and consists of wide variety of safety precautions that are to be undertaken, either singly or in combination, depending on the type of hazard by all medical, nursing and paramedical workers as well as by patients, attendants, ancillary staff and administrators in a hospital. Disinfection and sterilization are important procedures in biosafety.

Disinfection refers to procedures which reduce the number of microorganisms on an object or surface but not the complete destruction of all microorganism or spores (Table 5).

High level disinfectants like chlorine releasing compounds are used for disinfecting materials contaminated with blood and blood products. The recommended dilutions for these compounds are given in Table 4:

Table 4: Common chlorine-based disinfectants

<i>Name of Disinfectant</i>	<i>Available chlorine</i>	<i>Required chlorine</i>	<i>Required chlorine Contact period</i>	<i>Amount of disinfectant to be dissolved in 1 L of water</i>
Sodium hypochlorite	5%	0.5%	30 min	100 ml
Calcium hypochlorite	70%	0.5%	30 min	7.0 gm
Na OCl powder	–	0.5%	30 min	8.5 gm
Na Dichloro isocyanurate (NaDCC) tablets	60%	0.5%	30 min	4 tabs
Chloramine	25%	0.5%	30 min	20 gm

Table 5: Methods of disinfection of general use items in hospitals

<i>General use items</i>	<i>Disinfection</i>
Bath water	Add savlon when necessary
Bed pans	Wash with hot water and dry Disinfect with phenol after use by infected patients Autoclave
Bowls	Wash with hot water and keep dry Autoclave
Crockery, Cutlery	Wash with hot water/detergent and keep dry
Floors	Vacuum clean; No use of broom
Furnitures	Damp dust with detergent/phenol/2% Lysol
Mattresses/Pillows	Use water impermeable cover Wash cover with detergent and keep dry Disinfect with phenol/2%lysol
Trolley tops	Wipe with warm water and detergent to remove dust and keep dry
Thermometers	Wash with warm water/detergent and keep dry
Endoscopes/Arthroscopes/Laparoscopes/ Fiberoptic Endoscopes	Immerse in 2% Cidex solution Use latex gloves, eye protection plastic covering mask while handling Alternatively, use ethylene oxide sterilization
Endotracheal suction catheter	Should be disposable
Endotracheal tubes	Recycled after cleaning and autoclaving
Ambu Bags	Ideally heat disinfect Immerse in 2% glutaraldehyde and wash with sterile distilled water to reduce respiratory irritation
Oxygen delivery face mask	Wash and dry Use 70% isopropyl alcohol to remove mucus
Suction drainage bottles	Ideally autoclave
Ventilatory circuits, respiratory equipment in Neonatal/Pediatric unit	Heat disinfection for 800 F for 30 min Autoclave Ethylene oxide sterilization
Incubators	Clean thoroughly with warm water/soap Use 70% isopropyl alcohol
Humidifiers	Empty daily refill with sterile water Disinfect when contaminated with 1% Na hypochlorite Autoclave
Urinary Catheter	Should be disposable

Sterilization on the other hand, refers to procedures, which would remove all microorganisms, including spores, from an object. Sterilisation is undertaken either by dry heat (for 2 hours at 170°C in an electric oven – method of choice for glass ware and sharps) or by various forms of moist heat (i.e. boiling in water for an effective contact time of 20 min or steam sterilization in an autoclave at 15 lb/ sq inch at 121°C for 20 min) (Table 6).

Sterilization of common hospital instruments: Instruments should be disinfected for 30 min, cleaned and sent for sterilization. The following are the sterilization methods.

Incineration: It is a controlled combustion process where waste is completely oxidized and harmful microorganisms present in it are destroyed/denatured under high temperature. The emission standards for incineration:

- Standards and requirements for incineration
- Minimum height of the stack should be 30 meters above the ground
 - Below emission limits should be achieved (Table 7)
 - Waste to be incinerated not to be disinfected with chlorine substance

Table 6: Emission standards for incineration

Parameters	Conc. mg/N m ³ at 12% CO ₂ correction
Particulate matter	150
Nitrogen oxides	450
HCL	50

- Chlorinated plastics should not be incinerated
- Toxic metals in incineration ash should be limited to within regulatory quantities
- Only low sulfur fuels be used as fuel

Autoclaving is a low-heat thermal process where steam is brought into direct contact with waste in a controlled manner and for sufficient duration to disinfect the wastes. For ease and safety in operation, the system should be horizontal type and exclusively designed for the treatment of bio-medical waste. For optimum results, pre-vacuum based system be preferred against the gravity type system. It shall have tamper-proof control panel with efficient display and recording devices for critical parameters such as time, temperature, pressure and date and batch number.

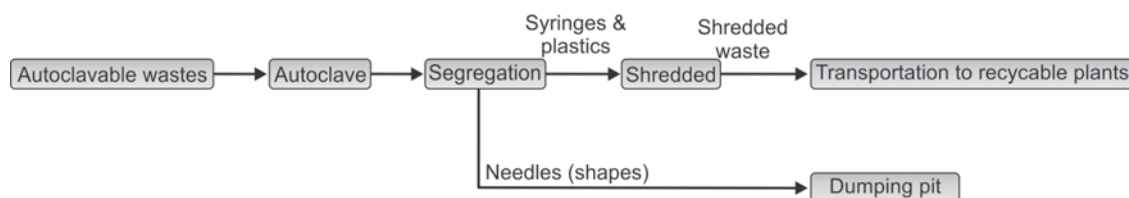
Microwaving: Microbial inactivation occurs as a result of the thermal effect of electromagnetic radiation spectrum lying between the frequencies 300 and 300,000 MHz. Microwave heating is an inter-molecular heating process. The heating occurs inside the waste material in the presence of steam. Microwave treatment shall not be used for cytotoxic, hazardous or radioactive wastes, animal carcasses, body parts and metal items. The microwave should be able to kill all bacteria and microorganism completely and consistently. The indicator organism is bacillus subtilis spores using vials or spore strips with at least 1X10⁴ spores per millimeter.

Hydroclaving is similar to that of autoclaving except that the waste is subjected to indirect heating by applying

Table 7: Methods of sterilization

	Dry Heat	Autoclave	Ethylene oxide	2% Glutaraldehyde	Formaline	Gamma radiation
Gloves	–	+	–	–	–	+
Plastic Syringe	–	–	+	–	–	–
Glass Syringe	–	+	–	–	–	–
Needles	–	–	–	–	–	–
Endoscopic instruments	–	–	–	+	+	–
Suction tubes	–	–	–	+	–	–
Suction bottles	–	+	+	+	+	+
Cautery cable	–	–	+	+	+	+
Cautery points	–	–	–	+	+	+
Laryngoscopes	–	–	–	+	+	+
Endotracheal tubes	–	–	+	+	+	+
Catheters	–	–	+	+	+	+
Cath Lab Material	–	–	+	+	–	+
Blanket	+	–	–	–	–	–
Mattresses	+	–	–	–	–	–
Suturing Material	+	–	–	+	–	+

Flow Chart 1: Autoclaving, segregation and shredding



steam in the outer jacket. The waste is continuously tumbled in the chamber during the process.

Shredding is a process by which waste are deshaped or cut into smaller pieces so as to make the wastes unrecognizable. It helps in prevention of reuse of bio-medical waste and also acts as identifier that the waste has been disinfected and is safe to dispose off (Flow chart 1).

- *Waste disposal:* The waste disposal methods vary in their capabilities, cost, availability to generation and impacts on the environment. The various disposal methods include incineration, autoclaving, chemical methods, thermal methods (low and high), ionizing radiation process, deep burial and microwaving.

Sharp pit: A sharp pit or a facility for sharp encapsulation shall be provided for treated sharps.

Effluent treatment plant: A suitable effluent treatment plant shall be installed to ensure that liquid effluent generated during the process of washing containers, vehicles, floors, etc. is disposed after treatment. The treated effluent shall comply with the stipulated regulatory requirements.

Composting and vermiculture: The organic wastes are easier to handle because it will decompose over a period of time. It is this which through the process of composting produce rich manure, which is safe and better than chemical fertilizers. The use of earthworms in the process of composting is known as vermiculture and is proving to be very useful and successful.

- *Waste minimization:* Whereas ordinary solid or liquid waste requires no treatment before disposal, practically all infectious waste must first be treated. The cost for disposal of infectious waste may be ten times the cost for disposal of ordinary solid waste. Any measures that decrease the amount of infectious waste generated will simultaneously decrease the cost of infectious waste disposal.

USEFUL REMEDIES FOR BIOMEDICALWASTE MANAGEMENT

- *Waste avoidance and waste minimization at source:* In the hierarchy of waste management, waste avoidance and waste minimization have to be attempted first.
- *Inventory of hazardous waste generation:* As per the hazardous waste regulations, industries are required to store

hazardous waste for a period not exceeding 90 days. The waste could either be recycled/reused or disposed of in captive or common treatment, storage and disposed facilities (TSDF) available in the state, or be incinerated.

- *Reuse, recovery and recycling of hazardous waste:* Industrial associations/industries should explore options/opportunities of reusing, recovery and recycling of hazardous waste in an environmentally sound manner. Establishment of 'waste exchange banks/centers' should be encouraged to provide information on wastes and promote reuse, recovery and recycling technologies which upscale the quality of resource recovery.

NEW EMERGING TECHNOLOGIES

- Plasma torch technology
- Detoxification technology
- Advanced wet oxidation technology
- Thermal dry heat technology
- Irradiation
- Gas sterilization

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Malaria Management Guidelines

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INTRODUCTION

It is estimated that 2 billion people are at risk for malaria world over with 300 to 500 million cases resulting in 1 to 2 million deaths 75 percent of which occur in children <5 years of age. Current WHO estimates suggest that in 2008, 8.8 million under-five children died world over of which 8 percent, i.e. 0.7 million deaths were due to malaria (mostly due to falciparum malaria), most of which occur in Africa where 16 percent of the 4.1 million under-five deaths, i.e. 0.65 million deaths occurred due to malaria. The matter is further complicated by increasing incidence of malaria in areas with rapid construction work happening, and due to emerging drug resistance and rampant misuse of antimalarials in treating fever of unknown origin in many developing countries where attempt to prove malaria by parasite isolation are far below expectations.

Malaria as we all know is spread by the bite of night biter female anopheline mosquito harboring the parasites of *Plasmodium* species in saliva. There are four types of plasmodia namely, *Falciparum*, *Vivax*, *Malariae* and *Ovale*. Each one can cause malaria in humans. Malaria control requires an integrated approach, including prevention (primarily vector control) and prompt treatment with effective antimalarial agents. In this chapter, we will go through the anti-malarial chemotherapeutic agents available with us and the recent guidelines for their rationale use in different types of malaria.

DIAGNOSIS

Prompt and accurate diagnosis of malaria is part of effective disease management. The diagnosis of malaria is based on clinical suspicion and on the detection of parasites in the blood (parasitological or confirmatory diagnosis). Parasitological diagnosis has the following advantages:

- Improved patient care in parasite-positive patients;
- Identification of parasite-negative patients in whom another diagnosis must be sought;

- Prevention of unnecessary use of antimalarials, reducing frequency of adverse effects in those who do not need the medicines, and thus preventing drug pressure selecting for resistant parasites;
- Improved malaria case detection and reporting;
- Confirmation of treatment failures.

The two methods in routine use for parasitological diagnosis are light microscopy and rapid diagnostic tests (RDTs).

Peripheral Smear (PS) Examination

Carefully examined thick smears are gold standard for diagnosis. Thick smears can detect 10 to 100 parasites/ μ l of blood provided at least 100 oil immersion fields are examined by a competent microscopist. Thin smears aid in species diagnosis. Microscopy also provides information on important prognostic indicators such as parasite count/presence of mature schizonts/malarial pigment in neutrophils and helps in assessing response to therapy. Parasitic index of >5 percent suggests severe disease with poor prognosis. One may have to repeat peripheral smear examination after 6 to 12 hours if malaria is strongly suspected and first smear examination is negative. However it needs trained personnel to conduct microscopy.

Rapid Diagnostic Test (RDT)

It detects parasite-specific antigens or enzymes and some have a certain ability to differentiate species. Rapid diagnostic test (RDT) is easy to carry out and does not need experienced personnel. However it is an expensive test and has limitations like it can not differentiate current infection from a recent infection, it can not differentiate parasitic stage, it is unsuitable in presence of low parasitic load (can detect when parasite load is 100 to 500/ μ l, it will be positive even in presence of gametes alone and it can not classify the severity of infection).

In any case antimalarial treatment should be limited to parasite positive cases and there is no role of empirical

treatment; besides, negative cases should be reassessed for other common causes of fever. The results of parasitological diagnosis should be available within a short time (less than two hours) of the patient presenting. In the absence or delay of parasitological diagnosis, patients with suspected severe malaria, and other high risk groups, should be treated immediately on clinical grounds.

The choice between RDTs and microscopy depends on local circumstances, including the skills available, patient case-load, epidemiology of malaria and the possible use of microscopy for the diagnosis of other diseases. Where the case-load of fever patients is high, microscopy is likely to be less expensive than RDTs, but may be less operationally feasible. Microscopy has further advantages in that it can be used for specification and quantification of parasites, and to assess response to antimalarial treatment. Microscopy can also be used in the identification of other causes of fever. However, a major drawback of light microscopy is its requirement for well-trained, skilled staff and, usually, energy source to power the microscope. In the diagnosis of severe malaria cases, microscopy is a preferred option; it not only provides the diagnosis of malaria, but it is useful in assessing other important parameters in a severely ill patient. In situations where an RDT has been used to confirm malaria, this allows for a rapid institution of antimalarial treatment, however, where possible a microscopic examination is recommended to enhance the overall management of the patients.

TREATMENT

Treatment of Vivax Malaria

Treatment of uncomplicated Vivax malaria

Vivax malaria accounts for nearly 60 to 80 percent of all malaria cases in India. Treatment of vivax malaria is simple and includes use of antimalarials and radical cure. Vivax malaria is universally sensitive to chloroquine with very few exceptions. Hence in areas with insignificant chloroquine resistant vivax malaria, chloroquine remains the drug of choice. It is preferable to give it along with some juice or food to minimize nausea and vomiting. Routine use of antiemetic before chloroquine is not recommended. The dose and schedule could be either:

- Chloroquine 10 mg of base/kg stat followed by 5 mg/kg at 6, 24 and 48 hours, or
- Chloroquine 10 mg base/kg stat followed by 10 mg/kg at 24 hours and 5 mg/kg at 48 hours.

Chloroquine Resistant Vivax Malaria

Relatively few data are available on chloroquine resistant vivax malaria. Studies have shown that mefloquine, quinine, Artemether-Lumefantrine, or Amodiaquine (in doses as used for falciparum malaria as discussed below) can be used. However clinical data at present is insufficient.

In cases of chloroquine sensitive vivax malaria, artemisinin compounds are less potent than chloroquine and hence should not be used. Also, irrational use of artemisinin compounds in all cases of vivax malaria is likely to induce resistance to this otherwise life saving drug.

Radical Cure

Radical cure is to prevent relapses of malaria. *P. vivax* forms hypnozoites, parasite stages in the liver that can result in multiple relapses of infection, weeks to months after the primary infection, primaquine should be given in the dose of 0.25 mg/kg OD for 14 days. As primaquine can cause hemolytic anemia in G6PD deficiency, they should preferably be screened for the same prior to starting treatment. As infants are relatively G6PD deficient, it is not recommended in this age group. In cases of borderline G6PD deficiency, 0.75 mg/kg of primaquine is given once weekly for 8 weeks. In severe G6PD deficiency primaquine should not be given at all.

Management of complicated vivax malaria: These type of cases are rare. Many times there is mixed infection with vivax and falciparum leading to severe disease where falciparum is missed on peripheral smear. Management of these cases is same as that for severe falciparum malaria as discussed below.

Treatment of Falciparum Malaria

Management of uncomplicated P. falciparum malaria: Uncomplicated malaria is defined as symptomatic malaria without signs of severity or evidence (clinical or laboratory) of vital organ dysfunction. Almost 40 to 60 percent of cases of falciparum malaria are resistant to chloroquine and SP combination world over. Hence these drugs are not used in management of falciparum malaria. To counter the threat of resistance of *P. falciparum* to monotherapy (Chloroquine and SP combination) and to improve treatment outcome, WHO recommends that artemisinin-based combination therapy (ACT) be used for the treatment of uncomplicated *P. falciparum* malaria. Antimalarial combination therapy is the simultaneous use of two or more blood schizontocidal medicines with independent modes of action and, thus, different biochemical targets in the parasite. The rationale is two-fold: (i) the combination is often more effective; and (ii) in the very rare event that a mutant parasite resistant to one of the medicines arises *de novo* during the course of the infection, this resistant parasite will be killed by the other antimalarial medicine. The ACTs that are currently recommended include (in alphabetical order) artemether + lumefantrine, artesunate + amodiaquine, artesunate + mefloquine or artesunate + sulfadoxine-pyrimethamine. The choice of ACT in a country or region will be based on the level of resistance of the partner medicine in the combination. In areas with multidrug resistance (South-East Asia), artesunate +

mefloquine or artemether-lumefantrine combinations can be used. The artemisinin derivative components of the combination must be given for at least 3 days for an optimum effect.

- Artemether-lumefantrine combination formulated tablets containing 20 mg of artemether and 120 mg of lumefantrine can be used as a six dose regimen twice a day for 3 days in following doses. Similar combination in each 5 ml is also available.

Timing and dose of tablet/ syp (5 ml) 5-14 kg	5-14 kg	15-24 kg	25-34 kg	>34 kg
0 hr	1	2	3	4
8 hr	1	2	3	4
24 hr	1	2	3	4
36 hr	1	2	3	4
48 hr	1	2	3	4
60 hr	1	2	3	4

Artesunate + amodiaquine: Artesunate 4mg/kg and amodiaquine 10 mg (base)/kg is given once a day for 3 days. It can be used only above 5 months of age. Separate scored tablets or coformulated tablets are not yet available.

- *Artesunate + sulphadoxin-pyrimethamine (SP)*: 4 mg/kg of artesunate is given once a day for 3 days and single dose of SP as 25mg/kg of sulfadoxine and 1.25 mg/kg of Pyrimethamine is given on day one.
- *Artesunate + mefloquine*: 4 mg/kg of artesunate is given once a day for 3 days and mefloquine 25 mg/kg in two (15 + 10) divided doses on day 2 and 3.

Radical cure is not required as there is no exoerythrocytic phase or relapses in falciparum malaria. However a single dose of 0.75 mg/kg of primaquine is given as gametocidal to prevent spread of infection to contacts. It is contraindicated in patients with severe G6PD deficiency though as discussed before.

Management of Treatment Failures with ACT

- *Failure within 14 days*: If fever and parasitemia fail to resolve or recur within 2 weeks of first course of treatment then this is considered as treatment failure. Whenever possible treatment failure must be confirmed parasitologically. Management is with second line antimalarials.
- *Failure after 14 days*: Recurrence of fever and parasitemia more than 2 weeks after initial treatment could be due to recrudescence or new infection. Parasitological confirmation is not a precondition. If there is recrudescence first line management is effective in most cases. Recommended second line antimalarials by WHO include
 - Alternative ACT known to be effective in that region
 - Artesunate (2 mg/kg OD) plus

Tetracycline (4 mg/kg qid) for >8 yr of age or Doxycycline (3.5 mg/kg OD) for >8 yr of age or Clindamycin (10 mg/kg bd)

Above drugs to be given for a period of 7 days:

- Quinine 10 mg of salt/kg/dose 3 times daily for 7 days plus tetracycline or doxycycline or Clindamycin (in doses mentioned above) for 7 days.

Management of severe falciparum malaria: In a patient with *P. falciparum* asexual parasitemia and no other obvious cause of symptoms, the presence of one or more of the following clinical or laboratory features classifies the patient as suffering from severe malaria

Clinical Features

- Impaired consciousness or unrousable coma
- Prostration, i.e. generalized weakness so that the patient is unable walk or sit up without assistance failure to feed
- Multiple convulsions—more than two episodes in 24 hours
- Deep breathing, respiratory distress (acidotic breathing)
- Circulatory collapse or shock with systolic blood pressure <70 mm Hg in adults and <50 mm Hg in children
- Clinical jaundice plus evidence of other vital organ dysfunction hemoglobinuria
- Abnormal spontaneous bleeding
- Pulmonary edema (radiological)

Laboratory Findings

- Hypoglycemia (blood glucose <2.2 mmol/L or <40 mg/dl)
- Metabolic acidosis (plasma bicarbonate <15 mmol/L)
- Severe normocytic anemia (Hb <5 g/dl, packed cell volume <15 percent)
- Hemoglobinuria
- Hyperparasitemia (>2 percent/100 000/ μ l in low intensity transmission areas or >5 percent or 250 000/ μ l in areas of high stable malaria transmission intensity)
- Hyperlactatemia (lactate >5 mmol/L)
- Renal impairment (serum creatinine >265 μ mol/L)

Treatment of Severe Falciparum Malaria

In low transmission areas or outside malaria endemic areas: artesunate 2.4 mg/kg IV/IM on admission then at 12 h and 24 h, then once a day for 7 days (change to oral once patient can tolerate orally) plus.

Tetracycline/doxycycline/clindamycin in doses as given above is added to artesunate as soon as patient can swallow and should be continued for 7 days.

In high transmission areas: One uses artesunate or artemether or quinine plus tetracycline/doxycycline/clindamycin as shown below.

- Artesunate 2.4 mg/kg IV/IM on admission then at 12 h and 24 h, then once a day for 7 days (change to oral once patient can tolerate orally) or
- Artemether 3.2 mg/kg IM on admission and then 1.6 mg/kg per day for 7 days or
- Quinine 20 mg of salt/kg diluted in 10 ml of isotonic fluid/kg by infusion over 4 hrs followed by 10 mg of salt/kg over 2 hrs after 12 hours and repeated every 8 hrs thereafter calculated from beginning of infusion, until patient can swallow when one switches to oral quinine tablets in dose of 10 mg salt/kg 8 hrly to complete a 7 days course PLUS.

Tetracycline/doxycycline/clindamycin (in doses as discussed above) as soon as patient can swallow and should be continued for 7 days.

Artesunate alone is not available in oral form and hence in a case of severe falciparum malaria one should use a complete course of ACT (as described above under management of uncomplicated falciparum malaria) irrespective of number of days of initial IV use once one shifts to oral therapy.

Radical cure is not required as there is no exoerythrocytic phase or relapses in falciparum malaria. However a single dose of 0.75 mg/kg of primaquine is given as gametocidal to prevent spread of infection to contacts. It is contraindicated in patients with severe G6PD deficiency though as discussed before.

Supportive Care

Role of Blood Transfusion in Malaria

In high transmission settings, blood transfusion is recommended for children with an Hb <4-5 gm/dl and in low transmission settings a threshold of 7g/dl is recommended. These general recommendations need to be tailored to the individual. Any patient with anemia with overt or occult cardiac failure should be transfused irrespective of Hb level.

Role of Red Cell Apheresis

In patients with very high parasitic index (>20 to 40 percent) red cell apheresis is indicated as it reduces complications and mortality in such cases. However this may not be available in all centers and is expensive.

Role of Concomitant Use of Antibiotics

The threshold for administering antibiotic treatment should be low in severe malaria. Septicemia is often associated with severe malaria and there is diagnostic overlap particularly in children. Although enteric bacteria (notably salmonella) have predominated in most trials, a variety has been

cultured, so broad spectrum antibiotic treatment should be given initially. Ceftriaxone is a good choice in such cases.

Treatment in Infants and Young Children

The acutely ill child requires careful clinical monitoring as she/he may deteriorate rapidly. ACTs should be used as first-line treatment for infants and young children with uncomplicated malaria, and careful attention should be paid to accurate dosing and ensuring the administered dose is retained. Referral to tertiary centre or hospital is indicated in young children who cannot swallow anti-malarial medicines reliably. If referral is expected to take more than six hours, prereferral treatment with rectal artesunate is indicated.

Role of Hematinics

As there is rapid red cell destruction in malaria it may tip the balance of folate and B₁₂ requirements especially in malnourished patients and hence folic acid and B₁₂ should be administered orally for 4 to 6 weeks. Similarly iron is prescribed at the time of discharge for 3 to 4 months in all cases of malaria.

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Dengue Fever

Vikas Taneja

EPIDEMIOLOGY

Dengue is the most rapidly spreading mosquito-borne viral disease in the world. In the last 50 years, there has been a 30-fold increase in the incidence along with geographic expansion to new countries and, in the present decade, from urban to rural settings. An estimated 50 million dengue infections occur annually and approximately 2.5 billion people live in dengue endemic countries. Some 1.8 billion (more than 70%) of the population at risk for dengue worldwide live in member states of the WHO South-East Asia Region and Western Pacific Region, which bear nearly 75 percent of the current global disease burden due to dengue.¹

Over the last 10 to 15 years, DF has become a leading cause of hospitalization and death among children in the South-East Asia Region of WHO, following diarrheal diseases and acute respiratory infections. In India dengue virus was first isolated in Kolkata, India in 1945 and the epidemic of dengue hemorrhagic fever (DHF) first occurred in Calcutta in 1963. Since then epidemics of dengue fever have been reported from Vishakhapatnam, Ajmer, Delhi and Kanpur, India, mostly attributed to strains DEN 2 and DEN 3.²

TRANSMISSION

The Virus

The dengue virus is an arbovirus, from genus flavivirus family flaviviridae. The mature particle of the dengue virus is spherical with a diameter of 50 nm containing multiple copies of the three structural proteins, a host-derived membrane bilayer and a single copy of a positive-sense, single-stranded RNA genome. The genome is cleaved by host and viral proteases in three structural proteins (capsid C, prM, the precursor of membrane M protein and

envelope, E) and seven nonstructural proteins (NS). Four serotypes: DEN-1, 2, 3, 4 have been identified for the virus. Each serotype provides specific life time immunity, but only a short-term cross-immunity. All serotypes can cause severe and fatal disease.³

The Vector

The vector for dengue is the *Aedes aegypti* mosquito which is also known as the tiger mosquito, due to the characteristic striped body appearance. It is a highly domesticated mosquito, lays eggs and produces larvae preferentially in artificial containers. Two peaks of biting activity are known for the mosquito—2 to 3 hours after the daybreak and in the evening a couple of hours before sunset. The mosquito is a silent and fearless biter and does not buzz. It often feeds on several persons during a single blood meal in a short period of time. If infective, it can transmit the virus even while probing without taking blood meal.³

The Host

After an incubation period of 4 to 10 days, infection by any of the four virus serotypes can produce a wide spectrum of illness, although most infections are asymptomatic or sub clinical. Primary infection is thought to induce lifelong protective immunity to the infecting serotype. Individuals after an infection are protected from clinical illness with a different serotype within 2 to 3 months of the primary infection but with no long-term cross-protective immunity.

Humans are the main amplifying host of the virus. Dengue virus circulating in the blood of viremic humans is ingested by female mosquitoes during feeding. The virus then infects the mosquito mid-gut and subsequently spreads systemically over a period of 8 to 12 days. After this extrinsic incubation period, the virus can be transmitted to other humans during subsequent probing or

feeding. The extrinsic incubation period is influenced in part by environmental conditions, especially ambient temperature. Thereafter the mosquito remains infective for the rest of its life.

During the acute phase of illness the virus is present in the blood and its clearance from this compartment generally coincides with defervescence. Humoral and cellular immune responses are considered to contribute to virus clearance via the generation of neutralizing antibodies and the activation of CD4+ and CD8+ T lymphocytes. In addition, innate host defense may limit infection by the virus. After infection, serotype specific and cross-reactive antibodies and CD4+ and CD8+ T cells remain measurable for years.

PATHOGENESIS OF DENGUE FEVER

The infected monocytes release vasoactive mediators, resulting in increased vascular permeability and hemorrhagic manifestations that characterize severe dengue. Early bone marrow suppression causing leukopenia, thrombocytopenia, decreased neutrophil and monocytes are seen in DHF. Decreased levels of fibrinogen, prothrombin, factor II, VII, VIII, IX, X, XII, ATIII, protein C and S have been reported. The classical markers of disseminated intravascular coagulation may be absent. PT, aPTT, TT may be normal or increased. The levels of C3 and C5 are depressed, and C3a and C5a are elevated.^{4,5}

The cause of thrombocytopenia in DF is controversial. It has been proposed that there is impaired megakaryocytic production and increased platelet destruction or consumption (peripheral sequestration and consumption). The causes of platelet injury have been attributed to the virus itself, circulating antiplatelet antibodies, immune complexes and DIC. Hemorrhage may be due to thrombocytopenia and associated platelet dysfunction or disseminated intravascular coagulation.^{4,5}

Plasma leakage, hemoconcentration and abnormalities in homeostasis characterize severe dengue. The mechanisms leading to severe illness are not well defined but the immune response, the genetic background of the individual and the virus characteristics may all contribute to severe dengue.

CLINICAL FEATURES

Dengue has a wide spectrum of clinical presentations, often with unpredictable clinical outcome. While most patients recover following a self-limiting non-severe clinical course, a small proportion progress to severe disease, mostly characterized by plasma leakage with or without hemorrhage. The group progressing from non-severe to severe disease is difficult to define, but appropriate treatment may prevent these patients from developing severe disease.

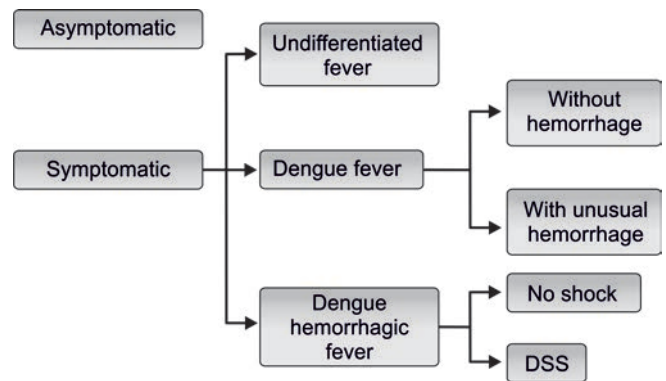


Fig. 1: Earlier WHO case classification dengue virus infections

According to the WHO classification², Dengue virus infection may be asymptomatic or may cause undifferentiated febrile illness (viral syndrome), dengue fever (DF) or dengue hemorrhagic fever (DHF) including dengue shock syndrome (DSS). Dengue fever could be with or without frank hemorrhage. DHF could present with or without shock. The clinical presentation depends on age of the host and the virus strain. The clinical spectrum of the illness is given in Figure 1.

Undifferentiated Fever

The first infection with dengue virus presents with an undifferentiated viral like illness. Maculopapular rashes may appear during the fever or during defervescence. Fever may be associated with nausea, vomiting, retro-orbital pain, asthenia and myalgias.

Dengue Fever

According to WHO, dengue fever is an acute febrile illness of 2 to 7 days duration (sometimes with two peaks) with two or more of the following manifestations:

- Headache
- Retro-orbital pain
- Myalgia/arthralgia
- Rash
- Hemorrhagic manifestation (petechiae and positive tourniquet test) and,
- Leukopenia.

Dengue Hemorrhagic Fever

The identification of a case of dengue hemorrhagic fever requires all of four criteria.

- Fever or history of acute fever lasting 2 to 7 days, occasionally biphasic
- Hemorrhagic tendencies evidenced by at least one of the following:
 - positive tourniquet test
 - petechiae, ecchymosis, purpura
 - bleeding from mucosa, GIT, other
 - hematemesis, melena

- Thrombocytopenia $<100,000/\text{mm}^3$
- Plasma leakage evidenced by at least one of the following
 - Rise in hematocrit >20 percent
 - Fall in hematocrit >20 percent after I/V fluids
 - Pleural effusion, ascitis, hypoalbuminemia

Tourniquet test is performed by inflating the sphygmomanometer cuff on the upper arm to midway between systolic and diastolic blood pressures for 5 minutes. A positive test is identified by appearance of more than 20 petechiae per 2.5 cm^2 . A variable sensitivity from 56.4 to 90 percent has been reported for the test in diagnosing dengue hemorrhagic fever. The test may be negative during profound shock and usually becomes positive after recovery from shock.⁶

Dengue Shock Syndrome

The identification of dengue shock syndrome requires all four DHF criteria and in addition a circulatory failure manifested by:

- Rapid and weak pulse
- Narrow pulse pressure ($<20\text{ mm Hg}$)
- Hypotension for age $<5\text{ yr}$ – $<80\text{ mm Hg}$, $>5\text{ yr}$ – $<90\text{ mm Hg}$
- Cold clammy skin, restlessness.

SEVERITY OF DHF

To decide about treatment, it is important to grade the severity of dengue infection. The severity of dengue infection is classified into the grades described in Table 1.

Revised Classification

Currently the classification into DF/DHF/DSS continues to be widely used. However changes in the epidemiology of dengue, lead to problems with the use of the existing WHO classification. Difficulties in applying the criteria for DHF in the clinical situation (Table 2), together with the increase in clinically severe dengue cases which did

not fulfill the strict criteria of DHF, led to the request for the classification to be reconsidered. A WHO/TDR-supported prospective clinical multicenter study across dengue-endemic regions was set-up to collect evidence about criteria for classifying dengue into levels of severity. The study findings confirmed that, by using a set of clinical and/or laboratory parameters, one sees a clear-cut difference between patients with severe dengue and those with non-severe dengue. However, for practical reasons it was desirable to split the large group of patients with non-severe dengue into two subgroups – patients with warning signs and those without them. Criteria for diagnosing dengue (with or without warning signs) and severe dengue are presented in Figure 2. It must be kept in mind that even dengue patients without warning signs may develop severe dengue.¹

Disease Course

Dengue infection has a wide clinical spectrum that includes both severe and non-severe clinical manifestations.¹ After the incubation period, the illness begins abruptly and is followed by the three phases - febrile, critical and recovery.

Febrile Phase

Patients typically develop high-grade fever suddenly. This phase usually lasts 2 to 7 days and is often accompanied by facial flushing, skin erythema, generalized body ache, myalgia, arthralgia and headache. Some patients may have sore throat, injected pharynx and conjunctival injection. Anorexia, nausea and vomiting are common. A positive tourniquet test in this phase increases the probability of dengue. In addition, these clinical features are indistinguishable between severe and non-severe dengue cases. Therefore monitoring for warning signs and other clinical parameters is crucial to recognizing progression to the critical phase.

Mild hemorrhagic manifestations like petechiae and mucosal membrane bleeds (e.g. nose and gums) may be seen.

Table 1: Grades of dengue fever/dengue hemorrhagic fever

DF/DHF	Grade	Symptoms	Laboratory
DF		Fever with two or more of the following signs: headache, retro-orbital pain, myalgia, arthralgia	Leukopenia occasionally. Thrombocytopenia, may be present, no evidence of plasma loss
DHF	I	Above signs plus positive tourniquet test	Thrombocytopenia $<100,000$, Hct rise $>20\%$
DHF	II	Above signs plus spontaneous bleeding (Skin and mucus membranes)	Thrombocytopenia $<100,000$, Hct rise $>20\%$
DHF	III	Above signs plus circulatory failure (weak pulse, narrow pulse pressure, hypotension, restlessness)	Thrombocytopenia $<100,000$, Hct rise $>20\%$
DHF	IV	Profound shock with undetectable blood pressure and pulse	Thrombocytopenia $<100,000$, Hct rise $>20\%$

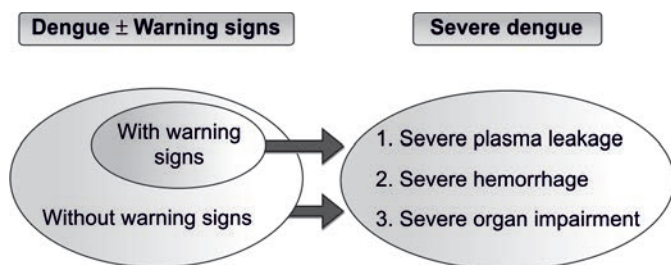


Fig. 2: Suggested dengue case classification and levels of severity

hypoperfusion results in progressive organ impairment, metabolic acidosis and disseminated intravascular coagulation. This in turn leads to severe hemorrhage causing the hematocrit to decrease in severe shock. Instead of the leukopenia usually seen during this phase of dengue, the total white cell count may increase in patients with severe bleeding. In addition, severe organ impairment such as severe hepatitis, encephalitis or myocarditis and/or severe bleeding may also develop without obvious plasma leakage or shock.

Table 2: Criteria for dengue in clinical situation

<i>Probable Dengue</i>	<i>Warning signs[#]</i>	<i>Severe plasma leakage leading to:</i>
Live in /travel to dengue endemic area	* Abdominal pain or tenderness	* Shock (DSS)
Fever and two of the following:	* Persistent vomiting	* Fluid accumulation with respiratory distress
* Nausea, vomiting	* Clinical fluid accumulation	* Lethargy, restlessness
* Rash	* Mucosal bleed	<i>Severe bleeding</i>
* Aches and pains	* Liver enlargement >2 cm	* As evaluated by clinician
* Tourniquet test positive	* Laboratory: increase in Hct	<i>Severe organ involvement</i>
* Leukopenia	concurrent with rapid decrease in platelet count	* Liver: AST or ALT >1000
* Any warning sign	# (requiring strict observation and medical intervention)	* CNS: Impaired consciousness
Laboratory-confirmed dengue (important when no sign of plasma leakage)		* Heart and other organs

Massive vaginal bleeding (in women of child bearing age) and gastrointestinal bleeding may occur during this phase but is uncommon. The liver is often enlarged and tender after a few days of fever. The earliest abnormality in the full blood count is a progressive decrease in total white cell count, with lymphocytic predominance.

Critical Phase

Around the time of defervescence, when the temperature drops to normal or subnormal levels, usually on days 3–7 of illness, an increase in capillary permeability in parallel with increasing hematocrit levels may occur. This marks the beginning of the critical phase. The period of clinically significant plasma leakage usually lasts 24 to 48 hours.

Progressive leukopenia followed by a rapid decrease in platelet count usually precedes plasma leakage. At this point patients without an increase in capillary permeability will improve, while those with increased capillary permeability may become worse as a result of lost plasma volume. The degree of plasma leakage varies. Pleural effusion and ascites may be clinically detectable depending on the degree of plasma leakage and the volume of fluid therapy. Hence chest X-ray and abdominal ultrasound can be useful tools for diagnosis. The degree of increase above the baseline hematocrit often reflects the severity of plasma leakage.

Shock occurs when a critical volume of plasma is lost through leakage. It is often preceded by warning signs. The body temperature may be subnormal when shock occurs. With prolonged shock, the consequent organ

Recovery Phase

If the patient survives the 24–48 hour critical phase, a gradual reabsorption of extravascular compartment fluid takes place in the following 48–72 hours. General well-being improves, appetite returns, gastrointestinal symptoms abate, hemodynamic status stabilizes and diuresis ensues. Some patients may have a rash of “isles of white in the sea of red”. Some may experience generalized pruritus. Bradycardia and electrocardiographic changes are common during this stage.

The hematocrit stabilizes or may be lower due to the dilutional effect of reabsorbed fluid. White blood cell count usually starts to rise soon after defervescence but the recovery of platelet count is typically later than that of white blood cell count.

Respiratory distress from massive pleural effusion and ascites will occur at any time if excessive intravenous fluids have been administered. During the critical and/or recovery phases, excessive fluid therapy is associated with pulmonary edema or congestive heart failure.

Severe Dengue

Severe dengue is defined by one or more of the following: (i) plasma leakage that may lead to shock (dengue shock) and/or fluid accumulation, with or without respiratory distress, and/or (ii) severe bleeding, and/or (iii) severe organ impairment.

As dengue vascular permeability progresses, hypovolemia worsens and results in shock. It usually takes place around defervescence, usually on day 4 or 5 (range days

3–7) of illness, preceded by the warning signs. During the initial stage of shock, the compensatory mechanisms which maintain a normal systolic blood pressure, produce tachycardia and peripheral vasoconstriction with reduced skin perfusion, resulting in cold extremities and delayed capillary refill time. Uniquely, the diastolic pressure rises towards the systolic pressure and the pulse pressure narrows as the peripheral vascular resistance increases. Patients in dengue shock often remain conscious and lucid. Finally, there is decompensation and both pressures disappear abruptly. Prolonged hypotensive shock and hypoxia may lead to multi-organ failure and an extremely difficult clinical course.

The patient is considered to have shock if the pulse pressure (i.e. the difference between the systolic and diastolic pressures) is ≤ 20 mm Hg in children or he/she has signs of poor capillary perfusion (cold extremities, delayed capillary refill, or rapid pulse rate). In adults, the pulse pressure of ≤ 20 mm Hg may indicate a more severe shock. Hypotension is usually associated with prolonged shock which is often complicated by major bleeding.

Patients with severe dengue may have coagulation abnormalities, but these are usually not sufficient to cause major bleeding. When major bleeding does occur, it is almost always associated with profound shock since this, in combination with thrombocytopenia, hypoxia and acidosis, can lead to multiple organ failure and advanced disseminated intravascular coagulation. Massive bleeding may occur without prolonged shock in instances when acetylsalicylic acid (aspirin), ibuprofen or corticosteroids have been taken.

Unusual manifestations, including acute liver failure and encephalopathy, may be present, even in the absence of severe plasma leakage or shock. Cardiomyopathy, encephalitis, renal failure and hemolytic uremic syndrome are also reported in a few dengue cases. However, most deaths from dengue occur in patients with profound shock, particularly if the situation is complicated by fluid overload. In unusual cases the dengue virus has been reported to cross the blood brain barrier and infect the central nervous system.

LABORATORY AND RADIOLOGICAL FEATURES OBSERVED IN DENGUE FEVER

Various laboratory abnormalities are observed in dengue fever. These include thrombocytopenia, rise in hematocrit and leucopenia. Other lab abnormalities like deranged KFT, metabolic acidosis are seen due to circulatory failure and shock.

Eighty percent of patients with severe dengue have an abnormal coagulation profile, suggesting a consumptive coagulopathy with thrombocytopenia, prolonged partial thromboplastin time (PTT) and decreased fibrinogen

levels. In dengue infection with liver dysfunction, the prothrombin time will be prolonged.

Laboratory diagnostic methods for confirming dengue virus infection may involve detection of the virus, viral nucleic acid, antigens or antibodies, or a combination of these techniques. After the onset of illness, the virus can be detected in serum, plasma, circulating blood cells and other tissues for 4 to 5 days. During the early stages of the disease, virus isolation, nucleic acid or antigen detection envelop/membrane (E/M) antigen and the non-structural protein 1 (NS1) can be used to diagnose the infection. The NS1 glycoprotein is produced by all flaviviruses and produces a very strong humoral response. High concentrations of these antigens in the form of immune complexes could be detected in patients with both primary and secondary dengue infections up to nine days after the onset of illness.

At the end of the acute phase of infection, serology is the method of choice for diagnosis. IgM antibodies are the first immunoglobulin isotype to appear. These antibodies are detectable in 50 percent of patients by days 3 to 5 after onset of illness, increasing to 80 percent by day 5 and 99 percent by day 10. IgM levels peak about two weeks after the onset of symptoms and then decline generally to undetectable levels over 2 to 3 months. Anti-dengue serum IgG is generally detectable at low titers at the end of the first week of illness, increasing slowly thereafter, with serum IgG still detectable after several months, and probably even for life.

Radiological investigations and ultrasound examination in patients with dengue fever have revealed ascitis, hepatomegaly, splenomegaly, gallbladder wall edema, perihepatic fluid collection, acalculous cholecystitis, and sludge in gallbladder. Gallbladder wall thickness (GBWT) of >3 mm on U/S in DHF patients can be used as a criterion indicating the need of hospitalization. GBWT >5 mm is useful as a criterion for identifying DHF patients at high risk of developing hypovolemic shock with sensitivity of 93.8 percent and specificity of 91.7 percent.²

DIFFERENTIAL DIAGNOSIS OF DENGUE FEVER

Conditions that mimic the febrile phase of dengue infection

Flu-like syndromes	Influenza, measles, chikungunya, infectious mononucleosis, HIV sero-conversion illness
Illnesses with a rash	Rubella, measles, scarlet fever, meningococcal infection, chikungunya, drug reactions
Diarrheal diseases	Rotavirus, other enteric infections
Illnesses with neurological manifestations	Meningo/encephalitis, febrile seizures

Conditions that mimic the critical phase of dengue infection

Infectious	Acute gastroenteritis, malaria, leptospirosis, typhoid, typhus, viral hepatitis, acute HIV seroconversion illness, sepsis, septic shock
Other clinical pictures	Acute abdomen <ul style="list-style-type: none"> – acute appendicitis – acute cholecystitis – perforated viscus Diabetic ketoacidosis Leukopenia and thrombocytopenia ± bleeding Platelet disorders Renal failure Systemic lupus erythematosus

MANAGEMENT OF DENGUE FEVER

On the basis of evaluations of the history, physical examination and/or full blood count and hematocrit, clinicians should be able to determine whether the disease is dengue, which phase it is in (febrile, critical or recovery), whether there are warning signs, the hydration and hemodynamic status of the patient, and whether the patient requires admission. Depending on the clinical manifestations and other circumstances, patients may be sent home (Group A), be referred for in-hospital management (Group B), or require emergency treatment and urgent referral (Group C).¹

Group A—Patients who may be sent home

These are patients who are able to tolerate oral fluids, pass urine at least once every six hours, and do not have any of the warning signs, particularly when fever subsides.

Ambulatory patients should be reviewed daily for disease progression (decreasing white blood cell count, platelets and increasing hematocrit, defervescence and warning signs) until they are out of the critical period. Those with stable hematocrit can be sent home after being advised to return to the hospital immediately if they develop any of the warning signs and to adhere to the following action plan:

- Encourage plenty of oral fluids to replace losses from fever and vomitings, e.g. oral rehydration solution (ORS), fruit juices and other fluids containing electrolytes and sugar. Adequate oral fluid intake may be able to reduce the number of hospitalizations.
- Give paracetamol for high fever if the patient is uncomfortable. The interval of paracetamol dosing should not be less than six hours. Tepid sponge if the patient still has high fever. Do not give acetylsalicylic acid (aspirin), ibuprofen or other non-steroidal

anti-inflammatory agents (NSAIDs) as these drugs may aggravate gastritis or bleeding.

- Instruct the care-givers that the patient should be brought to hospital immediately if any of the following occur: no clinical improvement, deterioration around the time of defervescence, severe abdominal pain, persistent vomiting, cold and clammy extremities, lethargy or irritability/restlessness, bleeding (e.g., black stools or coffee-ground vomiting), not passing urine for more than 6 hours.

Group B—Patients who should be referred for in-hospital management

Some patients may need to be admitted for close observation, particularly as they approach the critical phase. These include patients with warning signs or those with co-existing conditions that may make dengue or its management more complicated (such as infancy, dual infections or patients with congenital anomalies).

If the patient has dengue with warning signs, the action plan should be as follows:

- Obtain a reference hematocrit before fluid therapy. Give only isotonic solutions such as 0.9 percent saline, Ringer's lactate, or Hartmann's solution. Start with 5 to 7 ml/kg/hour for 1 to 2 hours, then reduce to 3 to 5 ml/kg/hr for 2 to 4 hours, and then reduce to 2 to 3 ml/kg/hr or less according to the clinical response.
- Reassess the clinical status and repeat the hematocrit. If the hematocrit remains the same or rises only minimally, continue with the same rate (2 to 3 ml/kg/hr) for another 2 to 4 hours. If the vital signs are worsening and hematocrit is rising rapidly, increase the rate to 5 to 10 ml/kg/hour for 1 to 2 hours. Reassess the clinical status, repeat the hematocrit and review fluid infusion rates accordingly.
- Give the minimum intravenous fluid volume required for maintaining good perfusion and urine output of about 0.5 ml/kg/hr. Intravenous fluids are usually needed for only 24–48 hours. Reduce intravenous fluids gradually when the rate of plasma leakage decreases towards the end of the critical phase. This is indicated by urine output and/or oral fluid intake that is/are adequate, or hematocrit decreasing below the baseline value in a stable patient.
- Patients should be monitored closely until the period of risk is over. A detailed fluid balance should be maintained. Parameters that should be monitored include vital signs and peripheral perfusion (1–4 hourly), urine output (4–6 hourly), hematocrit (before and after fluid replacement, then 6–12 hourly), blood glucose, and other organ functions (such as renal profile, liver profile, coagulation profile, as indicated).

Group C—Patients who require emergency treatment and urgent referral

Patients require emergency treatment and urgent referral when they are in the critical phase of disease, i.e. when they have:

- Severe plasma leakage leading to dengue shock and/or fluid accumulation with respiratory distress;
- Severe hemorrhages;
- Severe organ impairment (hepatic damage, renal impairment, cardiomyopathy, encephalopathy or encephalitis).

All patients with severe dengue should be admitted to a hospital with access to intensive care facilities and blood transfusion. Judicious intravenous fluid resuscitation is the essential and usually sole intervention required. The crystalloid solution should be isotonic and the volume just sufficient to maintain an effective circulation during the period of plasma leakage. Plasma losses should be replaced immediately and rapidly with colloid solutions in patients with hypotensive shock. If possible, obtain hematocrit levels before and after fluid resuscitation.

There should be continued replacement of further plasma losses to maintain effective circulation for 24 to 48 hours. A group and cross match should be done for all shock patients. Blood transfusion should be given only in cases with suspected/severe bleeding.

Fluid resuscitation must be clearly separated from simple fluid administration. This is a strategy in which larger volumes of fluids (e.g. 10–20 ml boluses) are administered for a limited period of time under close monitoring to evaluate the patient's response and to avoid the development of pulmonary edema. The goals of fluid resuscitation include improving central and peripheral circulation (decreasing tachycardia, improving blood pressure, pulse volume, warm and pink extremities, and capillary refill time <2 seconds) and improving end-organ perfusion, i.e. stable consciousness level, urine output ≥ 0.5 ml/kg/ hour, decreasing metabolic acidosis.

TREATMENT OF SHOCK

Compensated Shock

The action plan for treating patients with compensated shock is as follows (Flow chart 1):

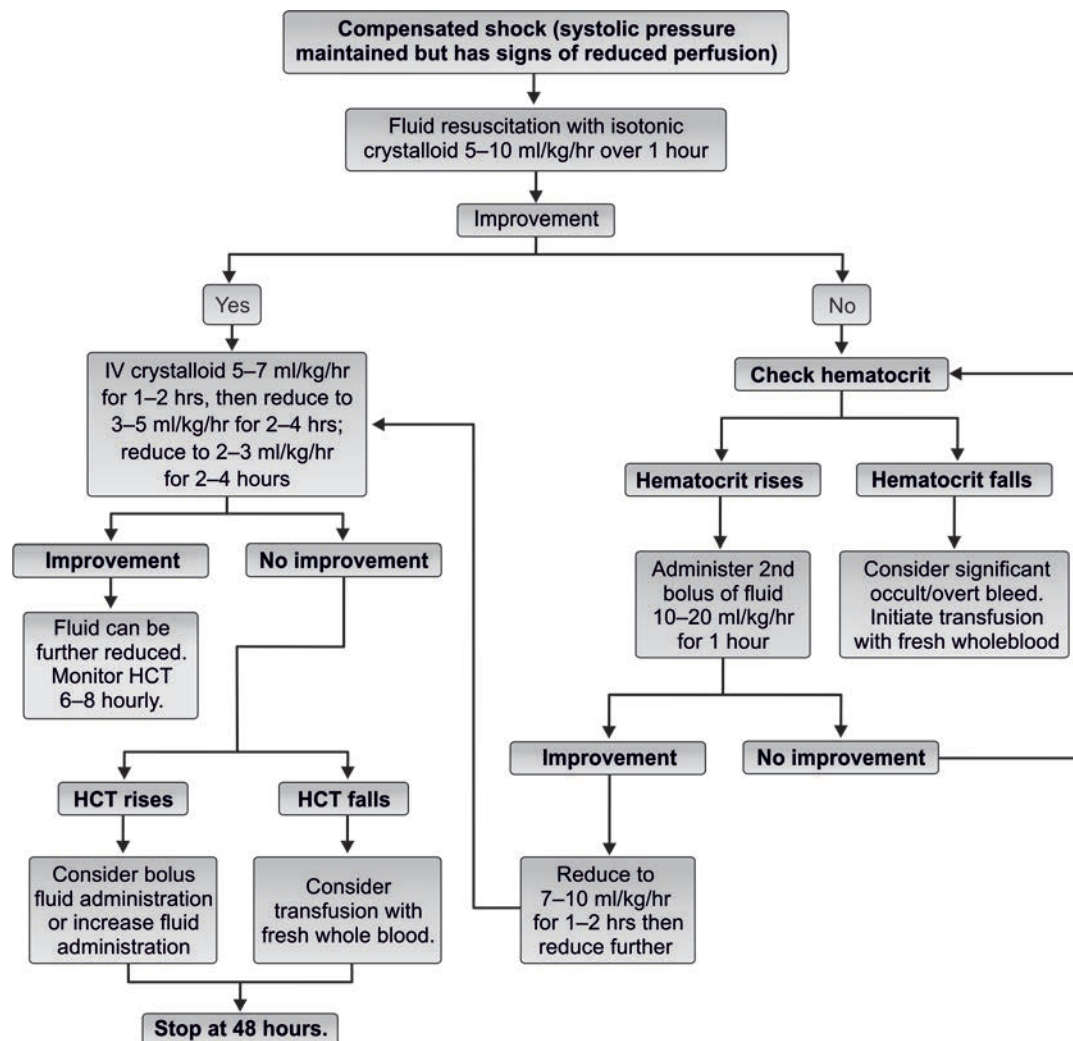
- Start intravenous fluid resuscitation with isotonic crystalloid solutions at 5–10 ml/kg/hour over one hour. Then reassess the patient's condition (vital signs, capillary refill time, hematocrit, urine output). The next steps depend on the situation.
- If the patient's condition improves, intravenous fluids should be gradually reduced to 5–7 ml/kg/hr for 1–2 hours, then to 3–5 ml/kg/hr for 2–4 hours, then to 2–3 ml/kg/hr, and then further depending on hemodynamic status, which can be maintained for up to 24–48 hours.

- If vital signs are still unstable (i.e. shock persists), check the hematocrit after the first bolus. If the hematocrit increases or is still high (>50%), repeat a second bolus of crystalloid solution at 10 to 20 ml/kg/hr for one hour. After this second bolus, if there is improvement, reduce the rate to 7 to 10 ml/kg/hr for 1 to 2 hours, and then continue to reduce as above. If hematocrit decreases compared to the initial reference hematocrit (<40% in children and adult females, <45% in adult males), this indicates bleeding and the need to cross-match and transfuse blood as soon as possible.
- Further boluses of crystalloid or colloidal solutions may need to be given during the next 24 to 48 hours.

Hypotensive Shock

Patients with hypotensive shock should be managed more vigorously. The action plan for treating patients with hypotensive shock is as follows (Flow chart 2):

- Initiate intravenous fluid resuscitation with crystalloid or colloid solution at 20 ml/kg as a bolus given over 15 minutes to bring the patient out of shock as quickly as possible.
- If the patient's condition improves, give a crystalloid/colloid infusion of 10 ml/kg/hr for one hour. Then continue with crystalloid infusion and gradually reduce to 5–7 ml/kg/hr for 1–2 hours, then to 3–5 ml/kg/hr for 2–4 hours, and then to 2–3 ml/kg/hr or less, which can be maintained for up to 24–48 hours.
- If vital signs are still unstable (i.e. shock persists), review the hematocrit obtained before the first bolus. If the hematocrit was low (<40% in children and adult females, <45% in adult males), this indicates bleeding and the need to cross match and transfuse blood as soon as possible.
- If the hematocrit was high compared to the baseline value, change intravenous fluids to colloid solutions at 10–20 ml/kg as a second bolus over 30 minutes to one hour. After the second bolus, reassess the patient. If the condition improves, reduce the rate to 7–10 ml/kg/hr for 1–2 hours, then change back to crystalloid solution and reduce the rate of infusion as mentioned above. If the condition is still unstable, repeat the hematocrit after the second bolus.
- If the hematocrit decreases compared to the previous value (<40% in children and adult females, <45% in adult males), this indicates bleeding and the need to cross-match and transfuse blood as soon as possible. If the hematocrit increases compared to the previous value or remains very high (>50%), continue colloid solutions at 10–20 ml/kg as a third bolus over one hour. After this dose, reduce the rate to 7–10 ml/kg/hr for 1–2 hours, then change back to crystalloid solution and reduce the rate of infusion as mentioned above when the patient's condition improves.

Flow chart 1: Algorithm for fluid management in compensated shock

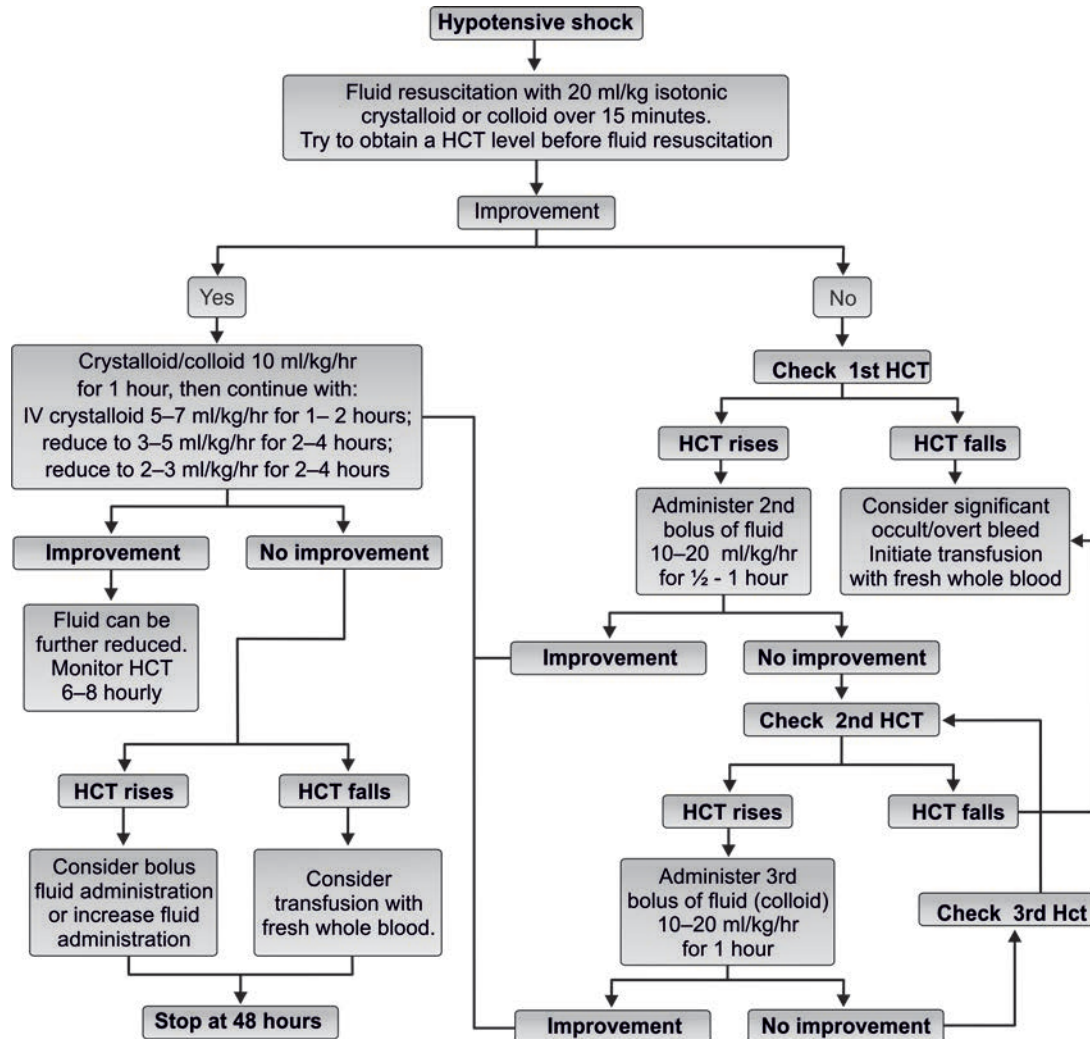
- Further boluses of fluids may need to be given during the next 24 hours. The rate and volume of each bolus infusion should be titrated to the clinical response.

Patients with dengue shock should be frequently monitored until the danger period is over. A detailed fluid balance of all input and output should be maintained. Parameters that should be monitored include vital signs and peripheral perfusion (every 15–30 minutes until the patient is out of shock, then 1–2 hourly). A patient with severe dengue should have an arterial line placed as soon as practical. The reason for this is that in shock states, estimation of blood pressure using a cuff is commonly inaccurate. The use of an indwelling arterial catheter allows for continuous and reproducible blood pressure measurements and frequent blood sampling on which decisions regarding therapy can be based. Monitoring of ECG and pulse oximetry should be available in the intensive care unit. In addition, there should be monitoring of arterial or venous blood gases, lactate, total carbon dioxide/bicarbonate, blood glucose and other organ functions (such

as renal profile, liver profile, coagulation profile, before resuscitation and as indicated).

Changes in the hematocrit are a useful guide to treatment. However, changes must be interpreted in accordance with the hemodynamic status, the clinical response to fluid therapy and the acid-base balance. For instance, a rising or persistently high hematocrit together with unstable vital signs (particularly narrowing of the pulse pressure) indicates active plasma leakage and the need for a further bolus of fluid replacement. However, a rising or persistently high hematocrit together with stable hemodynamic status and adequate urine output does not require extra intravenous fluid. In the latter case, continue to monitor closely and it is likely that the hematocrit will start to fall within the next 24 hours as the plasma leakage stops.

A decrease in hematocrit together with unstable vital signs (particularly narrowing of the pulse pressure, tachycardia, metabolic acidosis, poor urine output) indicates major hemorrhage and the need for urgent blood transfusion. Yet a decrease in hematocrit together with stable

Flow chart 2: Algorithm for fluid management in hypotensive shock

hemodynamic status and adequate urine output indicates hemodilution and/or reabsorption of extravasated fluids, so in this case intravenous fluids must be discontinued immediately to avoid pulmonary edema.

Treatment of Hemorrhagic Complications

Mucosal bleeding may occur in any patient with dengue but, if the patient remains stable with fluid resuscitation/replacement, it should be considered as minor. In patients with profound thrombocytopenia, ensure strict bed rest and protect from trauma to reduce the risk of bleeding. Do not give intramuscular injections to avoid hematoma. It should be noted that prophylactic platelet transfusions for severe thrombocytopenia in otherwise hemodynamically stable patients have not been shown to be effective and are not necessary.

Patients at risk of major bleeding are those who:

- Have prolonged/refractory shock;

- Have renal or liver failure and/ or severe and persistent metabolic acidosis;
- Are given non-steroidal anti-inflammatory agents;
- Have pre-existing peptic ulcer disease;
- Are on anticoagulant therapy;
- Have any form of trauma, including intramuscular injection.

Blood transfusion is life-saving and should be given as soon as severe bleeding is suspected or recognized. However, blood transfusion must be given with care because of the risk of fluid overload. Note that hematocrit of <30 percent as a trigger for blood transfusion, as recommended in the surviving sepsis campaign guidelines, is not applicable to severe dengue. The reason for this is that, in dengue, bleeding usually occurs after a period of prolonged shock that is preceded by plasma leakage. During the plasma leakage the hematocrit increases to relatively high values before the onset of severe bleeding. When bleeding occurs, hematocrit will then drop from this high level. As a result,

hematocrit levels may not be as low as in the absence of plasma leakage.

TREATMENT OF FLUID OVERLOAD

Fluid overload with large pleural effusions and ascites is a common cause of acute respiratory distress and failure in severe dengue. Other causes of respiratory distress include acute pulmonary edema, severe metabolic acidosis from severe shock, and acute respiratory distress syndrome (ARDS).

Causes of fluid overload are:

- excessive and/or too rapid intravenous fluids;
- incorrect use of hypotonic rather than isotonic crystalloid solutions;
- inappropriate use of large volumes of intravenous fluids;
- inappropriate transfusion of FFP, platelet concentrates and cryoprecipitates;
- continuation of intravenous fluids after plasma leakage has resolved;
- co-morbid conditions like congenital heart disease, chronic lung and renal diseases.

The management of fluid overload varies according to the phase of the disease and the patient's hemodynamic status. If the patient has stable hemodynamic status and is out of the critical phase, stop intravenous fluids but continue close monitoring. If necessary, give oral or intravenous furosemide 0.1 to 0.5 mg/kg/dose once or twice daily, or a continuous infusion of furosemide 0.1 mg/kg/ hour. Monitor serum potassium and correct the ensuing hypokalemia.

If the patient has stable hemodynamic status but is still within the critical phase, reduce the intravenous fluid accordingly. Avoid diuretics during the plasma leakage phase because they may lead to intravascular volume depletion.

Patients who remain in shock with low or normal hematocrit levels but show signs of fluid overload may have occult hemorrhage. Further infusion of large volumes of intravenous fluids will lead only to a poor outcome. Careful fresh whole blood transfusion should be initiated as soon as possible. If the patient remains in shock and the hematocrit is elevated, repeated small boluses of a colloid solution may help.

Supportive Care and Adjuvant Therapy

Supportive care and adjuvant therapy may be necessary in severe dengue. This may include:

- renal replacement therapy, with a preference to continuous veno-venous hemodialysis (CVVH), since peritoneal dialysis has a risk of bleeding;
- vasopressor and inotropic therapies as temporary measures to prevent life threatening hypotension in dengue shock and during induction for intubation, while correction of intravascular volume is being vigorously carried out;

- further treatment of organ impairment, such as severe hepatic involvement, encephalopathy or encephalitis, cardiac abnormalities, etc.

Choice of IV Fluids

Intravenous fluid therapy is the cornerstone for the management of dengue hemorrhagic fever. The amount of fluid and the nature of fluid should be decided judiciously. Based on the three randomized controlled trials comparing the different types of fluid resuscitation regime in dengue shock in children, there is no clear advantage to the use of colloids over crystalloids in terms of the overall outcome. However, colloids may be the preferred choice if the blood pressure has to be restored urgently, i.e. in those with pulse pressure less than 10 mm Hg. Colloids have been shown to restore the cardiac index and reduce the level of hematocrit faster than crystalloids in patients with intractable shock.^{7,8}

Crystalloids

- 0.9 percent saline ("normal" saline)
- Normal plasma chloride ranges from 95 to 105 mmol/L. 0.9 percent Saline is a suitable option for initial fluid resuscitation, but repeated large volumes of 0.9 percent saline may lead to hyperchloremic acidosis. Hyperchloremic acidosis may aggravate or be confused with lactic acidosis from prolonged shock. Monitoring the chloride and lactate levels will help to identify this problem. When serum chloride level exceeds the normal range, it is advisable to change to other alternatives such as Ringer's lactate.

Ringer's Lactate

Ringer's lactate has lower sodium (131 mmol/L) and chloride (115 mmol/L) contents and an osmolality of 273 mOsm/L. It may not be suitable for resuscitation of patients with severe hyponatremia. However, it is a suitable solution after 0.9 percent saline has been given and the serum chloride level has exceeded the normal range. Ringer's lactate should probably be avoided in liver failure and in patients taking metformin where lactate metabolism may be impaired.

Colloids

The types of colloids are gelatin-based, dextran-based and starch-based solutions. One of the biggest concerns regarding their use is their impact on coagulation. Theoretically, dextrans bind to von Willebrand factor/factor VIII complex and impair coagulation the most. However, this was not observed to have clinical significance in fluid resuscitation in dengue shock. Of all the colloids, gelatin has the least effect on coagulation but the highest risk of allergic reactions. Allergic reactions such as fever, chills and rigors have also been observed in Dextran 70. Dextran 40 can potentially cause an osmotic renal injury in hypovolemic patients.^{7,8}

Role of Platelet Transfusion in Dengue Fever

There are no clear indications of platelet transfusion in dengue fever as no benefit has been reported or recorded following platelet transfusion. Platelets should not be transfused blindly and decisions should be based on clinical judgment. The World Health Organization recommends that platelets should be transfused only if the patient is bleeding or has a platelet count less than 10,000/mm³.

Role of Steroids in Dengue Fever

It has been shown that corticosteroids which have been inadvertently used in treatment have no clear indication or therapeutic benefit in the management of dengue fever and shock.⁹ The World Health Organization does not mention corticosteroids in the treatment guidelines for dengue shock syndrome

Criteria for Discharge

A patient may be discharged from the hospital if all of the following are present—there is absence of fever for at least 24 hours without the use of antipyretics, there is return of appetite, visible clinical improvement, adequate urine output, no vomiting, no bleeding, a stable hematocrit, convalescent confluent skin rash, a platelet count >50,000/mm³ and no respiratory distress.

Vaccine against Dengue

Currently there is no licensed vaccine against dengue virus. Field testing of an attenuated tetravalent vaccine is currently underway.

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Chikungunya Fever

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INTRODUCTION

Chikungunya virus (CHIKV) is a re-emerging arboviral disease of public health concern. It is a relatively benign form but debilitating illness caused by chikungunya virus spread by the bite of infected mosquitoes. The disease resembles dengue fever without hemorrhagic manifestation and is characterized by severe, sometimes persistent joint pain (arthritis), fever and rash. Severe arthralgia especially in the small joints of hands and toes are the characteristics of the disease. Many outbreaks have occurred in Africa and Asia.

HISTORY

Historically the disease was described first in 18th century by Dr David Bylon, who himself suffered from high fever, severe joint pain, and prolonged persistent joint symptoms even after recovery from acute illness. This description would have probably referred to “Chikungunya”. The name chikungunya is given by Lumsden’s initial 1955 report, which is derived from the Makonde word ‘kungunyala’, meaning to dry-up or become contorted. Subsequently, Marion Robinson who first described the disease following an outbreak in 1952 on the Makonde Plateau, between Tanganyika and Mozambique, glossed the Makonde term more specifically as “that which bends up” this refers to the stooped posture adopted by the patient as a result of the arthritis symptoms that the patient develops.

EPIDEMIOLOGY

Chikungunya fever is endemic in parts of Africa (Transvaal, Uganda, Congo, Nigeria, Ghana, Zimbabwe, Senegal, Burkina Faso, and Cameroon), South-east Asia (Philippines, Malaysia, Cambodia) and the Indian subcontinent (Pakistan and southern India) (Fig. 1).

In India, a major epidemic of chikungunya fever was reported during the last millennium viz.; 1963 (Kolkata), 1965 (Puducherry and Chennai in Tamil Nadu, Rajahmundry, Vishakhapatnam and Kakinada in Andhra Pradesh; Sagar in Madhya Pradesh; and Nagpur in Maharashtra) and 1973 (Barsi in Maharashtra). Thereafter, sporadic cases also continued to be recorded especially in Maharashtra state during 1983 and 2000. Like malaria and dengue, this infection has almost become endemic in India, especially central and south India.

In 2006, there was a big outbreak in Andhra Pradesh in India where the initial cases were reported at Hyderabad and Anantpur districts in December 2005. There have been reports of large scale outbreaks of chikungunya in Gulbarga, Tumkur, Bidar, Raichur, Bellary, Kolar, and Bijapur districts in Karnataka state in December 2005. A separate outbreak of chikungunya fever was reported in Maharashtra (from Malegaon town in Nasik district) and Orissa in March 2006. In 2006, the Indian states of Tamil Nadu, Karnataka, Andhra Pradesh, Maharashtra, Madhya Pradesh, Gujarat and Kerala had reported 1.1 million cases. Many cases were recorded from Bengaluru and Tamil Nadu in May and June 2006 in Salem and Chennai. Recently, in August and September 2006, many cases of fever, arthralgia/arthritis and rashes have been reported from Ajmer, Bhilwara district of central Rajasthan, where 3 cases were found to be positive for chikungunya in Hurda village, district Bhilwara. The disease was reported in a total of 16 states of country in 2006 and within a period of 10 months of onset of epidemic there were over 1.25 million suspected cases on chikungunya rising to 1.39 million by the end of the year. In 2007, till October there were 37,683 reported cases.

The re-emergence of CHIKV in the Indian subcontinent as well as in southern India may be due to a variety of

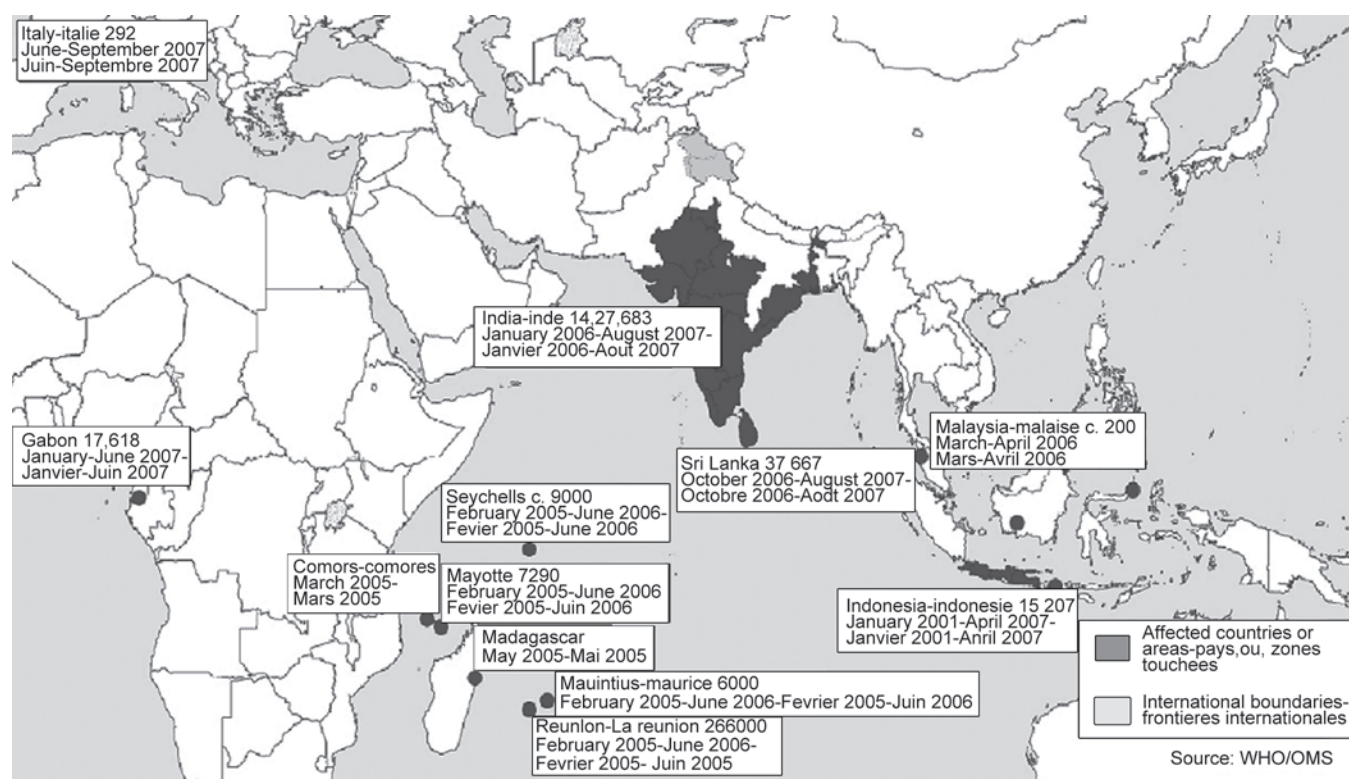


Fig. 1: Geographical distribution of Chikungunya cases 2001-2007

social, environmental, behavioral, biological and genetic factors. Genetic analysis of the recent outbreak has suggested that the increased severity of the disease may be due to a change in the genetic sequence, altering the virus' coat protein, which potentially allows it to multiply more easily in mosquito cells. Two distinct lineage of CHIKV have been delineated: one containing all isolates from Africa, and the second comprising all African as well as Asian strains. The Indian viruses isolated from 1963 through 1973 belonged to the Asian genotype, whereas the current isolates belonged to the central/East African genotype. Also, lack of herd immunity within the country was the contributing factor for the epidemics.

CHIKUNGUNYA VIRUS AND MODE OF TRANSMISSION

Chikungunya virus (CHIKV) is a member of the genus *Alphavirus*, in the family *Togaviridae*. It is a single stranded RNA virus, heat labile and sensitive to temperatures above 58°C. Its phospholipid envelope contains hemagglutinin protein spikes.

Chikungunya is spread by the bite of an infected *Aedes* mosquito, primarily *Aedes aegypti* and recently *A. albopictus* which appears to be the cause of the recent epidemic in Asia. *Aedes aegypti* is the common vector responsible for transmission in urban areas whereas *Aedes albopictus* has been implicated in rural areas. In 2007 outbreak in Kerala, it was seen that *A. albopictus* played a very important role. This was attributed to a change in the viral genome

(A226V mutation in the envelope glycoprotein of CHIKV) which was responsible for the increased infectivity. A larger range of *Aedes* species (*A. furcifer*, *A. vittatus*, *A. fulgens*, *A. luteocephalus*, *A. dalzielii*, *A. vigilax*, *A. camptorhynchites*) transmit the virus in Africa, and *Culex annulirostris*, *Mansonia uniformis*, and *Anopheles* mosquitoes have also occasionally been incriminated. The adult female mosquito rests in cool and shady areas in domestic and peridomestic settings and bites during day time. The *Aedes* mosquitoes that transmit chikungunya breed in a wide variety of manmade container (discarded tyres, flowerpots, old oil drums, animal water troughs, water storage vessels, and plastic food containers) which are common around human dwellings. Lack of public health infrastructure and all factors that promote uncontrolled mosquito breeding are responsible for outbreaks of chikungunya epidemic.

Humans are the major source of reservoir of chikungunya virus for mosquitoes. Some nonhuman primates like monkeys are the reservoir in Africa, in which it is transmitted by *Aedes fureifer* and Africans. CHIKV is believed to have a sylvatic cycle and is maintained in nature by vervet monkeys, baboons, lemurs and bald mice. In humans the virus has no age or sex specificities but it has been seen that children, elderly and immunocompromised are the most severely affected.

Few cases of mother to fetus infection have been reported from Asia, which occurs between 3 and 4 months of pregnancy. Infection appears to confer lasting immunity.

PATHOGENESIS

Detailed pathogenesis of chikungunya fever is not known. After the bite from an infected mosquito the virus multiplies in lymphoid and myeloid organs and subsequently induces cellular and humoral immunity which leads to manifestations of the disease. Inflammatory damage to the cartilage in the form of necrosis, collagenosis and fibrosis leads to articular symptoms. A study of the cytokine release pattern in a patient with chikungunya has shown that levels of IFN γ inducible protein 10, monocyte chemoattractant protein and IL 8 are elevated while the levels of IFN γ , TNF α , IL 1 β , 6, 10 and 12 notably normal. The low levels of IFN γ which is the antiviral cytokine possibly reflects a way in which chikungunya virus evades host defenses.

CLINICAL FEATURES

Clinical manifestations are very variable ranging from asymptomatic illness to severe debilitating disease. Children are among the group at maximum risk of severe manifestation of disease. After infection with chikungunya virus, there is a silent incubation period lasting 2 to 4 days on average (range 1 to 12 days). Viremia persists for up to 5 days from the clinical onset. Clinical onset is abrupt with high fever, headache, back pain, myalgia and arthralgia. The various clinical features are depicted in Table 1. In infants, acrocyanosis and symmetrical superficial vesiculobullous lesions are characteristic along with fever and meningoencephalitis.

Fever

The fever varies from low grade to high grade, lasting for 24 to 48 hours. Fever rises abruptly in some, reaching 39 to 40°C, with shaking chills and rigor and usually subsides with use of antipyretics. No diurnal variation was observed for the fever. Biphasic fever pattern like dengue can be seen.

Arthritis

Erratic, relapsing and incapacitating arthralgia is the hallmark of chikungunya, although it rarely affects children. It may persist for several months. Arthralgia/ arthritis

appear to affect 73 to 80 percent of patients with serologically confirmed chikungunya virus. Radiological findings are normal and biological markers of inflammation are normal or moderately elevated. In the recent outbreaks many patients presented with arthralgia without fever. The joint pain tends to be worse in the morning, relieved by mild exercise and exacerbated by aggressive movements. The pain may remit for 2 to 3 days and then reappear in a saddle back pattern. Migratory polyarthritides with effusions may be seen in around 70 percent cases, but resolves in the majority. Ankles, wrists and small joints of the hand were the worst affected. Larger joints like knee and shoulder and spine were also involved. There is a tendency for early and more significant involvement of joints with some trauma or degeneration. Occupations with predominant overuse of smaller joints predisposed those areas to be affected more. (e.g. interphalangeal joints in rubber tappers, ankle joints in those standing and walking for a long time). The classical bending phenomenon was probably due to the lower limb and back involvement which forced the patient to stoop down and bend forward.

Dermatological Manifestations

Transient maculopapular rash is seen in up to 50 percent patients. Approximately 73 percent of patients develop skin lesions during the acute phase of the illness (within 7 days), accompanying high fever and severe muscle and joint pain. Children may develop rash on day 1 of illness itself and though commonly truncal in location it may involve the face as well. Others may develop skin problems after the fever had gone but when muscle and joint pain are still present (within 1 month), and a handful of patients develop skin problems more than 1 month after the acute illness.

Intertriginous aphthous-like ulcers and vesiculobullous eruptions in infants can also occur. Stomatitis and oral ulcers can occur in 15 to 25 percent of patients. Nasal blotchy erythema followed by photosensitive hyperpigmentation was observed more commonly in the recent epidemic. Most skin lesions recovered completely except in cases where the photosensitive hyperpigmentation persist. Rash and bullous cutaneous manifestations frequently observed in chikungunya virus can be detected by PCR in blister fluid.

Table 1: Clinical manifestations of chikungunya fever

<i>Common clinical features</i>	<i>Infrequent manifestations</i>	<i>Rare in adults but seen sometimes in children</i>
Fever (92%)	Rash	Photophobia
Arthralgia (87%)	Stomatitis	Retro-orbital pain
Backache (67%)	Oral ulcer	Vomiting
Headache (62%)	Hyperpigmentation	Diarrhea
	Exfoliative dermatitis	Meningeal syndrome
		Acute encephalopathy

Neurologic Manifestations

Recent studies have described a wide range of neurologic manifestations, including meningoencephalitis, seizures and Guillain-Barré syndrome. During the outbreak period from January 2006 through October 2006, CHIKV was responsible for 14 percent of suspected CNS infections. Neurological complications such as meningoencephalitis were reported in a few patients during the first Indian outbreak in 1973, and during the recent Indian outbreak.

Ophthalmological Manifestations

The main ocular manifestation associated with the recent epidemic outbreak of chikungunya virus infection in South India included granulomatous and nongranulomatous anterior uveitis, optic neuritis, retrobulbar neuritis and dendritic lesions. Photophobia and retro-orbital pain have also been observed. The visual prognosis generally is good, with most patients recovering good vision.

Hemorrhagic Manifestation

Classical case of chikungunya is not thought to produce hemorrhagic manifestation. In 1963 to 1964 outbreak in Kolkata, hemorrhagic manifestation were seen. According to Thailand epidemiological study the incidence of chikungunya in children with hemorrhagic fever was nearly 7.6 percent.

SEQUELAE

Persistent arthralgia, joint stiffness, restriction of joint movement have been observed in recent outbreaks. Enthesopathy and tendonitis of tendo-Achilles was observed in up to 53 percent of those who had musculoskeletal involvement. Neurological, emotional and dermatologic sequelae are also described.

CHIKUNGUNYA IN PREGNANCY AND IN NEWBORN

There is a 48 percent risk of infection at birth if the virus is present in the mother's blood. IgG passes through the placenta and confers immunity to the fetus. Such an infection in the fetus is rarely serious, and more than 90 percent

of the infected newborns recover quickly without sequelae. The possible risks of embryopathy, fetopathy and late sequelae are unknown, and prospective follow-up of these "chikungunya virus babies" is warranted.

COMPLICATIONS

Chikungunya is a self-limiting illness. The major causes for acute morbidity are severe dehydration, electrolyte imbalance and hypoglycemia. Recovery is the rule, but 10 to 15 percent patients had chronic joint pain and stiffness. Major complications, though rare, are bleeding disorders (epistaxis, upper gastrointestinal bleed) as it causes thrombocytopenia, superadded by injudicious use of NSAIDs; neurological complications such as meningoencephalitis and paresis of limbs; cardiovascular decompensation; pneumonia and respiratory failure. Few deaths have been reported in the recent epidemics.

DIAGNOSIS

The chikungunya case definition adapted by World Health Organization (WHO) is derived from European Centre for Disease Control (ECDC) has clinical, epidemiological and laboratory criteria (Table 2). On this basis, cases are to be categorized as:

Possible case: A patient meeting clinical criteria.

Probable case: A patient meeting both the clinical and epidemiological criteria.

Confirmed case: A patient meeting the laboratory criteria, irrespective of the clinical presentation.

DIFFERENTIAL DIAGNOSIS

Due to similarity in symptoms with other arboviral (dengue, sindbis, ross river), viral (rubella, parvovirus B19, alphaviruses, mumps, VZV, EBV, CMV, measles, HTLV-1, HIV, hepatitis), bacterial (meningococcemia, scarlet fever, typhoid) and parasitic diseases (leptospirosis, malaria) differential diagnosis of CHIKV plays an important role. Chikungunya and dengue are among the most difficult diseases to distinguish, especially because simultaneous co-infection can occur. In the only published study

Table 2: Chikungunya case definition adapted derived from European Center for Disease Control (ECDC)

<i>Clinical criteria</i>	<i>Epidemiological criteria</i>	<i>Laboratory criteria</i>
Acute onset of fever >38.5°C and severe arthralgia/arthritis not explained by other medical conditions.	Residing or having visited epidemic areas, having reported transmission within 15 days prior to the onset of symptoms.	At least one of the following tests in the acute phase <ul style="list-style-type: none"> • Virus isolation • Presence of viral RNA by RT-PCR • Presence of virus specific IgM antibodies in single serum sample collected in acute or convalescent stage • Four-fold increase in IgG values in samples collected at least 3 weeks apart.

comparing the symptoms of chikungunya and dengue, done in Thailand, chikungunya symptom onset was more abrupt, fever was shorter lived, and rash, conjunctival injection, and arthralgia were more frequent than in dengue.

LABORATORY MARKERS

No significant pathognomonic hematological finding is seen. Leukopenia with lymphocyte predominance is the usual observation. Thrombocytopenia is rare. Erythrocyte sedimentation rate is usually elevated. C-Reactive protein is increased during the acute phase and may remain elevated for a few weeks.

Common laboratory tests for chikungunya include RT-PCR, virus isolation, and serological tests. Virus isolation provides the most definitive diagnosis but takes 1 to 2 weeks for completion and must be carried out in biosafety level 3 laboratories. The technique involves exposing specific cell lines to samples from whole blood and identifying chikungunya virus-specific responses. RT-PCR using nested primer pairs to amplify several chikungunya-specific genes from whole blood. Results can be determined in 1 to 2 days. Serological diagnosis uses an ELISA assay to measure chikungunya-specific IgM levels. Results require 2 to 3 days and false positives result can occur with infection via other related viruses such as O'nyong-nyong virus and Semliki forest virus. In some persons it may take 6 to 12 weeks for the IgM antibodies to appear in sufficient concentration to be picked up in ELISA.

TREATMENT

There is no specific antiviral drug for CHIKV. Treatment is entirely symptomatic. Paracetamol is the drug of choice with use of other analgesics if paracetamol does not provide relief. Aspirin is preferably avoided for fear of gastrointestinal and other side effects like Reye's syndrome. During the acute stage of the disease, steroids are not usually indicated because of the adverse effects. Adequate rest in a warm environment avoiding damp surroundings is advised. Heat may increase/worsen joint pain and is therefore best to avoid during acute stage. Cold compresses may help in reducing joint damage. Mild forms of exercise and physiotherapy are recommended in recovering persons. Hydroxychloroquine or chloroquine phosphate for period of 4 weeks can be used in cases where arthralgia is refractory to other drugs.

Hospitalization may be required if fever persists for more than 5 days, there is intractable pain, postural dizziness, cold extremities, decreased urine output, any bleeding under the skin or through any orifice, incessant vomiting, altered sensorium and if child is less than 1 year of age.

For chronic osteoarticular problems, since an immunologic etiology is suspected in chronic cases, a short

course of steroids may be useful. Care must be taken to monitor all adverse events. Proper and timely physiotherapy will help patients with contractures and deformities. Non-weight bearing exercises may be suggested. Surgery may be indicated in severe and disabling contractures. For progressive defects in vision due to uveitis or retinitis, steroids treatment may be warranted. Hyperpigmentation and papular eruptions may be managed with zinc oxide cream and/ or calamine lotion. Scrotal and aphthous like ulcers on the skin and intertriginous areas may be managed by saline compresses, and topical or systemic antibiotics if secondarily infected.

PROGNOSIS

Recovery from the disease varies by age. Younger patients recover within 5 to 15 days; middle-aged patients recover in 1 to 2.5 months. Recovery is longer for the elderly. The severity of the disease as well as its duration is less in younger patients and pregnant women.

PREVENTION

The best way to prevent chikungunya virus infection is to avoid mosquito bites. There is no vaccine or preventive drug currently available. Prevention tips are similar to those for other viral diseases transmitted by mosquitoes, such as dengue or West Nile. The following measures can reduce the chances of infections:

Personal Protection

- Using insect repellent containing DEET, picaridin.
- Wearing long sleeves and pants (ideally treat clothes with permethrin or another repellent).
- Having secure screens on windows and doors to keep mosquitoes out.
- Use of mosquito nets.

Reduction of Aedes Mosquito Breeding

- *Source reduction method:* (i) By elimination of all potential vector breeding places near the domestic or peridomestic areas. (ii) Not allowing the storage of water for more than a week. This could be achieved by emptying and drying the water containers once in a week. (iii) Straining of the stored water by using a clean cloth once a week to remove the mosquito larvae from the water and the water can be reused. The sieved cloth should be dried in the sun to kill immature stages of mosquitoes.
- *Use of larvicides:* (i) Where the water cannot be removed but used for cattle or other purposes, temephos can be used once a week at a dose of 1 ppm (parts per million). (ii) Pyrethrum extract (0.1% ready-to-use emulsion) can be sprayed in rooms.

- *Biological control*: (i) Like introduction of larvivorous fish, namely *Gambusia* and guppy in water tanks and other water sources.

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Leptospirosis

Prabhat Maheshwari, Vishal Vaidya

INTRODUCTION

Leptospirosis is an emerging infectious disease of global importance as illustrated by recent large outbreaks in Asia, central and South America and the United States. The spectrum of disease ranges from subclinical infections to a severe syndrome involving multiorgan involvement leading to high mortality.

ETIOLOGY

Leptospirosis is a zoonotic disease of ubiquitous distribution, caused by infection with spirochetes belonging to the order Spirochaetales and the family Leptospiraceae. The genus *Leptospira* contains two species *L. interrogans* sensu lato and *L. biflexa* sensu lato. The leptospires are thin, coiled, gram-negative, aerobic organisms, 6 to 20 μm in length. They are motile, with hooked ends and paired axial flagella (one on each end), enabling them to burrow into tissue. Motion is marked by continual spinning on the long axis. They are unique among the spirochetes as they can be isolated on artificial media. Growth is slow on primary isolation and may require up to 13 weeks.

EPIDEMIOLOGY

Leptospirosis is a zoonosis more commonly seen in tropical and subtropical areas. Large cluster of cases are seen around the monsoon season before and after heavy rainfall. The areas in India, where epidemics have been reported include Maharashtra, Gujarat, Orissa, Karnataka, Kerala and Andaman Islands. Cases of leptospirosis have been reported from Mumbai from the year 1999 to 2000 onwards, and concurrent outbreaks of leptospirosis and dengue have been shown to have occurred in the slums of Mumbai city.

Leptospira infect many species of animals, including dogs, cats, livestock, and birds; however, the rat (*Rattus*

norvegicus) is the main source of human infection. Infected animals excrete spirochetes in urine for several weeks, as the organisms can remain in the convoluted tubules of the kidneys of host animals for long periods. The majority of human cases worldwide result from occupational exposure to water (or flood waters) or soil contaminated with rat urine. Transmission to human occurs commonly through direct contact of abraded skin, mucous membrane or conjunctiva with urine, blood or tissue of an infected animal or through exposure to contaminated environment. Human-to-human transmission is rare. The majority of human cases worldwide result from occupational exposure to water or soil contaminated with rat urine. Occupational groups with a relatively higher incidence of this disease include farmers, agricultural workers, veterinarians, animal handlers, rodent control workers, laboratory workers and those exposed to flood waters. Recreational exposures in water sports are significantly associated with leptospirosis. Poor sanitation and hygiene affect the incidence of the disease. In children, the risk factors for acquiring the disease include school-going age, exposure to flood waters, contact of bare feet with mud, wading through river, and contact with domestic animals.

PATHOGENESIS

The pathogenesis of leptospirosis is incompletely understood (Fig. 1):

- Leptospires are believed to enter the host through abrasions in healthy skin, through sodden and water-logged skin, directly through intact mucous membranes especially the conjunctiva, and lining of oro and nasopharynx. Virulent organisms in a susceptible host gain rapid access to the bloodstream through the lymphatics, resulting in leptospiremia and subsequent spread to all organs. Multiplication takes place in blood and in tissues, and leptospires can be isolated from blood and cerebrospinal fluid during the first

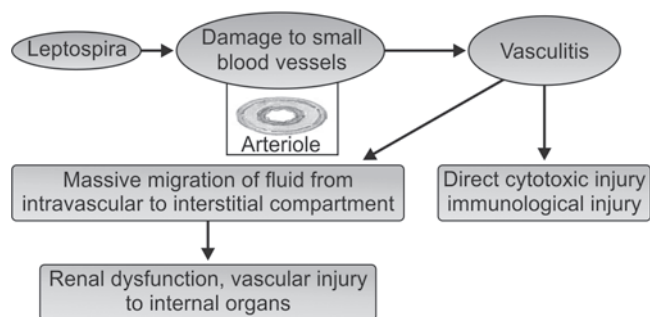


Fig. 1: Pathogenesis of severe disease

4 to 10 days of illness. During acute infection, leptospires are thought to multiply in the small blood vessel endothelium, causing damage and resulting in vasculitis. The major clinical manifestations of the disease are believed to be secondary to vasculitis, which can affect nearly any organ system. Kidneys and liver are the organs that are affected the most.

- In the kidneys, they cause interstitial nephritis and tubular necrosis. Hypovolemia due to impaired capillary permeability can result in renal failure. Liver involvement is marked by centrilobular necrosis and Kupffer cell proliferation, with hepatocellular dysfunction. Pulmonary involvement is secondary to alveolar and interstitial vascular damage resulting in hemorrhage. This complication is considered to be the major cause of leptospirosis-associated death. Skeletal muscle involvement is secondary to edema, myofibril vacuolization, and vessel damage. The damage to the vascular system as a whole can result in capillary leakage, hypovolemia and shock. Many patients with leptospirosis may develop disseminated intravascular coagulation (DIC), hemolytic uremic syndrome (HUS), thrombotic thrombocytopenic purpura (TTP), and vasculitis. Thrombocytopenia indicates severe disease and should raise suspicion for a risk of bleeding.

CLINICAL MANIFESTATIONS

Leptospirosis is characterized by broad-spectrum of clinical manifestations which vary from influenza like illness to fulminant fatal disease with hepatorenal dysfunction and hemorrhagic phenomena. The incubation period is usually 5 to 14 days but has been described from 72 hours to a month or more. Many leptospira infected persons remain asymptomatic. Clinical manifestations in symptomatic cases can vary from mild to serious or even fatal. The mild form constitutes majority of symptomatic patients and is usually the anicteric form of leptospirosis with or without meningitis. Around 5 to 10 percent constitutes the icteric form (Weil's syndrome).

The clinical presentation is biphasic. Initial or septicemic phase, which lasts 2 to 7 days, is characterized by flu-like illness. A brief period of well-being is followed by

second, immune or leptospiruric phase which is marked by appearance of circulating antibodies. After antibodies are formed, leptospires disappear from all sites except immunologically privileged sites like the proximal renal tubules, brain and anterior chamber of the eye. In humans, leptospires in the renal tubules and resulting leptospiruria rarely persist longer than 60 days.

ANICTERIC LEPTOSPIROSIS

This is characterized by sudden onset of fever, chills, headache, malaise, nausea, vomiting and myalgia. Muscle pain which typically affects the back, calves and abdomen is an important feature of leptospirosis. Fever with conjunctival suffusion is a common finding on physical examination. Less common findings are lymphadenopathy, rash, hepatosplenomegaly and pharyngitis. The rash may be macular, maculopapular, erythematous, urticarial or hemorrhagic. Some patients may have bradycardia and low blood pressures but circulatory collapse is uncommon.

Most patients become asymptomatic within a week. Illness recurs after a brief period of 1 to 3 days. The second phase is characterized by development of antibodies, which lasts for few days to weeks. Aseptic meningitis is an important development though only half of the patients show clinical manifestations. In case of meningeal reaction, polymorphonuclear leukocytes predominate initially in CSF and number of mononuclear cells increases later. Protein concentration in CSF may be elevated and CSF glucose levels are usually normal. Meningeal symptoms and pleocytosis usually disappear within few days but may persist for weeks in rare cases. Uveitis may occur, it can be unilateral or bilateral and is usually self-limited and rarely resulting in permanent visual impairment. Pulmonary involvement is not uncommon.

ICTERIC LEPTOSPIROSIS (WEIL'S SYNDROME)

Severe leptospirosis is characterized by onset of jaundice, renal dysfunction and hemorrhagic diathesis. There may be pulmonary involvement in many cases. The initial phase is similar to anicteric phase but the onset of immune phase is marked by hepatic and renal dysfunctions. Hepatic abnormalities include hepatomegaly, right upper quadrant pain, direct and indirect hyperbilirubinemia, elevation of alkaline phosphatase, hypoprothrombinemia, hypoalbuminemia, modest elevation of serum hepatic transaminases, and acalculous cholecystitis. The jaundice is due to hepatocellular injury and not hepatocellular necrosis (the liver function usually returns to normal after recovery). A hemolytic process can be documented in a few patients. Liver failure rarely leads to mortality. Renal pathology appears to vary during the course of the disease. Urinalysis may reveal sterile pyuria, hematuria, proteinuria, and granular casts. Acute tubular necrosis (ATN) and interstitial nephritis are the 2 classic renal lesions

associated with leptospirosis. Direct leptospira injury may cause ATN, whereas interstitial nephritis occurs later and is probably related to antigen-antibody complexes of the immune phase. Patients may rapidly progress from normal renal function to renal failure requiring dialysis. Acute renal failure marked by oliguria or polyuria may appear 4 to 10 days after the onset of symptoms in 15 to 40 percent of cases. This is a common cause of mortality.

Abnormal ECG is seen in most cases but congestive heart failure is uncommon. Hemorrhagic manifestations can occur which include epistaxis, petechiae, purpura and ecchymosis. Gastrointestinal, adrenal or subarachnoid hemorrhages are detected rarely. Disseminated intravascular coagulation (DIC) has not been described in cases of leptospirosis. Thrombocytopenia and elevations in prothrombin time (PT) may occur but do not appear causally related. Anemia may occur in the context of a bleeding diathesis. CBC may reveal an increase in erythrocytic sedimentation rate and leukocytosis. The mortality rate is about 5 to 15 percent in Weil's syndrome in children (which is less than that in adults).

DIAGNOSIS

The diagnosis of leptospirosis can be established by serologic testing or isolation of leptospira from the patient.

Serological Tests

Serologic testing is preferred mode of diagnosis. Enzyme-linked immunosorbent assay (ELISA) for detection of IgM antibodies (which is positive from the fifth day of illness) and IgM-specific dot-ELISA tests are now recommended in clinical practice. These tests have a sensitivity >80 to 90 percent and are done at many regular pathological and microbiological laboratories.

The slide agglutination method, Dri-Dot assay, LEPTO Dipstick, latex agglutination, complement fixation assay, indirect immunofluorescent test, and indirect hemagglutination test are also available; these tests too have good sensitivity of up to 85 percent. However, the microscopic agglutination test (MAT) (serogroup-specific assay), using live antigen suspension of leptospiral serovars, is the reference method. This is serogroup specific assay which requires live cultures of all serovars for use as antigen and is read by dark field microscopy for agglutination. A four-fold or greater increase in titer in paired sera confirms the diagnosis. Agglutinins appear by 12th day of illness and can reach a maximum titer by 3rd week.

Leptospire can be isolated from blood and CSF during first days of illness and in urine after 2nd week of illness. Cultures mostly become positive after 2 to 4 weeks, with a range of 1 week to 6 months. For isolation of leptospire from body fluids or tissues, Ellinghausen-McCullough-Johnson-Harris (EMJH) medium is useful. Other alternatives are Fletcher and Korthof medium.

Dark field examination of blood or urine frequently results in misdiagnosis and should not be used.

DIFFERENTIAL DIAGNOSIS

Leptospirosis should be differentiated from other febrile illness associated with chills, fever, myalgia, headache, nausea and vomiting. Common differential diagnosis are:

- Dengue
- Malaria
- Viral hepatitis
- Enteric fever
- Influenza
- Rickettsial infection
- Brucellosis
- Enteroviral infections
- Toxic shock syndrome
- Kawasaki disease.

History of direct contact with animals or soil and water contaminated with urine of animals should arouse suspicion of leptospirosis.

MANAGEMENT

Treatment of leptospirosis is divided in two parts, i.e. chemotherapy and organ specific care.

Chemotherapy

Antibiotic therapy should be initiated as soon as the diagnosis is considered.

Antibiotic administration (especially before the 7th day of illness) reduces length of hospitalization and leptospiruria. In children, even late institution of antibiotic treatment has been shown to reduce the extent of acute renal failure and thrombocytopenia. Treatment with penicillin or tetracycline (in children >8 years of age) should be instituted as soon as the diagnosis is suspected. It has been shown that treatment within one week of onset of fever can shorten the clinical course and decrease the severity of the infection. Parenteral penicillin G (6-8 million unit/m²/day given intravenously in divided doses every 4 hours for 7 days) is the drug of choice. Tetracycline (10-20 mg/kg/day given orally or intravenously in divided doses every 6 hours for 7 days) can be used in those allergic to penicillin. Doxycycline (4-5 mg/kg/day) has been successfully used in children more than 8 years old. Oral amoxicillin (25-50 mg/kg/day in two or three divided doses) is an alternative therapy for children <8 years of age. One comparative trial of the efficacy of ceftriaxone and penicillin for the treatment of severe leptospirosis found no significant difference between the two drugs in terms of complications or mortality rates. Another open labeled randomized study compared parenteral cefotaxime, penicillin G, and doxycycline for treatment of suspected severe leptospirosis. It showed no significant difference

with regard to associated mortality, defervescence, or time to resolution of abnormal laboratory findings.

Co-infection with malaria is also known to occur and it should be treated accordingly.

Organ Specific Care

Careful attention needs to be paid to the hydration status of the patient and their cardiac function must be monitored. Antipyretics (give paracetamol, avoid aspirin) can be used for controlling the fever. Any evidence of hemodynamic instability or hemorrhagic manifestations is an indication for transferring the patient to a pediatric intensive care unit. Intravenous fluids are required during the initial acute phase when the child is very sick and is not able to feed adequately. Complications of leptospirosis on various organs include renal, hepatic, pulmonary, cardiac, hematological and neurological. In general, the treatment of these organ involvements does not differ much from the same manifestations due to non leptospiral causes.

Renal failure needs correction of hypovolemia and management of fluid and dietary intake, avoidance of nephrotoxic drugs and dialysis.

Hepatic failure rarely leads to mortality in leptospirosis. Patient is given high carbohydrate diet with plenty of glucose to adequate calories. Protein restriction may be done in severe cases. Precipitating factors for hepatic encephalopathy like hepatotoxic drugs and toxins, hypovolemia, constipation, hypokalemia and alkalosis need to be avoided.

Pulmonary complications may require continuous oxygen therapy and mechanical ventilation with positive end expiratory pressure (PEEP) if respiratory failure develops.

Cardiac complications include shock and arrhythmias which are managed with fluids, vasopressors and antiarrhythmic agents.

Hematological complications include thrombocytopenia which may require platelet rich concentrate or platelet rich plasma. Coagulation defects require injectable vitamin K or fresh frozen plasma.

Neurological complication like aseptic meningitis requires symptomatic and supportive treatment.

PREVENTION

Individuals who may be exposed to leptospires through their occupation or their involvement in recreational water activities should be informed about the risks. Important measures for prevention are rodent control and avoidance of contact with contaminated water and soil. Parents should instruct children not to wade through flood waters or play in puddles/stagnant water. Immunization of livestock (cattle, sheep, pigs, and horses) and family pets (cats and dogs) has been recommended as a means of eliminating some of the animal reservoirs. Doxycycline (200 mg orally once a week) is used as prophylaxis in adults traveling to a highly endemic area

for a limited period of time and also during outbreaks, but its use in children has not been studied.

PROGNOSIS

Prognosis is determined by the severity of the illness, promptness with which the diagnosis is made, and the presence of complications such as renal failure, oliguria, thrombocytopenia, cardiac failure with hypotension and arrhythmias, respiratory failure, neurologic manifestations, gastrointestinal bleeding, and concomitant medical illnesses. Anicteric illness has good prognosis (with very occasional mortality due to myocarditis and fatal pulmonary hemorrhage). Patients with Weil's disease have mortality rates of up to 15 percent. Adults, especially those in the older age-groups, have higher mortality.

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Toxic Shock Syndrome

Shyam Kukreja, Tapisha Gupta

INTRODUCTION

Toxic shock syndrome (TSS) is a sudden onset, acute febrile illness caused by gram positive bacteria, with typical rapid progression to shock and multiorgan failure.

Capillary leak syndrome or massive fluid loss from capillaries into the interstitial space and loss of peripheral vascular resistance are characteristic of the disease.

It has certain unique clinical manifestations like diffuse erythroderma, delayed desquamation of palms and soles, conjunctival and pharyngeal congestion and rapidly accelerated renal failure that differentiate it from septic shock.

Also, TSS often occurs in young, previously healthy children, in contrast to severe septic shock.

This is caused by *Staphylococcus aureus* and *Streptococcus pyogenes* (Lancefield group A Beta hemolytic *streptococcus* (GAS) and can also occur with other non-group A streptococci.

The clinical case definition as proposed by CDC is as given in Table 1.¹

CLINICAL CASE DEFINITION OF TOXIC SHOCK SYNDROME

Involvement of three or more of the following organ systems:

Gastrointestinal: Vomiting or diarrhea at onset of illness.

Muscular: Severe myalgia or creatinine phosphokinase level greater than twice the upper limit of normal for the laboratory. Mucous membrane: vaginal, oropharyngeal, or conjunctival hyperemia.

Renal: BUN or serum creatinine greater than twice the upper limit of normal or >5 white blood cells per high – power field in the absence of a urinary tract infection.

Hepatic: Total bilirubin, AST, or ALT greater than twice the upper limit of normal for the laboratory.

Hematological: Platelets <100,000/mm³.

Central nervous system: Disorientation or alternations in consciousness without focal neurological signs when fever and hypotension are absent.

Negative results on the following tests, if obtained. Blood, throat, or cerebrospinal fluid cultures, blood culture may be positive for *Staphylococcus aureus*. Serologic tests for Rocky mountain spotted fever, leptospirosis.

Case Classifications

Probable: A case with 5 of the 6 clinical findings described above.

Confirmed: A case with 6 of the clinical findings described above, including desquamation could occur.

EPIDEMIOLOGY

Toxic shock syndrome was first described in a series of pediatric cases in 1978.² Later it was associated with menstruation, particularly tampon use and with a phenotypically distinct type of *Staphylococcus aureus*. By 1994, at least 42 percent of reported cases were nonmenstrual.³

Microbiologic studies have established that most patients with menstrual TSS have evidence of vaginal or cervical colonization with *S. aureus*. These strains make a characteristic super antigen toxin now known as TSS- toxin 1 or TSST-1.

Table 1: Clinical findings

Fever	Temperature >38.9°C
Rash	Diffuse macular erythroderma
Desquamation	1-2 weeks after onset of illness, particularly on palms, soles, fingers and toes
Hypotension	Systolic blood pressure <90 mm Hg for adults; <5th percentile by age for children <16 yrs old; orthostatic drop in diastolic blood pressure >15 mm Hg from lying to sitting; orthostatic syncope or orthostatic dizziness.

Table 2: Clinical differentiation between streptococcal and staphylococcal TSS

	<i>Streptococcal</i> TSS	<i>Staphylococcal</i> TSS
Mortality rate	30-60%	<3%
Positive blood cultures	60-80%	Low
Typical rash	Less common	Very common
Associations	Soft tissue infection	Tampon use
	Varicella Infection	Surgical procedures
	NSAID	NSAID
		Burns
		Influenza infection

STAPHYLOCOCCAL TSS

There was a fall in incidence of menstrual TSS, following the awareness of association between tampon use and *Staphylococcus* TSS. However, there has been an increase in the proportion of non menstrual cases associated with TSST-1 and other super antigens like staphylococcal enterotoxins (A to R).⁴ Of late, cases associated with community acquired methicillin resistant *S. aureus* (MRSA) have also been noted.⁵ Amongst children, cutaneous non surgical lesions are a commoner cause, leading to TSS. The typical rash is seen more commonly in staphylococcal TSS than streptococcal TSS (Table 2).

Streptococcal TSS and Invasive Gas Disease

Since mid 1980s, there have been increasing reports of invasive GAS disease and streptococcal TSS. Around 20 percent of all invasive GAS infections occur in children. Varicella and immune suppression are risk factors.

Invasive GAS infections are bacteremias or focal infections. Focal infections caused by GAS are necrotizing fasciitis, pneumonia, empyema, meningitis and bone and joint infections.

Out of these, necrotizing fasciitis (NF) is a potentially fatal soft tissue infection, though rare in children, but a common precursor of TSS. It usually involves limbs. Predisposing factors are local trauma, insect bites, burns, surgery and use of NSAIDS. The most common precipitating factor in children is varicella.⁶

It is frequently misdiagnosed as cellulitis and under-treated. Clues that suggest NF are severe pain out of proportion to skin findings,⁷ rapidly spreading edema, bullae formation, marked leucocytosis and elevated creatinine kinase levels. Local skin anesthesia antedates skin necrosis hence it is an important clue to NF. MRI has the highest sensitivity for diagnosing NF.⁸ Once NF is diagnosed, immediate surgical debridement and aggressive antibiotic therapy saves lives and prevents TSS.

Eleven GAS super antigen toxins have been identified. The mortality of streptococcal TSS is higher (30–50%)

than staphylococcal TSS (3%). However of late, the mortality trend in childhood TSS has shown a decline and has been reported to be as low as 4 percent in recent retrospective review.⁹

RISK FACTORS FOR MENSTRUAL TSS

These are adolescent age, white race and use of highly absorbent tampons during menstruation. Women who develop TSS are more likely to have used tampons for more days of their cycle and kept one in place for a longer period of time. Tampons create an aerobic environment in the vagina, oxygen is required for the production of TSST-1. This enhances toxin production.

RISK FACTORS FOR NONMENSTRUAL TSS

For TSS to develop, the necessary risk factors are colonization by a toxin producing strain of *Staphylococcus aureus*, absent protective antitoxin antibody and an infected site.

Primary deep tissue infections are rarely associated with TSS. Most cases occur in patients with skin or mucous membrane disruption, burns, insect bites, after nasal packing, following sinusitis, influenza, etc. Implanted sutures, central venous lines and surgical implants also enhance the risk of acquiring bacterial infection (Table 3).¹⁰

Many patients have been reported for whom no obvious focus of infection was found.

PATHOGENESIS

TSS is mediated by exotoxins produced by *S. aureus* and *S. Pyogenes*. More than 90 percent of isolates from patients with menstrual TSS and more than 40 to 60 percent of isolates from nonmenstrual TSS produce TSST-1 (TSS Toxin 1) and these patients have absent acute phase antibody to TSST-1.

Staphylococcal enterotoxins A, B and C are implicated in cases of staphylococcal TSS that are TSST-1 negative. These other toxins have higher virulence than TSST-1.

In a study of 32 *S. aureus* isolates from nonmenstrual TSS, 50 percent (Five out of ten) patients with a TSST-1 negative strain died, compared to 10 percent (two out of twenty) with TSST-1 positive strains.

Superantigens

These exotoxins cause disease, as they are superantigens. Superantigens are a family of immunomodulatory proteins that stimulate large numbers of T-cells, often up to 20 percent and this leads to massive cytokine release.¹¹⁻¹³

Conventionally, antigens are taken up by an antigen presenting cell, processed and expressed on the cell surface in complex with class II MHC complex in a groove formed by the alpha and beta chains of class II MHC and then recognized by an antigen specific T-cell receptor.

Table 3: Risk factors for nonmenstrual toxic shock syndrome

I	Colonization with toxin-producing <i>staphylococcus aureus</i>
II	Absence of protective antitoxin antibody
II	Infected site
A.	Primary <i>S. aureus</i> infection
	Carbuncle
	Cellulitis
	Dental abscess
	Empyema
	Endocarditis
	Folliculitis
	Mastitis
	Osteomyelitis
	Peritonsillar abscess
	Pneumonia
	Pyarthrosis
	Pyomyositis
	Sinusitis
	Tracheitis
B.	After surgery: wound infection
	Abdominal
	Breast
	Cesarean section
	Dermatologic
	Ear, nose, and throat
	Genitourinary
	Neurosurgery
	Orthopedic
C.	Skin or mucus membrane disruption
	Burns (chemical, scald, etc.)
	Dermatitis
	Influenza
	Pharyngitis
	Postpartum (vaginal delivery)
	Superficial/penetrating trauma (insect bite, needle-stick)
	Viral infection
	Varicella
D.	After surgical or nonsurgical foreign body placement
	Augmentation mammoplasty
	Catheters
	Diaphragm
	Sponge (contraceptive)
	Surgical prostheses/ stents/ packing material/ sutures
E.	No obvious focus of infection (vaginal or pharyngeal colonization)

Superantigens directly interact with the class II MHC molecule and then with the T-Cell receptor.

Activated T-cells then release interleukin-1 (IL-1), interleukin-2 (IL-2), tumor necrosis factor (TNF) alpha and beta and interferon gamma in large amounts resulting in signs and symptoms of TSS.

The massive amounts of cytokine release causes capillary leak and other clinical features typically seen in TSS.

CLINICAL FEATURES

The diagnosis is made based on the CDC criteria as outlined in Table 1.

In the acute phase, the illness onset is abrupt with fever with chills, headache, myalgia, gastrointestinal symptoms like vomiting, diarrhea and abdominal pain.

In the first two days, diffuse erythroderma, flushing of the body, conjunctival and pharyngeal, hyperemia, hypotension and decreased urine output occurs.

CNS involvement most commonly presents as toxic encephalopathy, which resolves slowly after 4 to 5 days of treatment. This probably occurs due to toxin mediated cerebral edema. CNS involvement can also present as cerebral infarction, meningismus and seizures.

Once treatment is started with antibiotics and aggressive fluid resuscitation is initiated, pulmonary edema becomes an area of concern. Also ARDS is common in patients with severe disease due to persistent capillary leak.

Acute renal failure leading to permanent renal damage is rare. Repletion of intravascular volume usually results in improvement. If acute tubular necrosis occurs, then hemodialysis is necessary.

Myocardial failure can also occur due to coronary vasculitis and arrhythmias need to be watched for. Skin changes are characteristic. Desquamation can start on trunk and extremities 10 to 12 days after onset of symptoms and can continue for a month. Some patients also have desquamation of oral mucous membranes.

In most of patients, erythema is more intense at the surgical site.

Telogen effluvium and nail loss can occur up to four weeks after the illness onset.¹⁰

LABORATORY CHANGES

Laboratory test reflect shock and organ failure. Neutrophilia is present with absolute lymphopenia. In the first few days, anemia, low platelet counts and deranged coagulation profile is seen.

High BUN and creatinine reflect renal involvement while raised CPK indicates muscle involvement. Hypocalcemia is common and can cause tetany. This occurs due to hypoproteinemia and high serum levels of a calcitonin like substance.

Table 4: Differential diagnosis of toxic shock syndrome based on clinical manifestations

Diagnosis	Fever	Exanthem	Shock
Severe invasive <i>Streptococcus pyogenes</i> infection	+	+	+
Meningococemia	+	+	+
Rocky mountain spotted fever	+	+	±
Ehrlichiosis	+	+	±
Kawasaki disease	+	+	–
Staphylococcal scalded skin syndrome	+	+	–
Toxic epidermal necrolysis	+	+	–
Viral syndromes	+	+	–
Leptospirosis	+	+	–
Systemic lupus erythematosus	+	+	–
Erythema multiforme	+	+	–
Septic shock	+	–	+
Hantavirus pulmonary syndrome	+	–	+
Salmonella infections	+	–	±
Gastroenteritis	+	–	–
Urinary tract infection	+	–	–
Drug reactions	+	+	±
Phenytoin (Dilantin)	+	+	±
Cocaine	+	+	±
Pseudoephedrine	+	+	±
Inhalational mercury	+	+	–
Quinidine	+	+	–
Sulfonamides	+	+	–
Beta-lactam antibiotics	+	+	–
Quinolones	+	+	–

Positive blood cultures are 60 to 80 percent in streptococcal TSS. *S. aureus* may be cultured from the focus of infection in patient's with nonmenstrual TSS and in more than 85 percent of patients with menstrual TSS from cervix or vagina.¹⁴

Diagnosis

Diagnosis is made by applying the CDC definition criteria, however these criteria should not be used to exclude a case that is highly suspicious for TSS, even if all criteria are not met.

Isolation of *S. aureus* is not required for diagnosis. In contrast to streptococcal TSS, *S. aureus* is rarely (5%) isolated in blood cultures toxin detection tests are of value only for research.

DIFFERENTIAL DIAGNOSIS

Clinical entities with rapid onset of fever, hypotension, erythroderma, and multisystem involvement come in differential diagnosis.

Table 4 shows the various diseases that have similar presentation.¹⁰

MANAGEMENT

The general principles of treatment can be broadly outlined in four headings. These are (1) surgical therapy (2) antibiotics (3) management of systemic complications of toxins (4) organism isolation.

- **Surgical therapy:** Source control is critical for early management. Any foreign body should be removed and infected sites must be drained.

GAS infection of soft tissue or necrotizing fascitis must be drained completely. Wide debridement substantially improves the outcome and reduces mortality.

In postsurgical patients, surgical wounds may not appear infected but must be explored and debrided, if the patient fulfills the criteria for TSS.

Surgical intervention is required less often in staphylococcal TSS. Culture of all materials obtained from infectious foci is important, as TSS is caused both by MRSA and MSSA.

- **Antibiotics:** The severity of TSS warrants initiating maximally effective therapy.

The initial empiric therapy is a combination of penicillin and clindamycin when streptococcal TSS is suspected and a combination of cloxacillin and clindamycin, when staphylococcal TSS is suspected. If there is a concern for an MRSA strain causing TSS, vancomycin should be added cautiously to the treatment regime, as most patients have some degree of renal failure. This is becoming an increasingly common scenario as community acquired MRSA strains become commoner. Also post surgical patients who develop hospital acquired infection and TSS come in this category. It is prudent to remember though that in India 40 percent of MRSA isolates show good sensitivity to clindamycin. Linezolid can also be used as a good alternative to vancomycin.

The advantages of protein synthesis inhibitors like clindamycin and linezolid have been shown in many lab experiments. These directly suppress toxin synthesis. Also clindamycin potentiates opsonization and phagocytosis of both GAS and *Staphylococcus*.

Subinhibitory concentrations of beta lactam antibiotics may actually increase TSST-1 production by *S. aureus*. "Eagle effect" was first described in 1952. It was seen that in a mouse model of streptococcal myositis, once streptococcal numbers reach a high level and a steady state, due to decreased cell division, penicillin becomes less effective. Clindamycin is not affected by the eagle effect.¹⁵

The total duration for which treatment should be continued is 10 to 14 days.

Management of Systemic Complications of Toxins

- *Fluid replacement:* Intravascular volume restoration is the key intervention to achieve adequate tissue perfusion. Due to capillary leak, pleural, pericardial and peritoneal effusions can occur and hence close monitoring in an intensive care unit is important. One must monitor for myocardial dysfunction, acute renal failure, encephalopathy, disseminated intravascular coagulation and ARDS.
- *Corticosteroids:* In hypotensive patients, not responding to fluid resuscitation, antibiotics and intravenous immunoglobulin, short courses of dexamethasone or methylprednisolone may be tried. However, there are no controlled prospective studies to recommend routine use.
- *Intravenous immunoglobulins:* Current treatment regimes advocate that IVIG should be used in cases of TSS that are recognized early but have not responded to fluids and vasopressors or in those who have an inaccessible infectious focus. A single dose of 400 mg/kg is given over several hours. This results in a serum antibody titer of more than 1:100, much higher than that required to provide immunity to TSST-1.

The rationale behind IVIG use is that it contains neutralizing antibodies to streptococcal super antigen toxins which may be protective to patients with streptococcal TSS. The same rationale may apply to staphylococcal TSS too.

However a recent (between 2003 and 2007) a largest ever multicenter retrospective study of children was done to study disease epidemiology, treatment regimes and outcome in streptococcal TSS.⁹ This study showed some interesting results. In this study the median age of patients was 8.2 years and IVIG was given to 44 percent children (84 out of 192). The overall mortality was found to be 4.2 percent (much lower than 30-60%), as previously reported. Also, it was found that the difference in mortality between IVIG recipients and non-recipients was not statistically significant, hence IVIG use did not correlate with better clinical outcome. Studies with larger numbers of subjects are needed to conclusively assess benefit of IVIG use.

- *Organism isolation:* Every effort should be made to obtain the organism for susceptibility testing, as in the last ten years incidence of community acquired MRSA infections has increased dramatically. They are acquired in the community by immunocompetent hosts and most strains are susceptible to clindamycin.

Outcome and Sequelae

Deaths occur in first few days, but may occur as late as 15 days after admission. Death occurs due to cardiomyopathy, arrhythmias, respiratory failure or bleeding caused by coagulation defects. Post discharge, patients can have

fatigue, muscle weakness, chronic dermatitis, impaired memory and poorly sustained concentration.

Patients with prolonged hypotension can have gangrene, telogen effluvium and chronic renal failure.

Prevention and Secondary Prophylaxis

Institute of medicine committee on TSS recommended that adolescent women should minimize their use of high absorbency tampons. Also, women who have had TSS should not use tampons. Use of any individual tampon for no more than 12 hours decreases the risk for menstrual TSS.

In postsurgical cases, efforts should be intensified to recognize wounds copiously and provide immediate supportive therapy.

Perioperative systemic antistaphylococcal antibiotics do not prevent TSS.

Out breaks of TSS occur in schools, communities and there is a potential risk of secondary attacks in close contacts of patients with invasive GAS disease. However, there is not enough data to be certain whether antibiotic prophylaxis actually prevents secondary cases.

THE FUTURE

The future is in research into superantigen toxin pathophysiology and vaccine development. Several immune modulating agents have been investigated in mouse models. These are TNF-alpha inhibitors and a peptides antagonist. The peptide antagonist is the most promising. It protected against death in the mouse model, by developing cross reactive antibiotics which protect against super antigens.

Vaccine development for GAS is underway. The most advanced vaccine candidates are those based on the M protein.

Vaccines against *S. aureus* are also being researched with the focus on capsular polysaccharides.

Finally, vaccination with non toxic super antigen toxins from both *S. aureus* and GAS have been shown to induce protective antibodies in animal models of TSS.

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Rickettsial Infections in Children

Atul Kulkarni, Tanu Singhal

INTRODUCTION

Rickettsial diseases are a group of specific communicable diseases caused by obligate intracellular gram-negative bacilli and transmitted to man by arthropod vectors (except *Q* fever). It is increasingly realized that rickettsial diseases are under-diagnosed and that they substantially contribute to the burden of preventable acute febrile illness, in many populations, all over the world.¹ This article emphasizes those rickettsial diseases that are prevalent in Indian children.

ETIOLOGY AND MICROBIOLOGY

Rickettsia is a group of motile, gram-negative, nonspore forming highly pleomorphic bacteria that present as cocci (0.1 micron), rods (1-4 micron) or thread like (10 micron), obligate, intracellular parasites. To survive, these have to enter, grow and replicate within the cytoplasm of eukaryotic host cells. Rickettsia cannot survive in artificial nutrient environments and hence are grown in either

tissue or embryo cultures. Growth of rickettsia is enhanced by presence of sulfonamides.

CLASSIFICATION

Table 1 denotes the classification of rickettsial disease on the basis of clinical features and epidemiological aspects.

Epidemiology of Rickettsial Infections in India

Spotted fever disease was first observed in India by Megaw (1917) in the foothills of the Himalayas. Reports of Indian tick typhus fever have come from all over the country including places like Jabalpur, Nagpur, Kanpur, Sagar, Pune, Lucknow, Bangalore, Secunderabad, etc.² Similarly, endemic typhus has been noted in many places in India like hills of Shimla, Mumbai, Jabalpur, Kashmir, Lucknow, Pune, etc. Rickettsial infections have also been reported from South India,³ Haryana,⁴ Karnataka⁵ and Himachal Pradesh.⁶ Scrub typhus broke out in an epidemic form in Assam and West

Table 1: Classification of rickettsial diseases

S.No	Disease	Rickettsial agent	Insect vector	Mammalian reservoir
I	<i>Typhus group</i>			
	a. Epidemic typhus	<i>R. prowazekii</i>	Louse	Humans
	b. Murine typhus	<i>R. typhi</i>	Flea	Rodent
	c. Scrub typhus	<i>R. tsutsugamushi</i>	Mite	Rodent
II	<i>Spotted fever group *</i>			
	a. Indian tick typhus	<i>R. conorii</i>	Tick	Dog/rodents
	b. Rocky mountain spotted fever	<i>R. rickettsii</i>	Tick	Dogs/rodents
	c. Rickettsial pox	<i>R. akari</i>	Mite	Mice
III	<i>Others</i>			
	a. Q fever	<i>C. burnetii</i>	Nil	Cattle sheep goat
	b. Trench fever	<i>Rochalimaea quintana</i>	Louse	Humans
	c. Ehrlichiosis	<i>Ehrlichia</i>	Tick	Deer/dog
	d. Anaplasmosis	<i>Anaplasma phagocytophilum</i>	Tick	Deer/dog

* More than 19 types of spotted fever varieties are described depending upon the geographical area where these are prevalent.

Bengal during Second World War. It was later found that scrub typhus was prevalent throughout India in humans, trombiculid mites and rodents.² Spotted fevers and typhus fever have been reported from Southern regions of India.^{3,5,7} Serological surveys indicate that *Q* fever is present in animal as well as human populations in Haryana, Punjab, Delhi, Rajasthan and various other places in India.² The overall prevalence rates in Rajasthan were reported as 18.6 percent in humans and 24.7 percent in animals.²

METHOD OF TRANSMISSION

Tick, mite, flea and louse are the natural hosts, reservoirs, and vectors of rickettsial organisms (except *q* fever). These maintain the infection naturally by transovarial transmission (passage of the organism from infected ticks to their progeny) and trans-stadial passage. Ticks transmit the infectious agent to mammalian hosts (including humans) by regurgitation of infected saliva during feeding. Dogs and rodents serve as reservoir hosts for these vectors. These reservoir vectors can themselves develop the diseases and are important vehicles for bringing potentially infected vectors into the environment shared by humans.

PATHOPHYSIOLOGY

Rickettsial microorganisms appear to exert their pathologic effects by adhering to and then invading the endothelial lining of the vasculature (microvasculitis) within the various affected organs. Once inside the cells, the rickettsial organisms either multiply and accumulate in large numbers before lysing the host cell (typhus groups) or they escape from the cell, damaging its membrane and causing the influx of water (spotted fever group). Rickettsiae proliferate on the endothelium of small blood vessels, release cytokines which damage endothelial integrity, with consequent fluid leakage and platelet aggregation. Polymorphs and monocytes proliferate leading to focal occlusive endarteritis. This results in microinfarctions as typical "Typhus nodules of Wollbach. This process especially affects the brain, cardiac and skeletal muscle, skin, liver, lungs and kidneys. This may also cause venous thrombosis and gangrene of the extremities.⁸

CLINICAL MANIFESTATIONS

Incubation period in children varies from two to 14 days. It may extend up to 28 days with a median of 7 days. A history of exposure to tick or close contact with an infected pet animal may be forthcoming. Often history of origin from an endemic area or a similar illness in family members is available. Severity of manifestations varies from a mild, self-limiting illness to a life threatening disaster.

Initially the illness appears to be nonspecific and patients present with headache, fever, anorexia, myalgias, and restlessness. Calf muscle pain and tenderness are

common in children. Gastrointestinal symptoms include nausea, vomiting, and diarrhea. Abdominal pain is a frequent complaint earlier in this disease. Skin rash is usually not present until after 2 to 4 days of illness. The typical triad of fever, headache and rash is observed in 44 percent of patients. Core body temperature may exceed 40 degree centigrade and can be persistently elevated or it can fluctuate dramatically. Headache is severe, unremitting and usually unresponsive to analgesics.

In spotted fever, rash is initially discrete. Pale rose red blanching macules or maculopapules appear characteristically on the extremities including the ankles, wrist, or lower limbs. Later, rash spreads rapidly to involve the entire body including palms and soles (Fig. 1). After several days, the rash becomes more petechial or hemorrhagic, sometimes with palpable purpura (Fig. 2). In severe form of the disease, petechiae may enlarge into ecchymosis, which can become necrotic (Fig. 3). Severe vaso-occlusive disease secondary to rickettsial vasculitis and thrombosis is infrequent but can result in gangrene of the digits, (Fig. 4) toes, earlobes, (Fig. 5) scrotum, nose or entire limbs. In scrub typhus, rash is seen initially on trunk or may not be present at all. Painless eschar, the tache noire, may be seen at the initial site of tick attachment and regional lymphadenopathy and is seen in scrub typhus.

Central nervous system infection often produces meningism, altered sensorium, seizures, ataxia, coma or auditory deficits. Pulmonary disease manifests as rales,



Fig. 1: Rashes on the sole (For color version see plate 7)

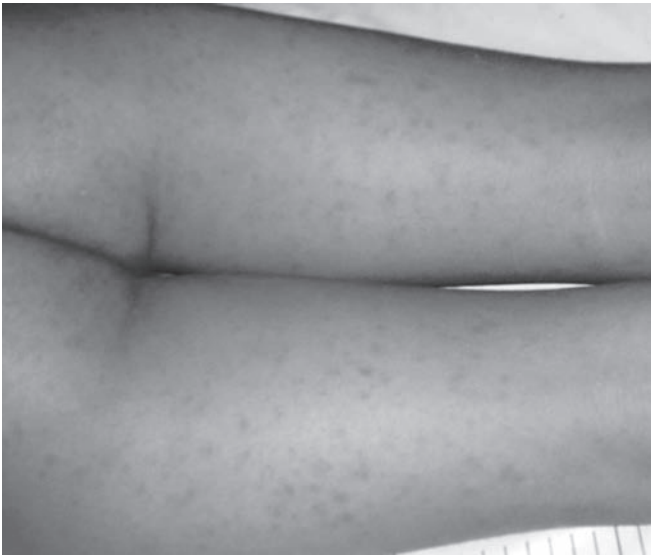


Fig. 2: Palpable purpura (*For color version see plate 7*)



Fig. 4: Gangrene of digits (*For color version see plate 7*)



Fig. 3: Necrotic rash (*For color version see plate 7*)



Fig. 5: Gangrene of earlobe (*For color version see plate 7*)

infiltrates and noncardiogenic pulmonary edema. Edema over the dorsum of hand or foot and periorbital edema are some times seen and so are hepatomegaly and generalized lymphadenopathy.

More severe form of disease may include myocarditis, acute renal failure and vascular collapse. Children with G6PD deficiency face an increased risk of developing a fulminant form of spotted fever disease.⁹

In Q fever no vector is involved. Transmission is by inhalation of infected dust from soil previously contaminated by urine or feces of diseased animals. This fever is rarely reported in children. This presents in acute as well as chronic forms. Rash which is typical of variants of

rickettsial fever is not seen in Q fever. Pneumonia, hepatitis and meningitis are some of the usual features of Q fever. Endocarditis is seen in chronic variety.

LABORATORY DIAGNOSIS

Laboratory findings are usually non-specific. Total leukocyte count may be initially normal or low but leukocytosis develops as the disease progresses. Anemia, thrombocytopenia, hyponatremia and elevated serum aminotransferases are some other features. CSF findings are usually normal but occasionally mononuclear pleocytosis (<10 to 300 cell/micro per) may be found. Roughly, 20 percent of the patients may have elevated CSF proteins (200 mg/dl).

Specific diagnosis of a rickettsial illness has most often been confirmed by serological testing. Serological evidence of infection occurs not earlier than the second week of illness in any of the rickettsial diseases and hence a specific diagnosis may not be available until after the patient has fully recovered or worsened.¹⁰

Immunofluorescence Assay

This is the gold standard test for serodiagnosis of rickettsial disease and allows for detection of IgG and IgM. IgM titer, which is more than 1:64, suggests acute infection. IgM titer starts appearing at 5 to 10 days and peaks at 3 to 4 weeks after the onset of illness. IgG titer of more than 1:254 suggests acute infection. IgG >1:64 but <1:254 indicates previous infection. Chief drawbacks of IFA are that it is expensive and not widely available.

Enzyme-linked Immunosorbent Assay

Enzyme-linked immunosorbent assay (ELISA) is specific and sensitive—allowing detection of IgG and IgM antibodies. Detection of IgM antibodies to scrub typhus and Indian spotted fever is now available in India is the preferred test for diagnosis.

Weil Felix Test

This depends on detection of antibodies to various *Proteus* species containing antigen with cross reacting epitopes to antigens from members of the genus rickettsia. OX 2—Cross reacts with spotted fever group. OX 19—Cross reacts with typhus group, RMSF. OX-K—Cross reacts with scrub typhus. It is a slide agglutination test. The kit tests serum dilution from 1:20 to 1:320. Significant titer is 1:80. Rising titers are more appropriate. Well-Felix test is a classic serological test, widely available but unacceptable for accurate diagnosis because of very low sensitivity and specificity. In conclusion, Weil-Felix test can be used in developing countries where other tests are not available for diagnosis of rickettsia infection. This test should be interpreted in conjunction with history and clinical presentation.

If clinical suspicion for rickettsia is high, then empirical therapy should be started without waiting for any confirmatory test.

DIFFERENTIAL DIAGNOSIS

Spotted fever can mimic a great number of febrile illnesses. Most important of these are meningococcemia, measles and enteroviral exanthemas. Other diseases included in differential diagnosis are typhoid fever, secondary syphilis, leptospirosis, toxic shock syndrome, scarlet fever, rubella, Kawasaki disease, parvoviral infection, idiopathic thrombocytopenic purpura (ITP), thrombotic thrombocytopenic

purpura (TTP), hemolytic uremic syndrome, Henoch-Schönlein purpura, acute abdomen, aseptic meningitis, hepatitis, dengue fever, infectious mononucleosis, drug reactions, malaria, tularemia, anthrax and other causes of pyrexia of unknown origin.

TREATMENT AND SUPPORTIVE CARE

Delay in diagnosing and treating rickettsial disease may result in increased severity and at times may prove fatal. Since no reliable diagnostic test is available to confirm rickettsial infection in the early stage, initial diagnosis and suitable treatment should be based on a high index of suspicion and appropriate clinical features. Epidemiological features (patient coming from an endemic area) and laboratory findings are important adjuvants.

Tetracycline and Chloramphenicol are the two time-tested drugs to effectively treat rickettsial infections in patients of all ages including children with spotted fever. Doxycycline is the drug of choice for all age groups. Chloramphenicol is reserved for patients with doxycycline allergy and for pregnant women. Tetracycline and doxycycline may cause discoloration of teeth in children who are less than eight years in age, whereas chloramphenicol can rarely result in aplastic anemia. Doxycycline can be used safely in young children because tooth discoloration is dose dependent and children are unlikely to require multiple courses. Further more the fact that increased mortality with chloramphenicol alone, compared with tetracycline alone, when other factors such as severity are considered have led to preference for doxycycline even in young children.¹¹

Recommended treatment regimens

- *Doxycycline*: 2.2 mg/kg/dose BID PO or IV, max 200 mg/day
- *Tetracycline*: 25 to 50 mg/kg/dose 6 hrly PO, max 2 gm/day
- *Chloramphenicol*: 50 to 100 mg/kg/day 6 hrly, max 3 g/day

The therapy should be continued for a minimum of 5 to 7 days and for at least 3 days until the patient is afebrile in order to avoid relapse. Patients treated with one of these regimens usually become afebrile within 48 hours and thus the entire therapy lasts for less than 10 days.

Mediterranean spotted fever has been effectively treated by azithromycin (10 mg/kg/day od for 3 days), clarithromycin (15 mg/kg/day bid for 7 days) and fluoroquinolones besides doxycycline and chloramphenicol. However doxycycline still remains the drug of choice. Specific fluoroquinolones regimens effective for children have not been established. Azithromycin or rifampicin may be used in doxycycline resistant scrub typhus. In patients with severe disease, admission to an intensive care unit and appropriate supportive therapy may be required.¹²

PREVENTION

No vaccines are available. Known tick infested areas should be avoided. Daily inspection of body for ticks is particularly important. Disinfection of dogs will minimize the tick population. Health education of people about mode of transmission by ticks and means of personal protection is equally important. Prophylactic antimicrobial therapy should not be administered because tetracycline and chloramphenicol are only rickettsiostatic. Such therapy simply delays the onset of illness and confuses the clinical picture by prolonging the incubation period.

CONCLUDING REMARKS

Rickettsia are potentially dangerous pathogens and unfortunately, specific serological tests are available in only a few specialized laboratories. Hence, it is imperative to have a high index of suspicion for rickettsial diseases and make a clinical diagnosis based on prudent history taking and appropriate physical findings. A therapeutic trial with a specific agent in these patients is justified because a delay in initiating treatment may prove costly. A rapid and favorable response is suggestive of a correct diagnosis.

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Acute Respiratory Tract Infections

Sunil Dutt Sharma

INTRODUCTION

Respiratory tract infection (RTI) is considered as one of the major public health problems in developing countries. It occurs both among children and adults. It is recognized as the leading cause of morbidity and mortality in many developing countries (Baqui et al. 2007). In developing countries, thirty percent of all patients' consultation and twenty-five percent of all pediatric admission are of acute respiratory tract infections (Rahman and Rahman, 1997) and which ultimately causes 3.5 million deaths in children each year (Hart and Kariuki, 1998). However, most infections are limited to the upper respiratory tract and only 5 percent involve the lower respiratory tract, respectively. Recent studies showed that *Streptococcus pneumoniae*, *Haemophilus influenzae* and respiratory syncytial virus are the main causes of RTI in children (Rudan et al. 2008). With effective management and appropriate drug RTI can be managed successfully (Chowdhury et al. 2008).

SECTION ONE: UPPER RESPIRATORY TRACT INFECTIONS (URTI)¹

Upper respiratory tract infections are common and cause a lot of absenteeism from work and school. Most of the URIs are caused by viruses but may have secondary bacterial infections. The common ones are:

- Common cold (coryza)
- Flu (influenza)
- Pharyngitis (sore throat)
- Laryngitis
- Laryngotracheobronchitis (croup).

Before going into details we should be aware of the details of the anatomy of the airways. Upper airway is up to the vocal cords and anything below the vocal cords is lower respiratory tracts/or airway (Figs 1 and 2).

General Description of URI

Symptoms of URIs commonly include:

- Congestion
- Cough
- Running nose
- Sore throat
- Fever
- Facial pressure
- Sneezing.

These symptoms may occur in isolation or in various combinations. They usually begin 1 to 3 days after exposure to a microbial pathogen, most commonly a virus. The duration of the symptoms is typically 7 to 10 days, however, it may persist longer.

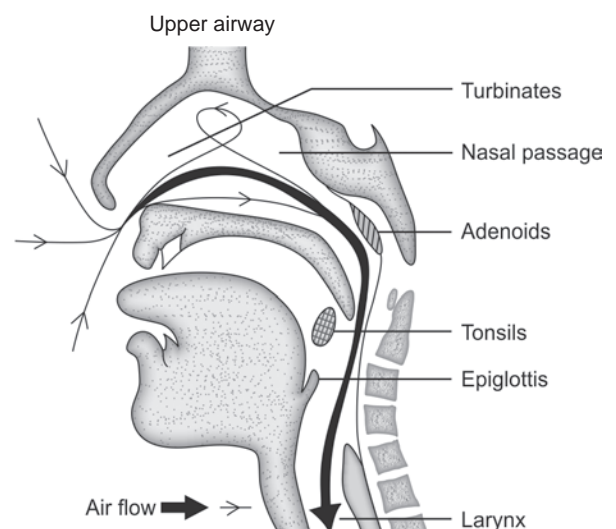


Fig. 1: Common anatomical structures of the upper airway

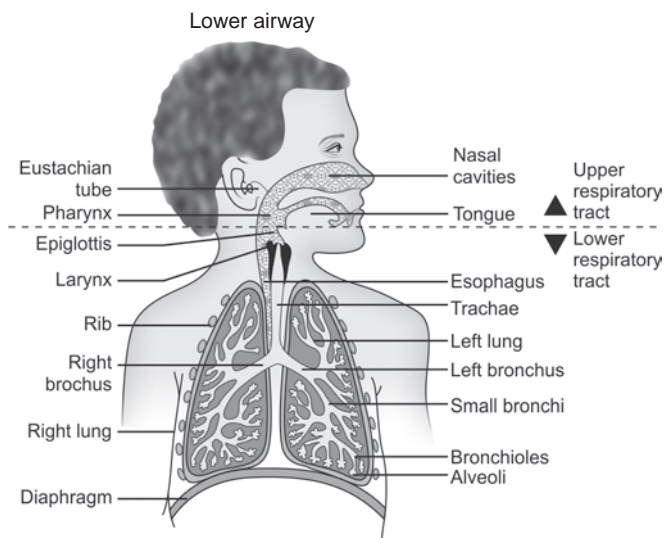


Fig. 2: Common anatomical features of the respiratory tract

It is important to mention that up to 15 percent of acute pharyngitis cases may be caused by bacteria, commonly Group A strep (“Strep throat”). Generally, patients with “Strep throat” start with a sore throat as their first symptom and usually do not have runny nose or cough or sneezing. Pain and pressure of the ear caused by a middle ear infection (Otitis media) is often associated with upper respiratory infections. Influenza (the flu) is a more systemic illness, which can also involve the upper respiratory tract, and which should be recognized as distinct from other causes of URI.

CORYZA (COMMON COLD)

Cause

Common cold is a mild, self-limiting viral infection. It spreads by direct contact with infectious secretions and

inhalation of droplets of infected respiratory secretions. This is the reason why it spreads fast from a person to another, especially those within close proximity with an infected person.

Clinical Features

Common cold is usually followed with sneezing, headache, malaise, nasal discharge and sore throat. Pediatric patients often have fever. Often they have nasal discharge which is initially clear, watery and profuse but later becomes thick. These initial symptoms may last up to 3 days. Cough and hoarseness may also occur early and persist for about a week.

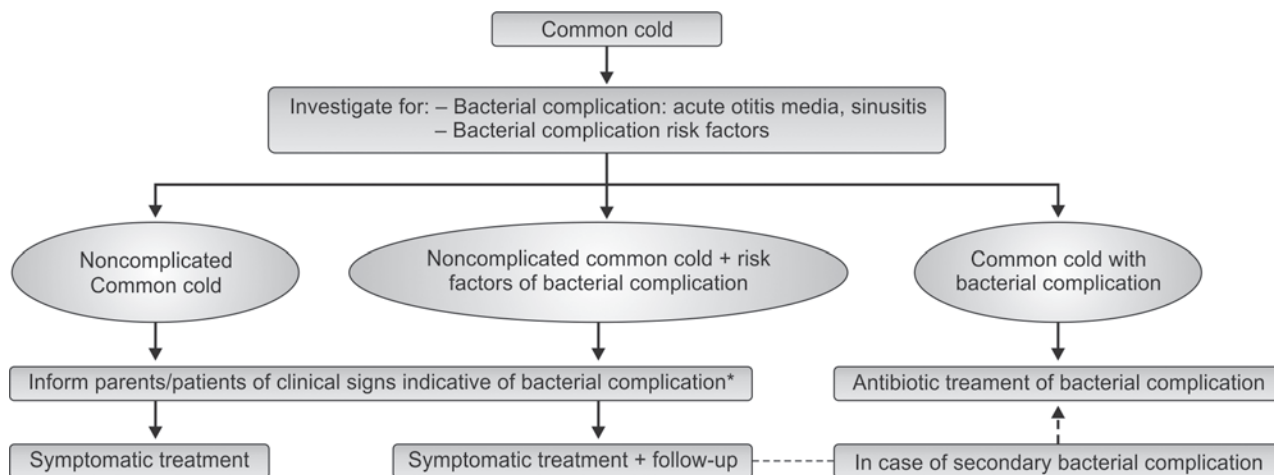
Diagnosis

It is always necessary to conduct an assessment to rule out other illnesses. Diagnosis of the specific virus is not possible on clinical observation alone. Acute onset and high fever from onset suggests viral etiology (It may not always be foolproof). Coryza or loose motions indicating generalized involvement of more than one system (more than one mucus membrane) and is in favor of a viral etiology. Conjunctival injection and red eyes is a feature seen in viral infection. Rash or exanthema indicate viral infection. Clustering of cases in the family or neighborhood would suggest a viral etiology. For an approach to treating coryza, (Flow chart 1).

Complications of Coryza

These complications usually are as a result of secondary infection and include; *Secondary bacterial sinusitis* which causes blocked nose and plenty of thick mucus discharge from the nose. Normally it is a main cause of nuisance, since one has to keep blowing nose. It may cause blocked nose hence, difficulty in breathing hence need to watch over them closely. It may lead to *Otitis media*, i.e. the

Flow Chart 1: Approach to treating common cold. *Respiratory discomfort, fever persisting for more than 3 days or more, other symptoms (rhinorrhea, cough, nasal obstruction) after 10 days with no improvement, irritability, otalgia, nocturnal awakening, purulent conjunctivitis, palpebral edema, gastrointestinal disorders (nausea, vomiting, diarrhea) and rash



infection of the middle part of the ear, may cause itchiness and discomfort to the affected ear. To detect them pharynx, nasal cavity, ears and the sinuses should be examined. The areas will appear inflamed. Malaise is the feeling of tiredness and unwillingness to do anything. It is a common feeling experienced when one has common cold. It may lead to reduced productivity although normally most people are able to continue with their usual activities. The best way to handle malaise is by resting.

Treatment

Various approaches have been proposed for the treatment of coryza. There are, however, basic rules to managing the condition. Antibiotics are not needed for uncomplicated colds. Symptomatic treatment is used for common colds. That is to treat fever, headache, running nose or any other symptom with medications suitable for the symptoms.²

Symptomatic Treatment

Nasal obstruction: This can be treated with decongestant nasal drops. This is useful especially for young children who experience nasal block and antihistamines like piriton (sedating) or cetirizine (nonsedating). This reduces the amount of mucus in the nose.

Cough: Cough can be irritating and if unchecked could lead to further damage of the mucus membranes lining the upper air way, resulting to secondary infections. It can be treated with preparations containing codeine or dextromethorphan. This minimizes the irritation that leads to cough reflex.

Sore throat: A sore throat is a nasty experience and in some people it may be painful to swallow and at time may lead to voice alteration or reduction. Various localized remedies have been tried some successfully others may be psychological. To treat this symptom following can be used:

- *Warm saline gargles:* Using warm water and a tinge of salt in a glass/cup. Then gurgle for a couple of minutes two to three times a day. Usually it should clear in a day or two.
- *Lozenges containing a topical anesthetic:* These help to ease the soreness resulting in relative comfort within a couple of hours.
- *Drinks:* A sore dry throat can be due to a blocked nose causing sleep with mouth open—probably snoring. For this recommended to drink lots of fluids—water or orange juice are good or sip warm drinks like a honey, lemon juice and hot water mixture.²

PREVENTION AND CONTROL OF CORYZA

Prevention of Transmission from Person to Person

The best measure to minimize transmission is to practice good hygiene. It is a good habit to cover coughs and sneezes with a handkerchief or disposable tissues.

Flu (Influenza)

Cause

The flu (full name is influenza) is caused by one of several different influenza viruses. The viruses are spread in the same way as those that cause common colds.

Transmission

The flu is transmitted in the same way as the common cold through:

- Sneezing
- Coughing
- Touching

To prevent its spread better to avoid visiting crowded sites if affected. Avoid contact with an infected person, especially if they are sneezing or coughing since this is when they are highly contagious.

The flu is different from colds since it comes on more quickly and there is more:

- Fever
- Headaches
- Aches in the rest of the body
- Shivering
- Feeling hot and cold than with colds
- Body aches
- Nose is not all drippy and runny like with a cold.

How to Avoid it Spreading to Others

- Preventive and control measures are similar to those of cold
- Washing hands every time you sneeze or cough into hand, to wash away the droplets that carry the virus
- Throw out those damp, germ-laden, used tissues as soon as used
- Stay away from school or work until you feel better
- No kissing on the mouth! Especially not those long passionate kisses
- The mouth and nose areas are where all the germs are concentrated
- Immunization against the flu but this is mainly recommended for preterm infants or those who are immune deficient or those with cardiac defect/chronic lung disease or chronic respiratory disease, e.g. asthma.

Treatment

Get plenty of rest, drink a lot and eat soft foods if there is a sore throat.

Acute Sinusitis

Sinuses are empty spaces in the skull (Fig. 4). They are found behind the nose, behind the cheeks, and above the eyes. Acute sinusitis is the inflammation of the sinuses lasting up to three weeks. Beyond that time it may be

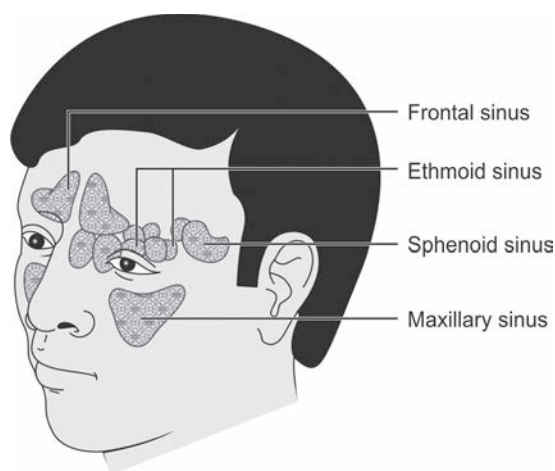


Fig. 3: Sinuses

subacute or chronic. Suspect sinusitis whenever the sign/symptoms (s/s) of URI persist beyond 2 weeks or in a child with s/s of a severe URI with features pointing towards diagnosis of sinusitis like facial swelling, pain or tenderness over maxilla, etc. Sinusitis is said to be acute when less than 30 days, chronic when more than 90 days and in between the 2 is subacute, i.e. more than 30 days and less than 90 days. There has to be a period of remission for at least 10 days to label a chronic sinusitis as recurrent sinusitis. Viral URI and allergic rhinitis is a common predisposing factor present in sinusitis. Careful examination should be done to rule out nasal polyps. Refluxing defects like cleft palate and GERD also predispose to sinusitis. One should keep in mind that mucociliary disorders may present with sinusitis. Dental carries and infections also predispose to sinusitis. The common trinity of *S. pneumoniae*, nontypable *H. influenzae* and *Moraxella catarrhalis* are the common offending agents in acute and subacute sinusitis. Bacteriology of chronic sinusitis is not well defined but usually it is a mix of multiple organisms in chronic sinusitis.¹

The sinuses are lined with mucous membranes. Normally the sinuses produce a small amount of mucus that drains into the nose. A bacterial infection of the upper respiratory tract can spread to the sinuses. When this happens, the mucous membranes in the sinuses become inflamed and produce large amounts of mucus. We call this sinusitis. The outlet of the sinus may become blocked. This causes a build-up of mucus and pus in the sinus. The development of sinuses begins at various age of gestation and extends well beyond birth, and so also the completion. Maxillary and ethmoid sinuses start developing at 10th week of gestation and are fully formed at birth. Sphenoid sinuses development is complete by 8 years. Frontal sinuses are the last to develop beginning at 8 years and completing by teenage (Fig. 3).

Symptoms of Sinusitis

Suspect sinusitis if URI persisting for 7 to 10 days or more:

- A recent cold or allergic rhinitis
- A *purulent nasal* discharge and often nasal blockage, i.e. rhinorrhea, nasal congestion
- A feeling of fullness in the cheeks and head, especially when leaning forward
- A headache
- A cough/daytime cough
- Infrequent low-grade fever
- Otitis media (50–60%)
- Irritability
- Headache
- Facial pain/maxillary dental pain
- Anosmia
- Pharyngitis

Signs of Sinusitis

- Fever and the person feels ill
- Tenderness on palpation over the sinuses and on pressing gently on the eyes and above the eye
- Red and inflamed mucous membranes of the nose
- A yellow green (purulent) discharge in the nose or a postnasal drip.

Diagnosis

Diagnosis of sinusitis is essentially clinical although sinus aspiration is gold standard for the diagnosis of acute sinusitis. It is an invasive, time consuming and potentially painful procedure and not recommended routinely. As the prediction based on history and clinical features is so high, X-rays are not routinely indicated. When done it may show complete opacification of the sinus, mucosal thickening of at least 4 mm or an air fluid level. In general, Waters, Caldwell and lateral views are obtained. It is difficult to achieve the correct position in young children. There is possibility of both underestimation and overestimation of the findings. X-rays are done when diagnosis is unclear, when patients do not improve or worsen on antimicrobial therapy or have complications.

Management of Sinusitis

The aims of treating sinusitis are:

- Clearing any blockage so that the sinuses will drain
- Treating the infection.

These aims are achieved through:

- Regular steam inhalation which helps to clear the blocked sinuses and to drain the mucus.
- Giving decongestants to improve the drainage of mucus.
- Giving antibiotics, to treat the infection.
- Following up the patient in two days.
- Referring the patient to a doctor if the sinusitis does not clear up.

Antibiotic therapy is the mainstay in the management of sinusitis. The drug of choice is amoxicillin or cefuroxime or co-amoxiclav; macrolides like azithromycin may also be used for their good cover for *Moraxella*. One may select any one based on cost and safety. Parenteral ceftriaxone or cefotaxime followed then by oral cefpodoxime may be used in severe disease or when the 1st line of drugs fail. Duration of treatment is very important. Treat for 10 to 14 days or 1 week beyond symptom resolution. If signs and symptoms persist; ask for imaging studies and seek ENT referral for aspiration. In addition to antral lavage, proper treatment and removal of predisposing factors may be required. Procedures like adenoidectomy, polypectomy, maxillary antrostomy, ethmoidectomy may have to be done.²⁻⁵

Complications of Sinusitis

If sinusitis does not clear up, it can lead to some dangerous complications. These complications result from the spread of the infection to the neighboring tissues and include:

- Orbital cellulitis that is infection of the orbit
- Periorbital cellulitis which is infection of the tissues surrounding the eye
- Osteomyelitis, that is, infection of the bone surrounding the sinuses
- Brain abscess or meningitis.

Some of these complications may require surgery. A complication must be suspected if a patient with sinusitis develops any of these symptoms:

- Purulent rhinorrhea
- High fever ($>39^{\circ}\text{C}$)
- Facial pain
- Severe headaches
- A stiff neck
- Severe swelling in the face
- Swelling of the eyelids
- Restricted movement of an eye.

Acute Pharyngitis (Sore Throat)

Acute pharyngitis is inflammation of the pharynx, the cavity behind the mouth. Pharyngitis infection is commonly called sore throat. It is caused by either viruses or bacterial. Pharynx is the region around the throat.

Symptoms

Classic symptoms of pharyngitis include acute onset of:

- Pharyngeal pain
- Dysphagia
- Fever
- Rhinorrhea
- Cough
- Hoarseness
- Conjunctivitis and diarrhea are rare, and, if present, strongly suggest a viral etiology.

On examination, the pharynx may be erythematous, and have a patchy exudate on the posterior pharynx and tonsils. Anterior cervical lymphadenopathy is common.

Cause

A variety of microorganisms are responsible for causing pharyngitis. They can be categorized into those that are common and others that are not common. Most cases of pharyngitis are caused by viruses. The most common infections are due to:

- Rhinovirus (common cold) (60%)
- Enterovirus, influenza virus, parainfluenza virus
- Adenovirus
- Special: HIV, cytomegalovirus, coxsackievirus, herpes simplex, Epstein-Barr virus, bird flu?).

Bacterial

- Group A β -hemolytic streptococci (GABHS), 15 to 30 percent >3 years
- *C. diphtheriae*, *Haemophilus influenzae*, *N. meningitides*.
- Special: *Gonococcus*, *A. haemolyticus*, and *Mycoplasma pneumoniae*.

Clinical Manifestations

It is important to differentiate the two categories of pharyngitis based on their causative agents. These are:

- Viral pharyngitis
- Bacterial pharyngitis.

Viral Pharyngitis

Viral infections begin gradually, cause less intense inflammation, produce a milder degree of illness, last a shorter period and produce fewer complications than the bacterial infection. Viral infections manifest with fever, refusal to feed, general malaise, headache and moderate throat pain:

- The fever is highest on the third or fourth day.
- Throat pain may be absent at the beginning.
- In some cases, throat pain appears early but is rarely as severe as in the bacterial pharyngitis.

Strongly suggestive of viral pharyngitis is presence of conjunctivitis, rhinitis, cough, hoarseness, anterior stomatitis, discrete ulcers, viral exanthems and diarrhea.

The cervical lymph nodes are moderately enlarged and may or may not be tender. The throat and the tonsils are moderately red with or without follicular exudate on the throat, the tonsils or both places. Unlike that of the bacterial pharyngitis, the exudate in the viral pharyngitis never joins to form one whole patch. The pharyngitis is often associated with enlarged tonsils and in children is often taken as pharyngotonsillitis. The white cell count and the differential may be normal, show leukopenia or show leukocytosis.

Bacterial Pharyngitis

Bacterial pharyngitis differs with the viral pharyngitis in the following characteristics:

- Begins more abruptly
- Higher rise of fever than the viral pharyngitis
- Refusal to feed, headache, and general malaise characteristically occur early
- Sore throat may be absent on the first day or there may be a feeling of dryness in the throat. Later the throat may become very painful during swallowing
- The throat and the tonsils appear mildly red or fiery red. Sometimes the soft palate and the uvula are also red
- There is often an abundant yellow exudate or coating that spreads to coalesce (come together and form one whole)
- The cervical lymph nodes are characteristically enlarged and tender with a tendency to form abscess.

Acute onset and high fever from onset suggests viral etiology (It may not always be foolproof). Coryza or loose motions indicating generalized involvement of more than one system (more than one mucus membrane) and is in favor of a viral etiology. Conjunctival injection and red eyes is a feature seen in viral infection. Rash or exanthema indicates viral infection. Clustering of cases in the family or neighborhood would suggest a viral etiology.

In infants, bacterial pharyngitis may present with refusal to feed, drooling, fever and diarrhea. Most suggestive of bacterial pharyngitis are diffuse redness of the throat and the tonsillar pillars with petechial mottling of the soft palate, absence of an upper respiratory infection symptoms, vomiting in ages 5 to 15 years. Gonococcal pharyngitis is usually asymptomatic but may present with a high fever and gingivostomatitis. Allergic rhinitis with nonpurulent postnasal drip may also cause sore throat.⁵

Diagnosis

If viral etiology suspected, no investigations are needed. If symptomatology in favor of bacterial origin then where possible, leukocytosis, rapid test to identify streptococcal antigen and throat culture for bacteria may be useful investigations. Acute phase reactants have a very little role to play and should not be asked for routinely. A negative throat culture has a high negative predictive value for bacterial pharyngotonsillitis (especially GABH pharyngitis). Throat culture is time consuming and many a times not available everywhere. However, it is considered a good treatment practice and perhaps we need to inculcate this. Rapid antigen detection tests (RADTs) have good sensitivity and specificity, but are expensive and not easily available. Streptococcal antibody testing (ASO), etc. has no role in the diagnosis of acute streptococcal pharyngitis. Table 1 gives the differential diagnosis.

Treatment

Treatment for viral pharyngitis/pharyngotonsillitis should be symptomatic, i.e. optimal rest and plenty of oral fluids should be taken. Take account of avoidance of irritants (e.g. smoke) and have analgesics and antipyretics for fever and malaise and for that paracetamol is the drug of choice. It is always good to have home remedies like tulsi, ginger/lemon with honey and good to soothe the throat and such home remedies may be encouraged. It is always good to have salt water gargling. Normal saline nasal drops may help <2 yrs with blocked nose, nasal decongestants may be used sparingly for short-term. 1st generation antihistamines useful in few with bothersome rhinorrhea, as relieve rhinorrhea by 25 to 30 percent. Role of cough suppressants is questionable but may be tried. And always counsel that it will take 5 to 7 days to resolve. Even if it is GABHS,

Table 1: Differential diagnosis for sore throat

<i>Diseases</i>	<i>Signs and Symptoms</i>
Tonsillitis	Redness most marked on or around the tonsils Often yellow spots on tonsils Cervical glands enlarged and tender
Pharyngitis, due to the common cold or other virus	All throat equally red, no exudates Glands not enlarged Little tenderness
Diphtheria	Whitish membrane on tonsils and palate, difficult to remove and bleeding on removal (refer any suspected patients)
Leukemia	Sore throat for more than a few days White count shows very many cells
Agranulocytosis	Sore throat for more than a few days White count shows very few polymorphs

it is self-limiting and 30 percent heal without antibiotics. Antibiotics are given to reduce morbidity and prevent complications. But risk of complication does not increase even when the antibiotics are started as late as 9th day of illness.⁵

Treatment of GABHS should be with:

- Amoxicillin oral
- Penicillin (dosed 2 to 3 times daily) for 10 days, or
- A single IM injection of benzathine penicillin.

It is recommended a second line status for amoxicillin in pharyngitis because of greater selective pressure for resistant flora:

- To date no GABHS resistance to beta-lactam antibiotics have been identified.
- Erythromycin is the drug-of-choice for penicillin allergic individuals and cephalexin can be used for patients with nonanaphylactic penicillin allergy.

It is recommended to treat only individuals with a positive laboratory test with antibiotics. Newer higher sensitivity tests (e.g. newer optical immunoassays) do not change the recommendations to culture individuals with a negative rapid test and a clinical picture strongly suggesting GABHS²⁻⁴ (Table 2).

Diseases That Present with Pharyngitis

Several other illnesses present with sore throat. They include:

Herpangina

- This is an uncommon type of sore throat, which is viral in origin. It primarily affects children.

- Small vesicles in the pharynx or ulcers are seen on examination and also presents with headache, poor feeding, vomiting, abdominal pain, fever and sore throat are present. In some cases the abdominal pain may mimic acute appendicitis.

HIV

- In HIV cases fever with pharyngitis may occur soon after infection with the virus sets in.
- Fungal infection with *Candida* is common in HIV infection and presents as whitish areas on the tongue and pharynx.

Diphtheria

This condition may occur in unvaccinated populations. It is characterized by tonsillar or pharyngeal membrane. The disease is associated with consumption of raw milk.

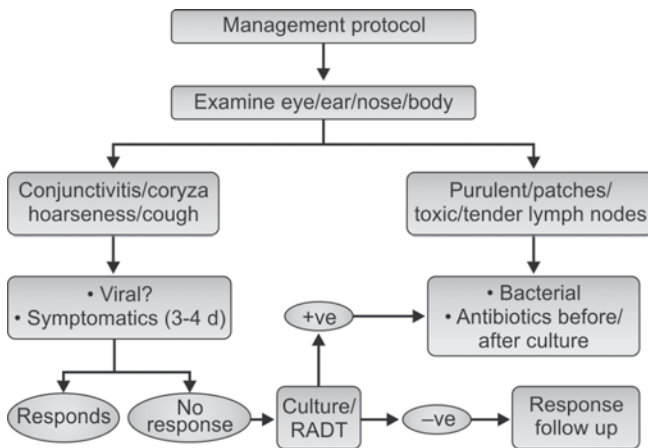
Influenza

Influenza is a contagious disease occurring in localized outbreaks. It may involve many people in many parts of the world if it occurs as a pandemic. After an incubation period of 1 to 3 days the illness will present with fever, sweating, headache, sore throat and muscular aches. A nonproductive cough and nasal obstruction may be present. The main danger of influenza is the complication of staphylococcal pneumonia. Management approach is given in Flow chart 2.

Table 2: Treatment of bacterial pharyngotonsillitis⁵

In children with no penicillin allergy		
Antibiotic (route) (days)	Children (<30kg)	Children (>30kg)
Penicillin V (oral) (10d)	250 mg BID	500 mg BID
Amoxycillin (oral) (10d)	40mg/kg/day (max 750 mg per day)	
Benzathine penicillin G (IM)	6 lakh units	1.2 Million units
In children with penicillin allergy		
Antibiotic (route) (days)	Children	
Erythromycin ethylsuccinate (oral) (10ds)	40-50 mg/kg/day TID	
Azithromycin (oral) (5days)	12 mg/kg OD	
I generation cephalosporin (oral) (10ds) (Non type I)	Cephalexin/cefaclor* in usual does	
II Line therapy		
Co-amoxyclavulinic acid	Children: 40 mg/kg/day in 3 equally divided doses	
Clindamycin (oral) (10days)	10-20 mg/kg	

*early second generation²⁸

Flow chart 2: Management approach to pharyngotonsillitis⁵

Complications

Viral infections have no complications except paving the way for secondary bacterial infection. The complications of bacterial pharyngitis include:

- Otitis media
- Retropharyngeal abscess
- Lateral pharyngeal abscess
- Sinusitis
- Acute cervical adenitis
- Septicemia
- Acute rheumatic fever
- Glomerulonephritis
- Meningitis (rarely)
- Large chronic ulcers in the pharynx in both viral and bacterial pharyngitis
- Pneumonia
- Rheumatic fever.

In view of the above complications, we should make every effort to recognize and treat acute pharyngitis timely and properly. There are two important complications of sore throat infections that we should be able to recognize: peritonsillar abscess and epiglottitis.

Peritonsillar abscess (Quinsy): Peri means around, so a peritonsillar abscess is an abscess around or near the tonsils. A large swelling forms around the tonsils. The patient usually cannot open the mouth very widely. We may see pus on the very swollen area around the tonsils. The danger is that the swelling may grow so large that the patient will have difficulty in breathing.

Epiglottitis: Epiglottitis is the infection of the epiglottis, the flap of tissue that covers the larynx when we swallow food. *H. influenzae* is supposed to be the common cause. X-ray neck lateral view shows thumb sign of swollen epiglottitis. If the epiglottitis is swollen it can be seen at the back of the throat, looking like a small red marble or cherry red swollen epiglottitis. Epiglottitis is very dangerous,

because the swollen epiglottis can block the airway and cause the patient extreme difficulty in breathing. It can also cause death. A patient with epiglottitis looks very ill, has a high fever and may have saliva dripping out at the side of his/her mouth. As the patient breathes, he/she produces a stridor as if he has croup. Establishing an airway by nasotracheal intubation or, less often, by tracheostomy is indicated in patients with epiglottitis, regardless of the degree of apparent respiratory distress, because as many as 6 percent of children with epiglottitis without an artificial airway die, compared with <1 percent of those with an artificial airway. No clinical features have been recognized that predict mortality. Pulmonary edema can be associated with acute airway obstruction.

Epiglottitis is a medical emergency and warrants immediate treatment with an artificial airway placed under controlled conditions, either in an operating room or intensive care unit. All patients should receive oxygen en route unless the mask causes excessive agitation. Racemic epinephrine and corticosteroids are ineffective. Cultures of blood, epiglottic surface, and, in selected cases, cerebrospinal fluid should be collected after airway stabilization. *Ceftriaxone*, *cefotaxime*, or a combination of *ampicillin* and *sulbactam* should be given parenterally, pending culture and susceptibility reports, because from 10 to 40 percent of *H. influenzae* type b cases are resistant to ampicillin. After insertion of the artificial airway, the patient should improve immediately, and respiratory distress and cyanosis should disappear. Epiglottitis resolves after a few days of antibiotics, and the patient may be extubated; antibiotics should be continued for 7 to 10 days. Chemoprophylaxis is not routinely recommended for household, child-care, or nursery contacts of patients with invasive *H. influenzae* type b infections, but careful observation is mandatory with prompt medical evaluation when exposed children develop a febrile illness. **Indications for rifampin prophylaxis** (20 mg/kg orally once a day for 4 days; maximum dose, 600 mg) for all household members are: (1) any contact <48 mo of age who is incompletely immunized; (2) any contact <12 mo who has not received the primary vaccination series; or (3) an immunocompromised child in the household. Acute laryngeal swelling on an allergic basis responds to epinephrine (1: 1,000 dilution in dosage of 0.01 mL/kg to a maximum of 0.5 mL/dose) administered subcutaneously or racemic epinephrine (dose of 0.25–0.75 mL of 2.25 percent racemic epinephrine in 3 mL of normal saline). Corticosteroids are frequently required (2–4 mg/kg/24 hr of prednisone). After recovery, the patient and parents should be discharged with a preloaded syringe of epinephrine to be used in emergencies. Reactive mucosal swelling, severe stridor, and respiratory distress unresponsive to mist therapy may follow endotracheal intubation for general anesthesia in children. Racemic epinephrine and corticosteroids are helpful.

Prevention

Vaccination is available and is recommended for patients who are prone to influenza, e.g. those with chronic bronchitis and emphysema other chronic respiratory disease and valvular heart disease. However, the vaccines have to be prepared annually as the virus tends to form new strains. Specific antiviral agents are available for treatment but these have to be given very early in the illness to have any effect. The antiviral agent may also be given for prevention for people who have been exposed to patients with influenza.

Guidelines for considering tonsillectomy:

- Seven or more episodes of tonsillitis in 1 year (true bacterial tonsillitis and not mere sore throat or URI).
- Five or more episodes per year over a 2 year period.
- Enlarged tonsils that create significant upper airway obstruction.
- An abscess in the tonsils.

Acute Laryngotracheobronchitis (Croup)

Is the infection of the structure below the pharynx namely the larynx, trachea and bronchi (hence the name laryngotracheobronchitis). Change in voice or cough character indicate laryngeal affection. Sudden onset symptoms of change in voice and barking cough with or without breathlessness (identical to viral croup) occurs in spasmodic croup. There may be history of similar episodes in the past in a child with recurrent croup. Playful child who is feeding well indicates a mild illness. Normal throat examination would rule out other causes of laryngeal obstruction like epiglottitis, laryngeal foreign body, retropharyngeal and peritonsillar abscess, infectious mononucleosis. Croup is divided into mild, moderate and severe depending on the symptoms as shown below: general appearance (activity and feeding), stridor at rest, respiratory distress and ability to maintain oxygenation are taken into consideration while grading the illness.

Mild croup

- The child appears happy, playful and is feeding well
- Stridor or change in voice is absent at rest and come up on coughing and crying
- Mild tachycardia and minimal chest wall retraction
- No stridor at rest and able to maintain saturations.

Moderate croup

- Stridor at rest and worsens with agitation
- Work of breathing is increased as indicated by increased HR and RR
- But the child is alert and able to maintain saturation
- Stridor at rest worsens on agitation but able to maintain saturations, i.e. >92 percent on room air.

Severe croup

- Worried and exhausted child
- Marked tachycardia

- Restlessness, agitation, irrational behavior, decreased level of consciousness, cyanosis and pallor
- Severe stridor, altered mentation and failing to maintain oxygenation, i.e. <92 percent saturation at room air or cyanosis⁵ (Table 3).

Causes

Many of the viral infections of the upper respiratory tract may be complicated by tracheitis and bronchitis. Acute respiratory failure may occur due to narrowing of the airways especially in children whose airways are generally narrow.

Clinical Features

- A characteristic brassy cough
- Stridor
- Wheeze
- Fever.

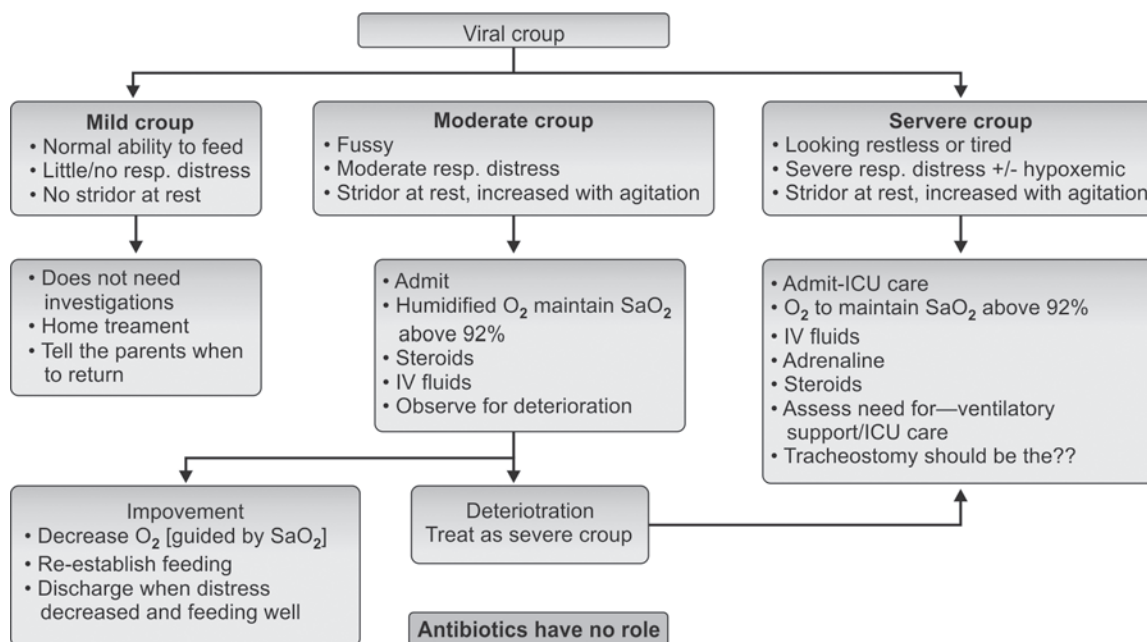
Diagnosis

Croup is a clinical diagnosis. Investigations not required in typical croup. In a child with airway obstruction, neck radiographs or blood tests cause anxiety which may precipitate further distress and obstruction. X-ray of the soft tissues of neck (AP and lateral view) if done—reveals a tapered narrowing (steep sign) of the subglottic trachea instead of the normal shouldered appearance. X-ray should be done if:

- Poor response to treatment
- Possibility of retropharyngeal abscess
- Toxic with high fever
- Difficulty in swallowing, drooling of saliva
- Malnourished child/staphylococcal skin stigmata, etc.

Treatment (Flow Chart 3)

Antibiotics have no role to play as it is a viral infection steroids and adrenalin nebulization with or without oxygen are the principles of treatment; role of steroid is doubtful in mild croup. A large RCT has shown that a single dose of steroid (dexamethasone—0.3–0.6 mg/kg every six hours for two to four doses) is effective in controlling mild to moderate croup. The child may be treated in the emergency room without hospitalization; use steroids and adrenalin nebulization (0.5 ml/kg – 1:1000 or maximum of 5 ml). Onset of action of adrenalin is rapid. The symptoms start improving in 30 min and the effect lasts for 2 hrs. The dose can be repeated every 2 to 4 hrs. At the end of 4 hrs look for improvement and if there is no improvement then hospitalize in a set up with ICU facility. While all routes are considered equi-efficacious for steroids; yet some authors do recommend repeat doses of nebulized Budesonide in those who are poorly responsive every 12 hrs to a maximum of 4 doses. When used orally/parenterally a single dose should suffice in most cases. Few studies have followed oral/parenteral dose by a nebulized dose in

Flow Chart 3: Management of croup⁵

case of a poor response. Few consider subsequent doses unnecessary, if there is no response to the first dose. Several texts initially recommended dexamethasone as a single dose of 0.6 mg/kg, however, the current suggestion is 0.3 mg/kg/dose; Budesonide is given as 2 mg nebulized dose; given up to 4 doses q12 h depending on the severity and response. The use of steroids has been associated with:

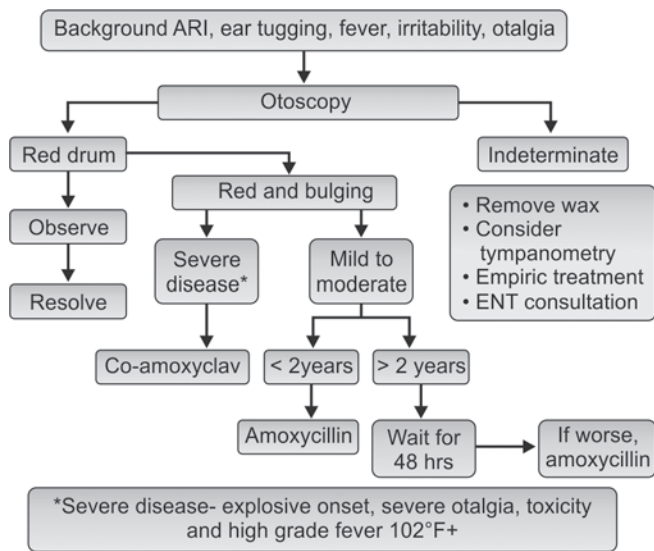
- Reduced average length of stay in the emergency
 - Decrease in the number of adrenaline nebulizations needed
 - Reduced need for endotracheal intubation
 - If intubation is still required, the duration is decreased.
- Current evidence more strong for its efficacy in moderate to severe croup.²⁻⁵

Acute Otitis Media (Flow Chart 4)

AOM is defined as presence of fluid in the middle ear in presence of signs and symptoms of acute inflammation of the middle ear. Middle ear fluid is evidenced by bulging tympanic membrane, limited or absent mobility, air fluid level behind the membrane or otorrhea. Erythema and otalgia would mean inflammation and not necessarily AOM. Red drum in all age group requires observation. While mild to moderate redness with bulge suggest treatment below 2 years. The child may present with acute onset pain in the ear, fever, vomiting and irritability. Child may also have dizziness and constitutional symptoms like reduced appetite and/or sleep. Paracetamol is used as analgesic. Decongestants have no role in the treatment.

In a child under 2 years not having severe disease, amoxycillin is started on diagnosis and used for 10 days. In our country the dose for amoxycillin is 45 mg/kg/d and higher dosage as recommended by western literature is not needed. If the child has severe disease, Co-amoxycylav may be used Cefaclor or Cefuroxime are other second line agents. In a child over 2 years, start antibiotics immediately only in those with severe disease. In unconfirmed cases or mild disease one may wait for 48 to 72 hrs for spontaneous resolution. Commence treatment if there is deterioration or no resolution at the end of 48 to 72 hrs. The duration of treatment should be 10 days except in children above 5 years when 7 days treatment is sufficient. Treat the symptoms like pain with analgesic agent. Stress on poor efficacy of Cefixime against *S. pneumoniae*. It is not an antibiotic for common respiratory tract infections. Every child with AOM should be evaluated by routine otoscopy at the end of 10 days treatment.

Middle ear effusion (MEE) is a common complication following AOM. Absence of acute inflammation differentiates it from AOM. MEE resolves most of the time, 40 percent by 4 weeks, 60 percent by 6 weeks and 70 percent by 8 weeks. Tympanometer has 3 channels—air, sound and reflective waves. One measures maximal reflectance and different air pressures. Shift of the peak to negative values suggests decrease mobility and necessitates an ENT review. Tympanometry is helpful to follow up for resolution. ENT referral is made in case of doubt or failure of resolution. Recurrent OM is defined as 3 or more episodes of AOM in 6 months or 4 or more episodes in a year. Careful search should be made for

Flow Chart 8: Approach for AOM⁵

predisposing factors like bottle feeding, day care center setting, adenoids, etc. Severe disease is one with explosive onset, severe otalgia and high grade fever – (102° F or above). Mild – moderate disease means a child with mild to moderate fever or pain 2 to 5 (For approach see Fig. 8).

Summary for indications for antibiotic use in URTI's

- Child less than 3 months of age
- Primary immunodeficiency states (not routinely in HIV infection)
- Proven strep. throat
- Severe symptoms of acute otitis media and
- Severe acute rhinosinusitis or disease lasting longer than 7 to 10 days.

Acute Lower Respiratory Infections

Lower respiratory tract infections place a considerable strain on the health budget and are generally more serious than upper respiratory infections. Lower respiratory tract infections are often endogenous – caused by microbes in the patient's commensal flora. Usually, the lower respiratory tract is sterile. Sterility is maintained by the mucociliary escalator. There are a large number of microbes that can cause infection in the lower respiratory tract. Initial diagnosis of lower respiratory tract infections includes a clinical examination and chest X-ray. The pattern of consolidated or inflamed lung tissue revealed in these examinations will yield invaluable clues as to the most likely causative agent.^{6,7}

In this section following diseases are encountered:

- Bronchiolitis
- Community acquired pneumonia
- Nosocomial pneumonia

- Recurrent pneumonia
- Empyema
- Bronchiectasis

Since approach to RTI's is syndromic, a combination of symptom complex of fever, cough and rapid or/and difficult breathing is strongly suggestive of either lower airways, parenchymal or plueral involvement. The most important features are rapid and difficult breathing. In fact rapid breathing alone is very sensitive screening sign of pneumonia as per the WHO guidelines. However, bronchiolitis/WALRI/asthma can present similarly with rapid breathing. "Prematurity" (particularly between 34 to 37 weeks gestation) and mechanical ventilation are few of the 'high risk factors' for the infant to develop bronchiolitis (describe other risk factors). Acute onset, short history is the presenting feature and "refusal of feeds" is one of the criteria for grading of "bronchiolitis". Mild tachypnea and mild tachycardia are suggestive of affliction of lower airways. Good perfusion and saturation in room air without supplementary oxygen, activity and interest in the surroundings and minimum or no subcostal indrawing are the 3 other main criteria to decide about the severity of bronchiolitis. Apart from tachypnea, tachycardia mild respiratory distress (subcostal indrawing) the add on features of bilateral scattered wheezing, acute onset with the preceding upper respiratory catarrh lead us to the most likely diagnosis of bronchiolitis. Define bronchiolitis as "viral induced clinical syndrome of young infants characterized with fever, cough, wheeze and rapid breathing with a prodrome of viral upper respiratory catarrh", between 1 months to 2 years of life with peak between 3 to 7 months.

Consider bronchiolitis if:

- First episode
- Age 1 month to 2 years
- Presence of upper respiratory catarrh
- Progressive increase in respiratory distress (tachypnea, retractions)
- Wheeze + crackles
- Clinical and radiological evidence of hyperinflation.

More facts:

- Risk of significant disease <6 months of age
- Up to 3 percent of all children in 1 year are hospitalized
- Fifty percent are associated with RSV infection, other causes being "influenza, parainfluenza, adenoviruses, coronavirus and rhinoviruses".

Most likely diagnosis is bronchiolitis in v/o

- Young age
- Acute onset
- Prodromal viral catarrh
- Wheeze
- Crackles
- Hyperinflated chest

Severity of the disease (Table 4) discussion should be steered to three important components viz. feeding difficulties; respiratory distress and saturations.

- Risk factors for increased severity
- Infants in day care
- Exposure to passive smoke
- Cow dung in the household
- Infants younger than 2 to 3 months
- Premature birth
- Congenital heart disease
- Chronic lung disease like CF, recurrent aspiration, BPD, congenital malformations, etc.

Risk factors for hospitalization:

- Infants younger than 3 months
- Oxygen saturation <92 percent
- RR >70/min
- Ill appearing child

Infants with one or more risk factors for a severe course merit admission. Stress upon the fact that “bronchiolitis is almost always a clinical diagnosis and seldom requires any investigations. Blood tests like ‘acute phase reactants’ are least specific and least significant and noncontributory. However ABG monitoring may be useful not for diagnosis but for monitoring of severe cases in ICU. Routine chest radiography is of very little significance and not indicated unless there is severe respiratory distress and diagnostic ambiguity, to rule out other conditions like pneumothorax, consolidation, empyema, etc. If at all chest X-ray is done it will reveal:

- Hyperinflated lung fields
- Diffuse infiltrates due to segmental atelectasis. These findings are also seen in viral pneumonia.

Feeding abilities, respiratory distress and saturations are the most important criteria to grade the severity of bronchiolitis into “mild – moderate and severe (Table 3).

Table 3: Grading severity of croup⁵

	<i>Mild</i>	<i>Moderate</i>	<i>Severe</i>
Feeding ability	Normal ability to feed	Appear short of breath during feeding	May be reluctant or unable to feed
Respiratory distress	Little or no respiratory distress	Moderate distress with some chest wall retraction and nasal flaring	<ul style="list-style-type: none"> • Severe distress with marked chest wall retractions, nasal flaring and grunting • Can have frequent and prolonged apnoeas
Saturations	Saturations >92%	Saturations <92%, correctable with O ₂	Saturations <92%, may or may not be correctable with O ₂

Table 4: Grading of bronchiolitis⁵

<i>Mild</i>	<i>Moderate</i>	<i>Severe</i>
<ul style="list-style-type: none"> • No treatment required • Reassure mother • To bring the baby back if distress increases 	<ul style="list-style-type: none"> • Admit • Humidified oxygen to maintain sats >92% • IV fluids • Observe for deterioration • Trial of adrenaline • If the child deteriorates treat as severe 	<ul style="list-style-type: none"> • Admit-ICU care • O₂ to maintain sats >92% • IV fluids • Adrenaline trial • Cardiorespiratory monitoring • ABG/CXR • Assess need for ventilatory support/ICU care

Treatment of Bronchiolitis

No active treatment or medications, reassurance to mother, close watch on the baby and to report back if the distress increases; form the core of management of “mild bronchiolitis”. A trial of adrenaline may benefit few cases; however, the studies on the matter are equivocal (It is worth remembering that they vary a lot in methodology and dosage and are therefore not comparable). Medications in bronchiolitis management are divided into two groups.

Noncontroversial

Since bronchiolitis is condition of air way resistance of bronchioles at both the ends with mucosal edema and the basic “pathophysiology” is “hypoxemia”. The drug of choice is oxygen and oxygen only. For decades it has never been subjected to any randomized trials. IV fluids are necessitated due to refusal of feeds to maintain fluid electrolyte balance and combat dehydration.

Controversial

Strictly speaking though bronchodilators are not absolute contraindications in bronchiolitis their role is highly controversial and theoretically there is no role of bronchodilator as they do not improve oxygen saturation and treat hypoxemia nor affect rate and duration of hospitalization. However in some indeterminate cases like early wheezers, wheezing of infancy or older infants (>6 months) with a strong history of personal or family atopy, a trial of nebulised beta agonists may be given and continued further if there is objective improvement. Oral feeding may be continued in mild to moderate respiratory distress if tolerated well. IV fluids should be administered in case of moderate to severe respiratory distress when there is marked tachypnea intermittent apneic spells and refusal or tiring during feeds. As discussed earlier, since “hypoxemia” is the basic pathophysiology in bronchiolitis –oxygen is the only drug of choice, absolutely noncontroversial since

decades and as testimony it has never been subjected to any randomized trials. One has to use oxygen to the tune of maintaining SpO_2 at or >92 percent saturation during acute phase and recovery, however a saturation 90 to 92 percent SpO_2 is acceptable if child is not distressed and feeding well. There is no role for routine bronchodilators in bronchiolitis as they do not improve oxygen saturation, or affect rate or duration of hospitalization.

A trial of nebulized bronchodilator can be given in older infant (>6 months) with wheeze or those with a strong history of atopy, or further therapy continued if there is an objective improvement.

Since mucosal edema is an important component of airway obstruction in bronchiolitis probably a combined alpha and beta adrenergic receptor agonist like adrenalin may be more useful. However many randomized control trials have failed to substantiate their usefulness in bronchiolitis. Whatever little improvement in symptoms seen has been short lived and inconsistent. Hence nebulized adrenalin may best be used as a “rescue” medication in those who are admitted. Stress upon the high dose of up to 0.3 ml/kg. Systemic side effects are not seen because only 1 to 2 percent absorption of the drug through nebulization. Minimum fill volume is decided by the nebulizing chamber being used. Most chambers need at least 3 ml of the fluid. So where needed add saline to achieve the minimum fill volume. Steroids have no role absolutely as multiple studies have failed to demonstrate any clear cut efficacy in bronchiolitis. There is absolutely no role of antibiotics routinely in bronchiolitis. However rarely in a very sick and toxic infant with high fever and significant

opacities on chest radiograph, when a secondary bacterial infection is strongly suspected, appropriate antibiotics may be used. Though RSV is the commonest cause of bronchiolitis specific antiviral therapy proved to be of very limited value. Unfortunately many clinicians seem to be tempted to sedate bronchilitic patients for excessive irritability, which is usually due to hypoxia. Paradoxically sedation decreases the oxygenation and increases hypoxemia and may prove to be dangerous and should be strictly avoided. Attempt to comfort the child should be done with- fever control, nasal clearing, breast feeding and supplemental oxygenation. Discharge can be planned when there is no fever, minimum or no respiratory distress, feeding orally adequately, no need for IV fluids, saturation >92 percent, and no supplemental oxygen for at least 10 to 12 hours⁵⁻⁷ (Flow chart 5).

Community Acquired Pneumonia

Childhood pneumonia remains a relevant and well discussed subject because of high mortality in developing countries. It is estimated that 13 million children aged less than 5 years die worldwide, annually; among them 4 million children die from pneumonia in developing countries. Because of such a high mortality, the World Health Organization (WHO) developed the Program for Control of Respiratory Infections in the 1980's, which was included as a component of the Integrated Management of Childhood Illness (IMNCI) strategy in the mid 1990's. This included the utilization of simpler signs and symptoms with high sensitivity and specificity for the first level health care personnel. The pneumonia was defined as per

Flow Chart 5: Management of bronchiolitis⁵

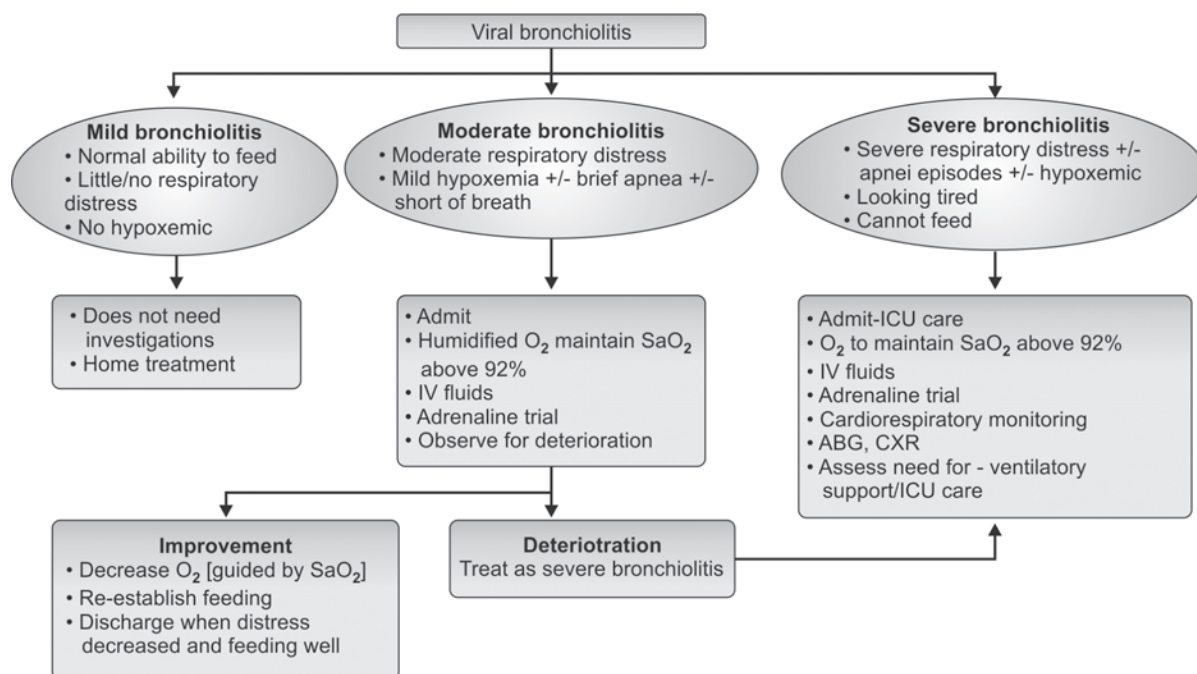


Table 5: Pneumonia as per WHO criteria*WHO defined pneumonia*

- < 2 months of age >60 breaths/min
- 2–12 months >50 breaths/min
- > 12 months >40 breaths/min

Severe pneumonia

- Tachypnea with accessory muscle working

Very severe pneumonia

- Tachypnea with accessory muscle working and
Altered sensorium, or
Cyanosis, or
Difficulty in feeding, or
Poor perfusion

Respiratory Tract Infections Group Education Module– IAP Action Plan 2006

respiratory rate as described in WHO criteria in Table 5. The main causation of death due to pneumonia in developing countries is bacterial etiology hence IMNCI recommends use of antibiotics when the child presents with tachypnea as defined previously. All this leads to excessive use of antibiotics in areas where wheezing is prevalent or those children who are known wheezer; which can be treated with bronchodilator without the need for antibiotics and they often also present with cough and tachypnea and less likely with fever. For a general practitioner community acquired pneumonia (CAP) is very important illness to deal with and this section will illustrate common facts about CAP.⁵⁻⁸

CAP as defined by Respiratory Tract Infections Group Education Module – IAP Action Plan, 2006 is an acute infection of the pulmonary parenchyma in a previously healthy child, acquired outside of a hospital setting not have been hospitalized within 14 days prior to the onset of symptoms, or has been hospitalized less than 4 days prior to onset of symptoms. It excludes:

- Child with any immune deficiency
- Severe malnutrition
- Postmeasles state
- Ventilator associated pneumonia/nosocomial spread
- Recurrent pneumonias

It is one of the most common causes of serious illness in children. In developing countries it accounts for 20 percent of all deaths in children.

Our knowledge of this deadly disease has increased greatly in the last few years, especially regarding its etiology. The principal change has been an increase in the number and type of organisms recognized as capable of causing pneumonia. This change in knowledge has necessitated a change in therapeutic recommendations as well. Antibiotics are an essential part of the management of pneumonia and appropriate choices could help avert much of the mortality associated with this disease.

Etiology

It is often difficult to elicit the etiology of pneumonia especially in children, but patient's age can help narrow the list of likely etiologies. Table 6 gives the etiology of CAP according to various age groups. The old belief that “atypical” organisms like *Mycoplasma pneumoniae* and *Chlamydia* species cause only mild disease no longer holds true. These organisms are important causes of community acquired pneumonia, including serious cases. One study in adults found a 5 percent mortality in patients with pneumonia caused by these “atypical” pathogens. Indeed, the 2001 British Thoracic Society guidelines recommend that the term “atypical pneumonia” no longer be used.

Indian studies have found a high prevalence of *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* in community acquired pneumonia in adults as well as children. There is also evidence of frequent coinfection with other organisms. These atypical organisms are more likely in older children. *Chlamydia trachomatis*, however, is involved in pneumonia at younger ages – 3 weeks to 3 months. Gram negative organisms, especially *Klebsiella* and *E. coli*, are also common at this age.

Streptococcus pneumoniae is the most common bacterial cause of pneumonia in childhood. Age is a good predictor of the likely pathogens. Viruses are most commonly found as a cause in younger children. In older children, when a bacterial cause is found, it is most commonly *S. pneumoniae* followed by mycoplasma and *Chlamydial pneumonia*. A significant proportion of cases of CAP (8–40%) represent a mixed infection. Viruses alone appear to account for 14 to 35 percent of CAP in childhood. In 20 to 60 percent of cases a pathogen is not identified. The mortality from CAP in children in developed countries is low.

Diagnosis

A diagnosis of pneumonia is often entertained on the basis of the initial presentation of symptoms and signs. The clinical presentation may be subtle; and radiographic and laboratory studies aid in the diagnosis and allow identification of the causative agent.

Clinical Characteristics

Fever, headache, abdominal pain, dyspnea, cough and crepitations are frequently found in children with pneumonia (Table 7). Tachypnea has been suggested as the best sign that a child has pneumonia rather than an uncomplicated upper respiratory tract infection, but there is no widely accepted definition of what it is, especially in febrile children.

Cough, dyspnea, rhinorrhea, and abdominal pain, as well as fever, crepitations, and otitis media, are present in similar proportions of children with viral or bacterial

Table 6: Causes of community-acquired pneumonia by age group

Age	Common causes	Less common causes
Birth to 20 days	Bacteria <i>Escherichia coli</i> Group B streptococci <i>Listeria monocytogenes</i>	Bacteria Anaerobic organisms Group D streptococci <i>Haemophilus influenzae</i> <i>Streptococcus pneumoniae</i> <i>Ureaplasma urealyticum</i> Viruses Cytomegalovirus Herpes simplex virus
3 weeks to 3 months	Bacteria <i>Chlamydia trachomatis</i> <i>S. pneumoniae</i> Viruses Adenovirus Influenza virus Parainfluenza virus 1, 2 and 3 Respiratory syncytial virus	Bacteria <i>Bordetella pertussis</i> <i>H. influenzae</i> type B and nontypeable <i>Moraxella catarrhalis</i> <i>Staphylococcus aureus</i> <i>U. urealyticum</i> Virus Cytomegalovirus
4 months to 5 years	Bacteria <i>Chlamydia pneumoniae</i> <i>Mycoplasma pneumoniae</i> <i>S. pneumoniae</i> Viruses Adenovirus Influenza virus Parainfluenza virus Rhinovirus Respiratory syncytial virus	Bacteria <i>H. influenzae</i> type B <i>M. catarrhalis</i> <i>Mycobacterium tuberculosis</i> <i>Neisseria meningitis</i> <i>S. aureus</i> Virus Varicella-zoster virus
5 years to adolescence	Bacteria <i>C. pneumoniae</i> <i>M. pneumoniae</i> <i>S. pneumoniae</i>	Bacteria <i>H. influenzae</i> Legionella species <i>M. tuberculosis</i> <i>S. aureus</i> Viruses Adenovirus Epstein-Barr virus Influenza virus Parainfluenza virus Rhinovirus Respiratory syncytial virus Varicella-zoster virus

pneumonia.¹⁶ Wheeze occurs more frequently with viral infections but is also a common finding in *Mycoplasma pneumoniae*. Therefore, children with viral or bacterial pneumonia cannot be distinguished by clinical signs only. Bacterial pneumonia should be considered in children aged up to 3 years when there is fever of $>38.5^{\circ}\text{C}$ together with chest recession and a respiratory rate of $>50/\text{min}$ (Tables 8 to 10). For older children a history of difficulty in breathing is more helpful than clinical signs. If wheeze is present in a preschool child, primary bacterial pneumonia is unlikely.

Radiographic Findings

A chest radiograph is generally regarded as the gold standard for confirming the presence of pneumonia but routine use of a chest radiograph for every child with mild uncomplicated acute lower respiratory infection is not appropriate (Table 11).

One large study of the value of chest radiography in ambulatory children with acute lower respiratory infection, aged 2 months to 5 years, concluded that chest radiography did not affect the clinical outcome of the children. A chest radiograph is advisable, however, in a child

Table 7: Features of viral lower respiratory tract infection (LRTI)⁵*Infants and young children*

- Wheeze
- Fever <38.5°C
- Marked recession
- Hyperinflation
- Respiratory rate normal or raised
- Radiograph shows hyperinflation and, in 25%, patchy collapse
- Lobar collapse when severe

Table 8: Features of mycoplasma lower respiratory tract infection (LRTI)⁵*School children*

- Cough, wheeze, pneumonia
- Interstitial infiltrates, lobar consolidation and hilar adenopathy

Table 9: Features of bacterial lower respiratory tract infection (LRTI)⁵

- Fever >38.5°C
- Respiratory rate >50 breaths/min
- Chest recession
- Wheeze not a sign of primary bacterial LRTI (other than mycoplasma)
- Other viruses may be concurrent
- Clinical and radiological signs of consolidation rather than collapse

younger than 5 years with a fever of unknown origin. Chest radiographs do not discriminate between bacterial, atypical, and viral pneumonia. Lobar consolidation has been associated with pneumococcal infection and interstitial infiltrates with viral infections. Both lobar consolidation and interstitial infiltrates, however, have been identified in all types of infection, viral, bacterial, or mixed. Virkki et al studied 254 consecutive children hospitalized with community-acquired pneumonia. A potential causative agent was identified in 85 percent of them. Bacterial infection was documented in 71 percent of 137 children with alveolar infiltrates, while half of the 77 patients with solely interstitial infiltrates had evidence of bacterial infection, suggesting that alveolar pneumonia, especially with lobar infiltrates, is mostly seen in bacterial pneumonia but interstitial infiltrates are seen in both viral and bacterial pneumonias. Follow-up chest radiography in asymptomatic children with prior radiologic evidence of pneumonia is not helpful and should only be performed after lobar collapse, round pneumonia, or for persisting symptoms.

Chest radiography should not be performed routinely in children with mild uncomplicated acute lower respiratory tract infection. Radiographic findings are poor

Table 10: Assessment of severity^{6 to 8}*Severity assessment*

	<i>Mild</i>	<i>Severe</i>
Infants	Temperature <38.5°C RR <50 breaths/min Mild recession Taking full feeds	Temperature >38.5°C RR >70 breaths/min Moderate to severe recession Not feeding Nasal flaring Cyanosis Intermittent apnea Grunting respiration
Older Children	Temperature <38.5°C RR <50 breaths/min Mild breathlessness No vomiting	Temperature >38.5°C RR >50 breaths/min Severe difficulty in breathing Nasal flaring Cyanosis Grunting respiration Signs of dehydration

Table 11: Indications for CXR in either primary care or hospital

- For diagnosis of child, 5 years with fever of 39°C of unknown origin
- If complication (for example, pleural effusion) suspected
- Atypical symptoms or unresponsive to treatment
- For follow up of children with lobar collapse or ongoing symptoms

indicators of etiology. Follow up chest radiography should only be performed after lobar collapse, an apparent round pneumonia, or for continuing symptoms.

Bacterial or Viral?

Watery nasal discharge, involvement of more than one mucosa and similar illness in more than one member in the family point to a viral illness. Again pharyngeal erythema and/or tender cervical lymphadenopathy have a high negative predictive value for a bacterial pharyngotonsillitis. No single sign is definitive but predictability improves with presence of more number of features in a given case.

Bacterial and viral pneumonias differ in laboratory and clinical features, but there is enough overlap to prevent reliable differentiation. Neither X-ray appearance, white cell count, ESR, nor CRP, can reliably distinguish viral from bacterial pneumonia. CRP concentrations above 40 mg/L suggest bacterial involvement, though viral infections such as adenovirus can also induce high CRP levels.

Several prospective studies have shown that these acute-phase reactants have a low sensitivity and specificity between bacterial and viral infection and no combination

of these markers is sufficiently sensitive and specific to be used in clinical practice. Procalcitonin has been evaluated as a potentially useful marker for distinguishing between viral and bacterial infections and for the early detection of invasive infections. Procalcitonin offers better specificity than C-reactive protein for differentiating between viral and bacterial cause of fever with similar sensitivity and high values indicate the presence of bacterial infection. Other studies concluded, however, that measurement of serum procalcitonin is of little value in differentiating between bacterial and viral pneumonia in children.

Immunofluorescence and serology are the most useful for identifying viral infections, and their general use may help in rationalizing antibiotic treatment.⁷⁻⁹

Microbiologic Investigations

In most children with community-acquired pneumonia, identification of the causative organism is not critical, but in hospitalized children with severe or complicated pneumonia it may be important, and microbiologic investigation should be performed. Blood cultures are rarely positive in pneumonia.

In a recent study of children aged 2 to 24 months with pneumonia, the prevalence of bacteremia was 1.6 percent, suggesting that the widespread use of the heptavalent conjugate pneumococcal vaccine may further decrease the prevalence of bacteremia in pneumonia. Therefore blood cultures are not recommended as routine studies for outpatients but may help direct treatment in inpatients with more severe form of pneumonia.

Sputum Gram stain and culture should be considered in older children and adolescents with severe disease. When pleural effusion is present it should be aspirated and sent for microscopic examination and culture. A negative throat culture has a high negative predictive value for bacterial pharyngotonsillitis (esp. group A beta hemolytic pharyngitis). Throat culture is time consuming and many a times not available everywhere. However, it is considered a good treatment practice and perhaps we need to inculcate this.

Rapid antigen detection tests (RADT) have good sensitivity and specificity, but are expensive and not easily available. Streptococcal antibody testing (ASO), etc. has no role in the diagnosis of acute streptococcal pharyngitis.

Antigen detection of bacteria in serum lacks specificity and sensitivity to be of diagnostic value and it is not recommended. Rapid antigen tests such as immunofluorescence assay and solid-phase immunoassay are available for RSV; parainfluenza 1,2 and 3; influenza A; and B; and adenovirus. Nasopharyngeal aspirates from children under the age of 18 months should be sent for viral antigen detection or PCR assay. The best test for rhinovirus is PCR assay. Serologic testing for IgM or at least quadrupling of

serum IgG between the acute phase and convalescence for children with suspected *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* is a satisfactory test but has limited clinical value to the physician who needs interpretation quickly for decision making. Cold agglutinins are often used as an acute test for diagnosis of *M. pneumoniae* but there are false-positive results with viral diseases and the positive predictive value of the test is 70 percent. PCR assay may be helpful for rapid diagnosis of *C. pneumoniae* and *M. pneumoniae*.

Acute phase reactants do not distinguish between bacterial and viral infections in children and should not be measured routinely. There is no indication for microbiological investigation of the child with pneumonia in the community. Blood cultures should be performed in all children suspected of having bacterial pneumonia. Acute serum samples should be saved and a convalescent sample taken in cases where a microbiological diagnosis was not reached during the acute illness. Nasopharyngeal aspirates from all children under the age of 18 months should be sent for viral antigen detection (such as immunofluorescence) with or without viral culture. When significant pleural fluid is present, it should be aspirated for diagnostic purposes, sent for microscopic examination and culture, and a specimen saved for bacterial antigen detection.¹⁰

Management

General Management

The child cared for at home should be reviewed by a general practitioner if deteriorating, or if not improving after 48 hours on treatment. Families of children who are well enough to be cared for at home need information on managing pyrexia, preventing dehydration, and identifying any deterioration. Patients whose oxygen saturation is 92 percent or less while breathing air should be treated with oxygen given by nasal cannulae, head box, or face mask to maintain oxygen saturation above 92 percent. Agitation may be an indication that the child is hypoxic. Nasogastric tubes may compromise breathing and should therefore be avoided in severely ill children and especially in infants with small nasal passages. If used, the smallest tube should be passed down the smallest nostril. Intravenous fluids, if needed, should be given at 80 percent basal levels and serum electrolytes monitored. Chest physiotherapy is not beneficial and should not be performed in children with pneumonia. Antipyretics and analgesics can be used to keep the child comfortable and to help coughing. In the ill child, minimal handling may reduce metabolic and oxygen requirements. Patients on oxygen therapy should have at least 4 hourly observations including oxygen saturation. Pulse oximetry should be performed in every child admitted to hospital with pneumonia.

Treatment (Table 12)

The treatment of pneumonia is always empirical, as it is extremely rare that the causative organism is identified before antibiotics are selected. Empiric therapy should be based on knowing the most likely pathogen in each community, as the relative frequency varies from one region to another, but also the risk for resistant organisms, infectious diseases and the age of the child. Recent serologic studies have confirmed that *S. pneumoniae* is an important causative agent for community-acquired pneumonia of all ages. *M. pneumoniae* is common from the age of 5 years onwards and *C. pneumoniae* is common from the age of 10 years onwards. Because it is difficult to distinguish between bacterial, viral, and mixed infections, most children with community acquired pneumonia are treated with antibiotics. Treatment decisions regarding selection of antibiotic should be based on the age of the child and epidemiologic factors and sometimes the results of chest radiography. GABHS is self limiting disease recovering within 3 to 4 days. The goals of pharmacotherapy are to reduce morbidity and to prevent complications. Complications can be prevented even if the antibiotics are started as late as by the 9th day of illness.

Duration of the antibiotics is 10 days except azithromycin (5 days). Here the issue is of bacterial eradication and not merely clinical cure as one is more concerned about the prevention of rheumatic fever. The duration therefore is 10 days therapy for penicillin. Likewise 60 mg/kg total dose of azithromycin (12 mg/kg/d \times 5 days) is considered most potent. However, it must be borne in mind that the GABHS resistance to macrolides is high and therefore they are used only if the child is intolerant to the first line drugs.

Infants between 3 weeks and 3 months of age in whom pneumonia is suspected are best treated as inpatients, particularly if they are febrile and have a toxic appearance (Table 13). The most likely causes of pneumonia in this age group are *C. trachomatis*, which causes afebrile, subacute interstitial pneumonia, and RSV. *B. pertussis* and *S. aureus* are now a days less common causes of pneumonia.

Afebrile patients are treated as outpatients with oral erythromycin or with intravenous erythromycin if they are hospitalized. Patients with lobar or lobular infiltrates or pleural effusion alone or in combination should be treated with cefotaxime or ampicillin. Indications for transfer to ICU are given in Table 14.

Preschool-aged Children (6 Months to 5 Years)

Viruses are the predominant pathogen in preschool-aged children (6 months to 5 years), RSV being the most common cause of pneumonia followed by parainfluenza and influenza viruses and adenovirus and rhinovirus. hMPV is also responsible for pneumonia in this age group. *S.*

pneumoniae is the most common bacterial pathogen in preschool children. *Hemophilus influenzae*, a common cause of pneumonia in the past, is very rare nowadays in areas with wide vaccine coverage. In children who present symptoms of viral infection such as pharyngitis, rhinorrhea, and diarrhea, especially during an epidemic, and who have a mild disease, withholding treatment seems appropriate if a close follow-up of the patient is ensured (Flow chart 6).

When bacterial pneumonia is suspected because *S. pneumoniae* is the most common cause of pneumonia in this age group, the patient should be treated with amoxicillin in high dose, if resistance to it is anticipated. Other alternatives are amoxicillin/clavulanate and second-generation cephalosporins. Macrolides such as erythromycin or clarithromycin may be used when *Mycoplasma* infection is suspected. Patients who require hospital admission are treated with ampicillin or cefuroxime or cefotaxime intravenously.

Children 5 to 15 Years

Mycoplasma pneumoniae is the main pathogen causing pneumonia in children aged 5 to 15 years, *C. pneumoniae* being less common. *S. pneumoniae* remains a significant pathogen in school-aged children. Macrolides are the first choice in this age group because of the increased prevalence of *Mycoplasma* and because they are effective against pneumococci sensitive to penicillin. Outpatients with pneumonia are treated with erythromycin or clarithromycin or azithromycin. Hospitalized patients are treated with intravenous erythromycin or intravenous azithromycin, and if there is strong evidence of a bacterial infection ampicillin, cefuroxime, or cefotaxime is added.

Flow Chart 6: Algorithm for differentiating children with pneumonia from children with bronchospasm

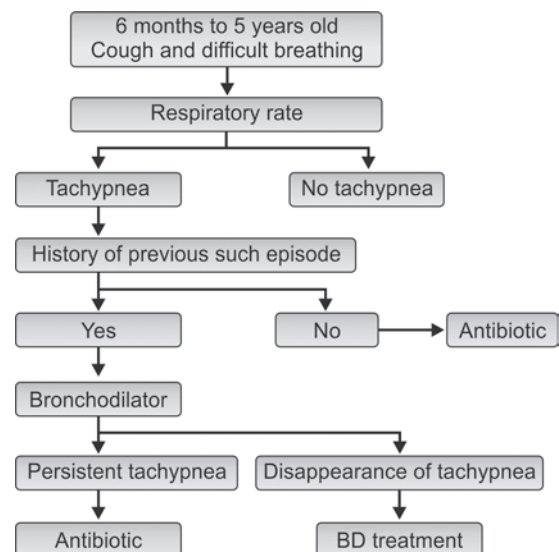


Table 12: Treatment protocol⁵

<i>Disease setting</i>	<i>Pneumonia domiciliary</i>		
<i>Age</i>	<i>First line</i>	<i>Second line[#]</i>	<i>Suspected Staphylococcus ds</i>
<i>Up to 3 months</i>	<i>Usually severe, treated as inpatients</i>		
<i>3 month – 5 years</i>	Amoxycillin	Co-amoxy clavulanic acid Or Chloramphenicol	Cefuroxime Or Co-amoxy clavulanic acid*
<i>5 years+</i>	Amoxycillin	Macrolide Or Co-amoxy clavulanic acid Or Chloramphenicol	Cefuroxime Or Co-amoxy clavulanic acid Or Amoxycillin – cloxacillin*

Second line domiciliary therapy is for patients who show inadequate or no response to first line treatment after 48 hours, though have no deterioration or increase in severity.
*Use separately in 1:2 ratio as combinations available are not scientifically correct

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<i>Severe – very severe pneumonia Treat as in-patient</i>		
<i>Age</i>	<i>First line</i>	<i>Second line</i>
<i>0 to 3 months</i>	Inj 3rd gen. cephalosporins: Cefotaxime/ceftriaxone ± Aminoglycoside (genta/amika)	Inj. Co-amoxy clavulanic acid + Aminoglycoside (Genta/Amika)
<i>3 months to 5 years</i>	Inj. ampicillin Or Inj. chloramphenicol Or Inj. ampicillin + Inj. chloramphenicol (<2 yrs of age) Inj. co-amoxy clavulanic acid	Inj. Co-amoxy Clavulanic acid Or Inj. 3rd gen. cephalosporins Cefotaxime/ceftriaxone
<i>5 yrs +</i>	Inj. ampicillin Or Inj. Co-amoxy clavulanic acid Macrolides (If mycoplasma suspected)	Inj. Co-amoxy clavulanic acid Or Inj. 3rd Gen. cephalosporins: Cefotaxime/ceftriaxone and macrolides

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<i>Severe – Very severe disease Suspected staphylococcal disease</i>	
Inj. 3rd gen cephalosporins: Cefotaxime/Ceftriaxone + Cloxacillin Or Inj. cefuroxime Or Inj. co-amoxy clavulanic acid	
Second line: Vancomycin/teicoplanin + injection 3rd gen cephalosporins	

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Duration of Antibiotic Therapy

Antibiotics should be given for 7 to 10 days, or at least for 5 days after the fever has subsided. However, for

microbiologically undiagnosed and severe pneumonia, and pneumonia caused by gram-negative bacilli, staphylococci, or *legionella* species, longer courses of 10 to 21 days are needed (Table 15).

Table 13: Indications for admissions to hospital¹⁰

- Oxygen saturation <92% in air
- RR >70/min in infants, >50/min in older children (say 20+ breaths/min above cut-off for the age)
- Signs of severe breathing difficulty; chest wall in-drawings, nasal
- Flaring, grunting, apnea
- Feeding less than half normal intake
- Signs of dehydration
- Family not able to provide appropriate observation or supervision
- Failure of OPD treatment

Table 14: Indications for transfer to PICU¹⁰

- Failure to maintain $\text{SaO}_2 > 92\%$ in $\text{FiO}_2 > 0.6$
- Cyanosis
- Shock
- Rising respiratory and pulse rates with clinical evidence of severe respiratory distress and exhaustion with or without raised PaCO_2
- Recurrent apnea or slow irregular breathing.
- Excessive diaphoresis

Route of Administration

Most children with community-acquired pneumonia can be treated as outpatients with oral antibiotics with the exception of the patient who cannot absorb oral antibiotics because of vomiting or who otherwise is averse to a first dose of oral medication. Initiating treatment with a single parenteral dose of ceftriaxone in these children has been shown to be effective.

The intravenous route is reserved to treat severe pneumonia in hospitalized patients, but a switch from intravenous administration to oral antibiotics should be considered when fever has abated and the patient can tolerate oral medication and is otherwise improving.

In a recent study treatment of severe pneumonia in hospitalized patients, oral amoxicillin was found to be equivalent to treatment with injectable penicillin. The trial involved 1702 children, 3 to 59 months of age, with severe pneumonia according to World Health Organization (WHO)-defined criteria. Patients were randomly allocated to receive oral amoxicillin in a dose of 45 mg/kg per day in three doses or parenteral penicillin G 200000 IU/kg per day in four doses.¹⁰⁻¹²

Drug Resistance and Complications (Table 16)

All the major pathogens of community acquired pneumonia are developing resistance to antibiotics, but the impact on therapy is not the same for all pathogens.

Table 15: Duration of therapy

- Domiciliary: 5 to 7 days
- If admitted: Switch to oral after 48 to 72 hours or earlier if can accept orally. Total 5 to 7 days
- If on second line then IV for 7 to 10 days
- If *Staphylococcus*:
 - 2 weeks if no complications
 - Else 4 to 6 weeks

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Resistance in pneumococci is spreading all over the world. Pneumococci become resistant by target alteration—they change the cell wall protein that beta lactam antibiotics bind to. Higher levels of beta lactams can overcome this type of resistance in most, but not all strains. Since beta lactamase production is not the basis for resistance, adding a beta lactamase antagonist (like clavulanic acid) has no effect.

Apart from beta-lactams, resistance to macrolides, lincosamides, trimethoprim-sulfamethoxazole, and the tetracyclines has been seen in pneumococci. Some strains are resistant to more than one class of antibiotic and their treatment is difficult. Patients likely to harbour resistant organisms include young children, particularly those attending day care, and children who have received recent antibiotic therapy, suffer from underlying diseases including HIV, or have nosocomial or polymicrobial pneumonia. The best drug for multidrug resistant *S. pneumoniae* is vancomycin; others are linezolid, teicoplanin, imipenem, and the extended spectrum cephalosporins.

Resistance in pneumococci leads to a rise in MIC (minimum inhibitory concentration). Since higher blood and tissue levels of amoxycillin and other beta-lactam antibiotics can be safely achieved by giving higher doses, the presence of resistance does not usually lead to treatment failure with these drugs. In contrast, resistance to the macrolides, tri-methoprim-sulfamethoxazole, or fluoroquinolones makes these drugs unusable for the treatment of community acquired pneumonia. Treatment failures have been reported with both macrolides and fluoroquinolones in community acquired pneumonia. Knowledge of local resistance patterns is very important in choosing the correct antibiotic in a given clinical situation.

In India, pneumococci have a very low incidence (1.3%) of resistance to penicillin. However, the high incidence of resistance to cotrimoxazole (56%) and chloramphenicol (17%) means that these drugs are undependable in the treatment of pneumonia.

Another important pathogen of serious invasive disease in childhood, *Hemophilus influenzae*, is often drug resistant. In India, up to 50 percent of isolates are resistant to chloramphenicol; resistance to ampicillin, co-trimoxazole, and erythromycin is also high. No resistance was found to the third generation cephalosporins.

Pleural Effusion and Empyema

Pleural effusions develop in at least 40 percent of patients with bacterial pneumonias admitted to hospital, and up to 60 percent of the effusions progress to empyema. During the past decade increasing rates of complicated pleural effusion associated with community-acquired pneumonia were reported. Consider empyema if fever chills, dyspnea, rapid breathing, chest pain, cough with dullness on percussion with decreased air entry is present or no response to antibiotics/worsening after 48 hrs of initiation in cases of pneumonia. Staphylococcal disease is likely in case of postmeasles state or if there are coexisting skin infections, boils, arthritis, pyomyositis, etc.

Chest X-ray should be done in such cases, other supportive evidence are leukocyte counts and CRP but not necessary. USG plays an important role in identifying the presence, site, extent and even the type of effusion. However, it is observer dependent. CT had major side effect of high radiation; and has limited role, often needed prior to surgery but not for routine management. Investigations in favor of empyema are purulent nature of aspirated fluid with pH < 7.1, fluid glucose < 40 mg/dl, proteins > 3 g/dl and LDH > 1000 IU/L, and moreover cell count more than 1000/mm³ and if fluid is positive for gram stain or culture is diagnostic for that. Antigen tests for bacteria only support the diagnosis.

The management of empyemas remains controversial. There are several options available to treat empyema. Antibiotics with ICD remains the primary mode in most. If the child presents late with thick loculated empyema many surgeons like to go for primary decortication. It is an acceptable alternative but may not be always necessary. Fibrinolytics are of limited use in our opinion in our setting. Other options in place of ICD are; ICD plus fibrinolytics/or video assisted thoracic surgery (VATS)/or open decortications or rib resection/thoracoplasty/lobectomy. Primary antibiotic cover should be intravenous and broad enough to treat *S. pneumoniae*, *Staphylococcus* and *H. influenzae* 3 most common causes at all ages in children. Duration of antibiotics is till afebrile/or removal of tube which is usually 7 to 14 day and then total for 4 to 6 weeks. Among the current treatments video-assisted thoracic surgery has been suggested as the best method because of decreased length of stay in hospital.

Role of fibrinolytics: Streptokinase, urokinase, alteplase—equally effective options. Only recommended for a somewhat shorter stay in hospital, or in complicated parapneumonic effusion (thick fluid with loculations). These are mainly used in UK, studied in a pediatric RCT; BTS. Agents employed are urokinase : 40,000 U in 40 ml normal saline for more than 10 kg and in children less than 10 kg use 10,000 U in 10 ml NS. At least 4 hours dwell time is needed. Another agent which can be used is streptokinase—up to 15,000 units per kg per instillation; q12 h × 3d. Fibrinolytic therapy can be complicated

by hemorrhage, fever, pleural pain, arthralgia, antigenic response (streptokinase), formation of adhesion—VATS becomes difficult.^{13,14}

Prevention

Widespread use of vaccines against pertussis, measles, *H. influenzae*, and influenza in selected cases has resulted in preventing many cases of pneumonia in children. The impact of the conjugate *H. influenzae* type b vaccine (Hib) in preventing pneumonia is not known. A recent study documented a vaccine effectiveness of the Hib vaccine of 31 percent in infants with radiologically confirmed pneumonia, showing the potential benefit of Hib immunization in the prevention of community-acquired pneumonia. The seven-valent polysaccharide pneumococcal conjugate vaccine that was incorporated in the vaccination schedule for infants and children in the United States in 2000 produces immunity for the seven most common disease-producing serotypes of *S. pneumoniae* in children.

The vaccine proved to be highly effective (97%) in preventing invasive disease in normal children, especially children under 2 years of age. In this group of children the rate of disease was 69 percent lower one year after licensure than the baseline rate. The rate of disease caused by vaccine and vaccine-related serotypes declined by 78 and 50 percent, respectively. Disease rates also fell in adults, suggesting herd immunity from the use of the vaccine. Although the vaccine is less effective in preventing pneumonia, it has been shown that the immunization of children younger than 2 years is associated with a 10-fold greater reduction in pneumonia than previously reported in culture-confirmed invasive disease in children less than 2 years old.

The most dramatic effect has been documented in cases of pneumonia with a positive radiograph, an overall reduction of 17 percent. This effect was more evident in children less than 1 year old—there was a 32.3 percent reduction in children older than 2 years.

A recent review in Cochrane Database of Systematic Reviews on the effect of the pneumococcal conjugate vaccine in reducing radiologically confirmed pneumonia concluded that there were uncertainties about definition of this outcome and suggested data from more trials should be evaluated.¹⁵

Influenza

The contribution of influenza to the total cases of viral pneumonia varies year to year, and by age, but averages 8 percent. A recent study using PCR showed that the clinical burden of influenza A pneumonia was much more common than it was previously thought and was comparable to that of RSV pneumonia. Pneumonia caused by *S. aureus* and *S. pneumoniae* has been associated with preceding

Table 16: Complications of CAP

- Treatment failure caused by antibiotic resistance
- Pleural effusion and empyema
- Lung abscess
- Septicemia
- Metastatic infection—for example, osteomyelitis or septic arthritis

influenza infection. This association is based on observations of simultaneous epidemics of influenza and pneumonia and on serologic evidence of previous influenza infection among patients with bacterial pneumonia. Prevention of pneumococcal pneumonia may be a potential benefit of influenza vaccination. The live attenuated cold-adapted intranasal influenza vaccine has a high efficacy against influenza, is well tolerated, and has the advantage that it requires no injection. These properties raise the possibility of incorporating the vaccine in the immunization schedule for children.

Respiratory Syncytial Virus

Respiratory syncytial virus is the main cause of hospitalization in the first year of life for bronchiolitis and pneumonia in infants and young children. Premature babies born at 30 to 35 weeks of gestation and infants with congenital anomalies, especially congenital heart disease, are at significantly greater risk for complications.

Ribavirin is the only antiviral therapy available against RSV but trials of ribavirin therapy lack sufficient power to provide reliable estimates of the effects. Passive immunization with humanized monoclonal antibody (palivizumab, Synagis, MedImmune, Inc., Gaithersburg, MD) offers the prospect of preventing hospitalization in infants at high risk for severe RSV infection, but because of the high costs of therapy the use of palivizumab is restricted to infants who fulfil certain criteria established by advisory bodies. Vaccination in future may reduce morbidity. Progress is currently being made in developing vaccines, but it may be some time before these become available.

Recurrent Pneumonia (Flow Chart 7)

Recurrent pneumonia is defined as at least two episodes of pneumonia occurring in one year or three episodes over any period of time. Recurrent pneumonia is a symptom of an underlying disease and not a diagnosis in itself.

Causes include:

Commonest

- Asthma (mis-diagnosis), aspiration syndromes

Less common

- Congenital anomalies, FB, CVS shunts, TB, tumors
- Not infrequent
- CF, immunodeficiency, ciliary dyskinesia.

It differs with persistent or nonresolving pneumonia. Stress upon the fact that recurrent pneumonia is not a diagnosis in itself but a 'symptom complex', a clinical manifestation of an underlying disease. Emphasize more on the rational and correct approach to this problem, which will lead to the diagnosis of the underlying condition. Since recurrent pneumonia is a "process of approach" to the basic problem the clinician must be inquisitive to elicit certain salient or key points which will help lead to the probable diagnosis. So "ASK" age at onset/first documented pneumonia—usually aspiration syndromes, congenital anomalies or mucociliary defects manifest early in infancy while asthma or FB usually in toddlers or older infants. History of "delayed cord fall" may suggest leukocytes adhesion defects or some time other chronic granulomatous diseases.

History suggestive of aspiration or setting for aspiration are clear cut indicators of aspiration syndrome as the basic problem; while temporal relation of cough to feeding or posture is suggestive of aspiration syndrome like GER. Family or personal history of atopy, nocturnal cough, wheezing and bronchodilator relief is obviously indicative of asthma. Choking while eating a nut or any similar object in the past is an obvious manifestation of partially obstructive retained FB. History of consanguinity, malabsorptive stools, history of similar problems in other sibs, failure to thrive are highly suggestive of CF and primary ciliary dyskinesias. History of multifocal, multiple, recurrent infections and H/O contact are imperative for primary immunodeficiencies and tuberculosis, though tuberculosis usually presents as "persistence" rather than "recurrence" of the problem. Then "look" for some key findings so as to help simplify the diagnosis.

Oropharyngeal examination for anatomical causes for aspiration, e.g. cleft palate. Usually it is "one airway one disease" but in recurrent pneumonia ensure whether both lower and upper airways are involved or symptoms are confined to lower airways every time in past. Another most important "clue" is whether the same lobe is involved in every episode or different lobes on different episode. These two very pertinent clues will simply classify recurrent pneumonias in two groups and make the diagnosis very simple. When symptom are confined to both upper and lower respiratory tracts like rhinitis, nasal polyposis, sinusitis, otitis, wheeze and other signs of lower respiratory tract affliction chances of these (Asthma, immunodeficiency, ciliary's dyskinesia, cystic fibrosis) are very likely. While when symptoms are confined to only lower airways or respiratory tract these (Aspiration syndromes, congenital anomalies, CVS shunts, FB, TB, tumors) are the most frequent possibilities.⁵

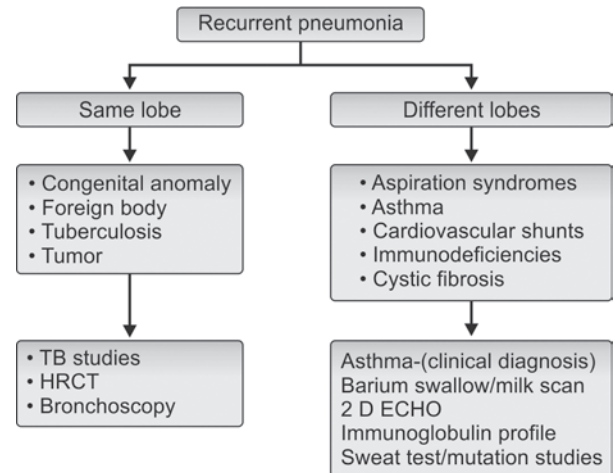
Multifocal, multiple and recurrent infections like otitis media, diarrhea and pneumonia in different lobes are strongly suggestive of an immunodeficiency state like *A/hypogammaglobulinemia*.

Cough and Expectoration

Chronic productive cough with predominant features of expectoration usually purulent, copious with or without long-standing fever and mild to moderate respiratory embarrassment, associated with signs of chronic hypoxia like clubbing are usually strongly suggestive of “Chronic Suppurative Lung Disease” like bronchiectasis (long standing history) or Lung Abscess (shorter history). The causes of bronchiectasis may be multiple either acquired or congenital. The term bronchitis is seldom used in pediatric practice and should better be confined to adults. Stress should be given on “persistent” cough and expectoration with intermittent exacerbations suggestive of production-accumulation and stagnation of secretions in the distorted terminal bronchia and bronchioles of lower airways, most probably due to bronchiectasis. Need for a course of antibiotics each time indicates a possibility of infective etiology. In a suspected case of suppurative lung disease, a salient history should be obtained keeping in mind the various etiologies like:

- History of—preceding infections like pneumonia, measles, atelectasis, pertussis, etc. (postinfectious)
- Obstruction—FB inhalation, exo or endo bronchial TB lymph node
- Immune deficiency like agammaglobulinemia (involvement of other system and organs)

Flow Chart 7: Approach to recurrent pneumonia

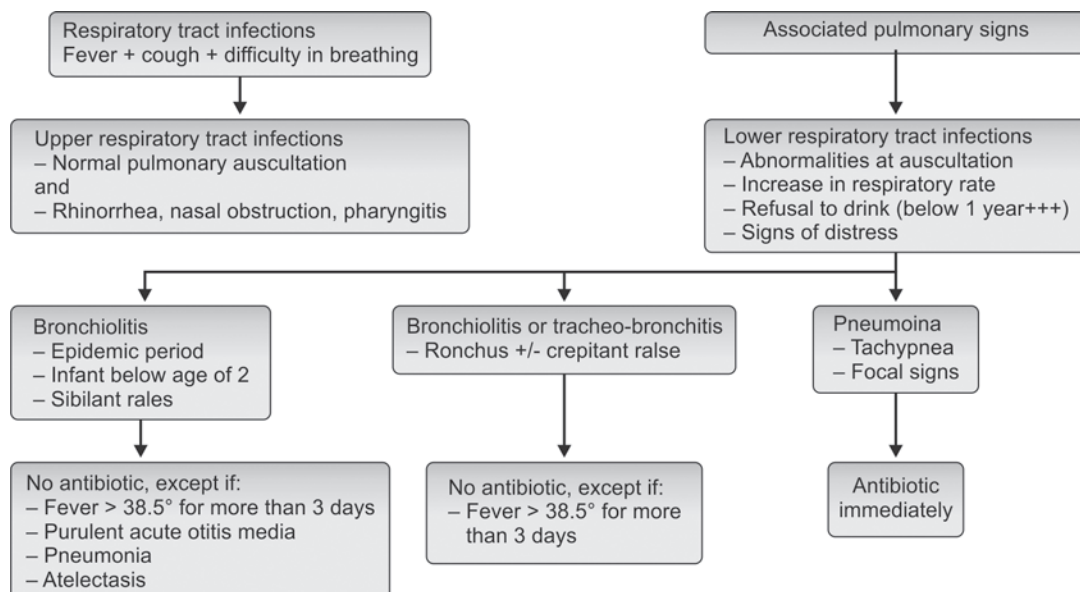


- Metabolic disorder like cystic fibrosis (h/o malabsorption and FTT)
- Defects in ciliary functions like PCD, immotile ciliary disease (Kartagener syndrome).

Investigations in bronchiectasis are 3 fold:

- To ascertain and establish the diagnosis—HRCT or radiology.
- Pulmonary function tests to assess the functional capacity of the lungs.
- Further investigations to find out the underlying cause, e.g. bronchoscopy for FB.

Flow Chart 8: Approach to respiratory tract infection in children



Immunoglobulins for Immunodeficiency:

24 hours pH study for GER: Sweat chloride estimation and identification of genetic mutation for CF—sputum culture, BAL and lung puncture in cases of pneumonias.

PPD Test for TB: Electromicroscopy on nasal mucosal scrapping for ciliary dyskinesias, etc. Findings on chest X-ray are nonspecific, however X-ray chest may be taken, which may show the findings enlisted. These findings are results of permanent and abnormal gross congenital or acquired structural abnormalities in the tracheobronchial tree, such as bronchomegaly, bronchomalacia, bronchial stenosis and cysts. Obstruction due to a FB, mucus plug or a TB lymph node can cause unequal aeration, recurrent infections, atelectasis and hyperinflation. HRCT of chest is very sensitive and noninvasive test with hi-specificity. It has almost replaced “bronchography” done in good old days being a very invasive test. The findings are suggestive of or due to distorted, linear, nontapering bronchi with thickened walls and fluid accumulation. Sputum cultures and BAL yields may be helpful in isolation of microorganisms and thereby choice and selection of correct antibiotics as per their sensitivity. Ideally choice of antibiotics should be according to isolates and their sensitivity, however, empirical antibiotic therapy may be justified, preferably should be Co-amoxycylav/ceftriaxone with or without fluroquinolones if pseudomonal colonization is suspected like in CF. Airway cleaning, bronchial lavage and hygiene with chest physiotherapy to bring out sputum is very important and prudent should be promoted.⁵

Lung Abscess

Lung abscesses are frequently a complication of either bacterial pneumonia or obstruction due to retained FB or bronchial cyst, congenital anomaly like sequestration of lung tissue may also lead to lung abscess. The common bacteria responsible for lung abscess are *S. pneumoniae*, *Kleb pneumoniae*, *Pseudomonas* but the commonest and most frequent is *S. aureus*. They may often present as multiple thin walled “pneumatocoles”. Pyoneumothorax is often a complication of lung abscess mostly of *S. aureus* origin. Antibiotics are the mainstay of treatment. Ideally appropriate antibiotics to which the isolates are sensitive should be administered for 4 to 6 weeks. Rational empirical antibiotics include a combination of third generation cephalosporin + cloxacillin to which most of the

lung abscesses acquired from community are responsive. If, however, MRSA is highly suspected, cloxacillin may be replaced with vancomycin/Teicoplanin. Physiotherapy is another important modality for effective drainage of pus. Lung abscess refractory to conservative medical therapy may require surgical resection (Lobectomy).^{5,6}

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Section 3

Hematology Oncology

Editors

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Newer Advances in Management of Hematological Malignancies

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Abstract

There have been significant improvements in the outlook for children with acute leukemia but these advances are only available to a minority of the world's children. There is still room for improvement in conventional chemotherapy and this needs evaluation in randomized trials. The role of bone marrow transplants in first remission is evolving as chemotherapy becomes more effective. New treatments are needed for relapsed patients. Molecular diagnosis has refined the assessment of prognosis but the extra value afforded by measurement of minimal residual disease is not clear. International collaboration is needed to evaluate treatment for rare subtypes of leukemia.

In most cases, childhood leukemia has a fetal origin, but multiple molecular events are required after birth for pre-leukemic cells to progress to leukemia. Cure rates for acute lymphoblastic leukemia (ALL) now approach 80 percent. A high level of minimal residual disease detected by polymerase chain reaction in patients with ALL in remission has profound prognostic importance and is the focus of studies attempting to prevent relapse in these children. Cytogenetics play huge role in predicting prognosis. Greater awareness of the late effects of chemotherapy has led to changes in the treatment protocols for ALL, with improvement in neurocognitive outcomes and reduced rates of second malignancies.

Pharmacogenetics is a new field of research that aims to enhance treatment efficacy by assessing the individual's metabolism of and response to chemotherapeutic agents. Targeted therapies currently being developed show some promise of being able to further improve cure rates adolescents with ALL have a better prognosis if treated with pediatric rather than adult protocols.

INTRODUCTION

Leukemia accounts for about a third of all childhood malignancies. About 80 percent of children with leukemia have acute lymphoblastic leukemia (ALL), 17 percent have acute myeloid leukemia (AML), and the remainder rare forms of chronic leukemia.¹ Collaborative clinical trials research has brought about dramatic improvements in cure rates for children with acute leukemia, but about 20 percent of children still relapse. Most of those who relapse will die of the disease. Moreover, some survivors face an uncertain future of health problems because of treatment side effects. Here we review selected recent developments in childhood leukemia.

Why did my Child Develop Leukemia?

When confronted with the diagnosis of childhood leukemia, one of the first questions asked by parents is "why did this happen to our child?" Unfortunately, the answer to

this question largely remains unknown. Although a small proportion of children with leukemia have an underlying predisposition, such as Down's syndrome or Fanconi's anemia (a congenital form of aplastic anemia), most have no known cause. However, in recent years, a molecular basis of childhood leukemia has become clearer.

Evidence now supports the concept that, for a substantial number of patients, childhood leukemia begins as an *in utero* event. Much of this evidence arises from studies of monozygotic twins who concordantly develop leukemia,²⁻⁴ and from recent polymerase chain reaction studies of neonatal Guthrie card blood spots. The latter studies have shown that 70 percent of children presenting with ALL up to 13 years of age had molecular evidence of their disease at birth: Preleukemic cells that were present at birth bore the same molecular markers as their leukemic cells.^{5,6}

This evidence has led to general consensus that most cases of childhood leukemia begin *in utero*, but major questions remain as to what leads to these initial genetic

abnormalities. Although no specific causes have been identified which result in these *in utero* molecular changes, several antenatal factors are important in increasing the risk of leukemogenesis. These include maternal and paternal marijuana use both before and during pregnancy, which significantly increases the risk of both AML and ALL in offspring.^{7,8} It has also been suggested that medications used in pregnancy, such as antihistamines and amphetamines, may increase the risk of ALL.⁸ A retrospective Western Australian study found that, in children whose mothers took folate during pregnancy, the risk of ALL was reduced by 60 percent.⁹

Whatever events initiate the development of preleukemic cells in the fetus, other genetic changes are needed for the development of overt leukemia — consistent with the “multi-hit” model of leukemogenesis.¹⁰ One study has shown that 1 percent of cord blood samples from healthy babies contained molecular evidence of the commonest leukemia-specific chromosomal translocation seen in ALL: t(12;21), or the TEL-AML1 fusion gene.¹¹ This incidence of a molecular abnormality is almost 100 times greater than the incidence of ALL, suggesting that a second event must occur in 1 percent of those children with preleukemic cells to allow progression to overt leukemia. The nature of this “second hit” is unknown. Exposure to electromagnetic fields has been ruled out as playing any significant role.¹² Other possibilities still being investigated include exposure to chemicals, such as pesticides, and childhood infections.^{13,14} The hypothesis that more than one hit is required for leukemogenesis has been supported by recent studies into children with Down’s syndrome who develop acute megakaryoblastic leukemia. About 10 percent of all Down’s syndrome patients develop a transient myeloproliferative disorder (TMD) in the neonatal period. This is indistinguishable from acute leukemia, and undergoes spontaneous remission. However, a fifth of patients with TMD subsequently develop acute megakaryoblastic leukemia.¹⁵ Recently, mutations in a gene called GATA1, necessary for normal development of erythroid and megakaryocytic cells, have been found in almost all Down’s syndrome patients with TMD or acute megakaryoblastic leukemia.¹⁶ This suggests that constitutional trisomy 21, together with the GATA1 mutation, causes the excessive megakaryocyte proliferation seen in TMD, and that another hit is necessary to cause overt leukemia in a smaller subset of patients.¹⁷

ACUTE LYMPHOBLASTIC LEUKEMIA

Prognosis and Minimal Residual Disease Testing

One of the great successes of pediatric oncology has been the dramatic improvement in cure rate for ALL in recent decades.¹⁸ Expected current cure rates approach 80 percent for all children diagnosed with ALL, of all lineages.¹

However, relapse remains a problem for the remaining 20 percent of patients. Although some children have known indicators of poor prognosis, such as a high initial white cell count or cytogenetic abnormalities, most who relapse do not have any clinical markers to indicate increased risk for treatment failure.

The extent of clearance of leukemic cells from the blood or bone marrow during the early phase of therapy is an independent prognostic factor in acute lymphoblastic leukemia (ALL). Several methods are available to measure the minimal residual disease (MRD) remaining after initial intensive chemotherapy. The most promising are flow cytometric detection of aberrant immunophenotypes and polymerase chain reaction analysis of clonal antigen-receptor gene rearrangements. When applied together, these techniques enable one to monitor MRD in virtually all cases of ALL. Patients who achieve a ‘molecular’ remission (i.e. leukemic involvement of, 0.01% of nucleated bone marrow cells at the end of remission induction therapy) are predicted to have a better clinical outcome than patients whose remission is defined solely by morphologic criteria.¹⁹ In studies to date, patients with MRD at a level of 10^{-2} or more at the end of induction have fared poorly. Sequential monitoring of MRD can improve the clinical utility of risk assessment still further.^{20,21} Additional studies are needed to determine the critical levels of MRD at various times of treatment.

Role of Cytogenetics in ALL

Recurrent chromosomal abnormalities are a hallmark of lymphoblastic leukemias and provide insight into the molecular mechanisms of leukemogenesis. The most common translocation found in childhood B-precursor ALL is the t(12;21) (p13; q22). Although standard karyotypic analysis does not identify most TEL-AML1 translocations, molecular techniques demonstrate the presence of this translocation in approximately 25 percent of childhood ALL (Fig. 1). Microarray-based gene expression studies have shown that TEL-AML1-rearranged ALLs represent a unique biologic subset of B-precursor ALL.²²

TEL-AML1 expression is associated with an excellent prognosis, with event-free survival rates approaching 90 percent.²²⁻²⁵ In addition, the favorable prognostic impact of TEL-AML1 is independent of age and leukocyte count and was consistently favorable among patients treated on several different protocols.^{26,27} Thus, TEL-AML1 expression identifies a large subset of B-precursor ALL patients who may be candidates for less-intensive therapy.

The Philadelphia chromosome is the result of the t(9;22) (q34;q11) translocation in which the 5’ domain of the BCR (breakpoint cluster region) gene from chromosome 22 is fused with the 3’ tyrosine kinase domain of the ABL gene from chromosome 9. The Philadelphia chromosome is the resultant shortened chromosome 22. It is

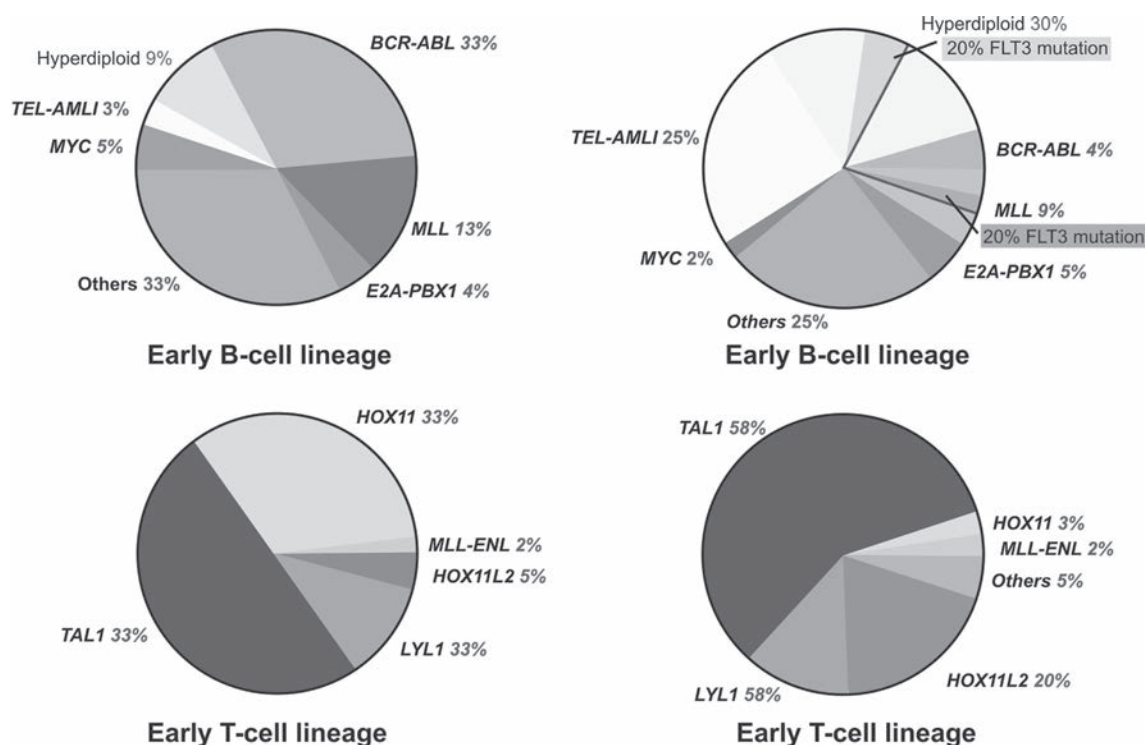


Fig. 1: Chromosomal abnormalities in acute lymphoblastic leukemia. The relative frequencies of chromosomal aberrations found in lymphoblastic leukemias are shown for (A) adult and (B) childhood (right) acute lymphoblastic leukemias. The groups are divided into early B-cell lineage and early T-cell lineage. (For color version see plate 8)

the most frequent recurring translocation in adult ALL, occurring in 15 to 30 percent of patients, and also is present in 5 percent of pediatric B-ALL. It is an adverse prognostic factor in children and adults.

Another common chromosomal aberration found in B-precursor ALL is the presence of more than 46 chromosomes (hyperdiploid ALL). As with TEL-AML1-rearranged ALL, gene expression studies demonstrated that hyperdiploid ALL represents a separate genetically defined subset of B-precursor ALL.²² But, the lack of a recurrent abnormality in specific genes identifiable by karyotypic analysis has prevented the identification of initiating events in this leukemia. Potential insight into the mechanism of leukemogenesis in hyperdiploid ALL came recently when activating mutations in the receptor tyrosine kinase FLT3 were identified in approximately 20 percent of hyperdiploid ALL.^{26,27} This finding is intriguing not only in that it points to activated tyrosine kinases as potential oncogenes in hyperdiploid ALL, but also in that it suggests that small-molecule tyrosine kinase inhibitors might be of benefit to patients with this leukemia. Given that patients with hyperdiploid ALL have an extremely good prognosis with event-free survival rates near 90 percent, it will be a challenge to determine how to incorporate such therapeutics into treatment regimens.

Infant ALL

Leukemias bearing translocations involving chromosome 11q23 are found in leukemic blasts from >70 percent of leukemias in patients younger than 1 year of age whether the immunophenotype is designated AML or ALL.²⁸ Some infant leukemias express antigens characteristic of both lymphoblasts and monoblasts, and are sometimes designated acute biphenotypic leukemias. Infants diagnosed with ALL harboring an 11q23 rearrangement have a particularly poor prognosis as compared to other children with ALL.²⁹ The association of 11q23 rearrangements with either ALL or AML is unique in that most other translocations tend to be associated with leukemias of a particular hematopoietic lineage. These observations prompted the name mixed-lineage leukemia (MLL) for the gene on 11q23.

It has been recently found that the receptor tyrosine kinase FLT3 is highly expressed in MLL-rearranged ALL as compared with other acute leukemias.³⁰ This prompted further assessment of FLT3 in this disease, in which it was found that approximately 20 percent of MLL-rearranged ALL samples to possess activating mutations in the activation loop region.³¹ These data support the idea that leukemogenic fusion proteins such as MLL fusions cooperate with activated kinases to promote leukemogenesis (Fig. 2).³² Furthermore,

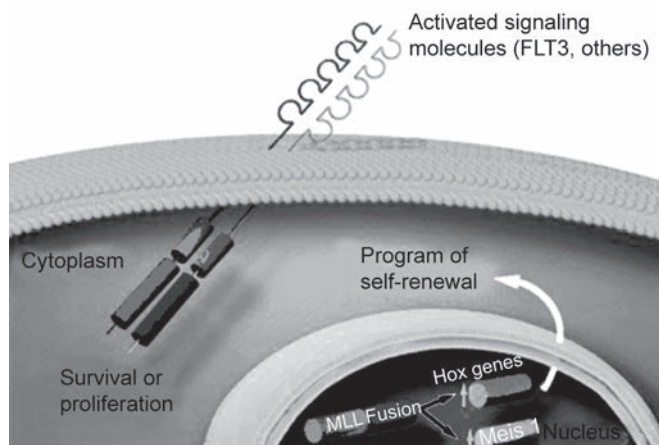


Fig. 2: Multi step pathogenesis of MLL-rearranged lymphoblastic leukemias. MLL translocations induce self-renewal in hematopoietic progenitors as a first step in leukemogenesis. The presence of FLT3 mutations in MLL-rearranged ALLs support activation of FLT3 or other kinases as cooperating events in this disease. Clinical trials designed to assess the efficacy of FLT3 inhibitors in MLL-rearranged ALL are being developed. (For color version see plate 8)

FLT3 inhibitors appear to have activity against MLL-rearranged and hyperdiploid ALL, *in vitro* and in murine models.^{31,33} Clinical trials to assess the efficacy of FLT3 inhibitors in MLL-rearranged ALL are in development.

Bone Marrow Transplantation

Allogeneic hematopoietic cell transplantation (HCT) is an established treatment for children with very high-risk acute lymphoblastic leukemia (ALL). As contemporary chemotherapy becomes more effective, the proportion of patients undergoing HCT is reduced. The question, "Is there a place for transplant in childhood ALL" must be asked often as progress continues. Since, acute transplant-related mortality rates remain high, transplant is clearly only appropriate for children unlikely to be cured with routine chemotherapy, and identifying these children requires knowledge of current outcomes with chemotherapy, of ALL biology as applied to prognosis, and of likely transplant outcomes. Tyrosine-kinase inhibitors have completely changed the landscape of therapy for Philadelphia positive ALL. Historically, children with Ph+ ALL and a matched sibling donor have been transplanted in CR1. But now with the use of tyrosine kinase inhibitors transplant is no longer routinely needed for Ph+ ALL in CR1.³⁴ MRD can be used to identify the small subset of children with primary induction failure and a poor prognosis based on MRD who may be candidates for transplantation in CR1. MRD measurements can also serve as a guide to the effectiveness of chemotherapy prior to transplantation in children in CR1 or beyond, because outcomes of transplantation are clearly improved in those with the lowest disease burden at the time of transplant.

Children relapsing early (before 36 months) have a poor prognosis and transplantation should be considered for all of them. Similarly, children with a bone marrow relapse of T-lineage ALL at any time have poor outcomes and should be considered for transplant.

Late Effects

With the dramatic improvements in survival of children with ALL over the past few decades, attention has increasingly turned to reducing the late effects of treatment, such as the high incidence of impaired neurocognitive outcomes in children receiving prophylactic cranial irradiation.³⁵ As a consequence of randomized trials comparing intrathecal chemotherapy with radiation for central nervous system prophylaxis, irradiation is now omitted in almost 80 percent of patients. Intrathecal chemotherapy combined with high-dose methotrexate has been shown to be equally effective at preventing meningeal relapse in most patients.³⁶ A large extended follow-up study of survivors of childhood ALL showed that non-irradiated patients had similar employment and marital prospects to the rest of the population.³⁷ That study also found that non-irradiated patients who had survived at least 10 years did not have an increased risk of second malignancy. An earlier, very large cohort study of 8831 patients confirmed that with current treatment protocols the risk of second malignancy in the first 10 years after treatment is now as low as 1.18 percent.³⁸ This low rate is, in part, because of the avoidance of epipodophyllotoxins such as etoposide, and because of the reduction in radiation dosage.

Cranial irradiation has also been implicated as a cause of growth impairment by causing growth hormone deficiency in children treated for ALL. However, a recent study found that children treated for ALL had some impairment of growth irrespective of treatment modality, with the worst outcomes in younger patients.³⁹ Children with poor growth following treatment for ALL need careful follow-up and endocrinological review.

Anthracyclines, which can be responsible for clinical cardiac toxicity, are used in most treatment protocols for ALL. Although the doses used are low enough to avoid causing acute cardiomyopathy during treatment, it is now apparent that children may be at a greater risk of late-onset cardiac failure than previously suspected.^{40,41} Attempts to reduce the cardiac toxicity of anthracyclines have, to date, been disappointing. The administration of doxorubicin by continuous infusion has not been found to offer significant cardioprotection.⁴² The iron chelator dexrazoxane has been shown to have some cardioprotectant effect in anthracycline based therapies of selected adult malignancies.⁴³ A recent study has also suggested that it is protective in children with ALL, but this needs confirmation with long-term assessment.⁴⁴ Meanwhile, careful monitoring and follow-up of children at risk of cardiac disease is essential.

Prospects for Targeted Therapy: Small Molecule Inhibitors of Tyrosine Kinase Receptors

Tyrosine kinases are recognized as valid therapeutic targets in multiple types of cancer including leukemia, and inhibition of constitutively active kinases has clear therapeutic benefit.⁴⁵⁻⁴⁸ Kinase inhibition is highly successful in the treatment of chronic myelogenous leukemia (CML), in which imatinib mesylate, a small-molecule inhibitor of the BCR-ABL kinase, is remarkably effective.⁴⁵ Imatinib induces complete hematologic remission in approximately 95 percent of patients, and complete cytogenetic responses in approximately 75 percent of patients with chronic phase CML.⁴⁹ Imatinib also has significant activity in patients with BCR-ABL-positive ALL, in which remission is frequently achieved with imatinib alone.⁵⁰ Unfortunately these responses are transient, with most patients experiencing a relapse of their disease within months. The transient nature of the responses has prompted a number of clinical trials in adults and children in which imatinib will be incorporated into multiagent chemotherapy for patients with BCR-ABL-positive ALL.⁵¹ These early trials combining imatinib and chemotherapy are of significant interest; it is likely that other kinase inhibitors currently in development for both leukemias and other cancers also will need to be combined with either chemotherapy or other targeted therapy because resistance to single kinase inhibitors is becoming an expected outcome.⁵² Because multiple inhibitors are in clinical development, the imatinib trials will provide the groundwork for future combinations.

Pharmacogenetics

Pharmacogenetics is a new field of research in ALL. It examines how genetic differences between individuals affect their responses to drug therapy. Because of the narrow therapeutic range of most drugs used in treating childhood ALL, genetic variations in drug metabolism may have an important effect on treatment outcome.⁵³ 6-mercaptopurine, a key medication in ALL treatment, is inactivated by thiopurine methyltransferase in the liver. Mutations have been identified which result in reduced enzyme activity. ALL patients who are homozygous for the deficiency are at risk of life-threatening toxicity from their inability to metabolize normal doses of 6-mercaptopurine. Such patients require substantial reduction in doses of mercaptopurine. However, heterozygotes have improved overall survival, because they have higher levels of systemic 6-mercaptopurine, which are both tolerable and more effective against leukemic cells.⁵⁴ Deficient thiopurine methyltransferase activity has also been associated with significantly greater risk of brain tumors in patients receiving both mercaptopurine and cranial irradiation.⁵³ Similarly, patients with polymorphisms in the gene coding

for methylene tetrahydrofolate reductase, an important enzyme in folate metabolism, have an increased risk of toxicity during methotrexate treatment.⁵⁵

Although it is not yet standard practice to assess individual patients for genetic polymorphisms, our knowledge of inter-patient variability in drug metabolism is already affecting clinical practice. For example, it has been demonstrated that individualizing dosages of mercaptopurine and methotrexate during maintenance therapy, by increasing them to the maximal tolerated level, can improve survival provided that prolonged neutropenia is avoided.⁵⁶

Adolescents

There is now substantial evidence that adolescents treated with pediatric protocols for ALL have better outcomes than those treated with adult protocols. In one study, the 6-year-event-free survival (EFS) rate was 64 percent for the pediatric protocol compared with 38 percent for the adult protocol, and in another, the 5 years EFS rate was 67 percent, compared with 41 percent.^{57,58} Additionally, adolescents and young adults with ALL treated in adult centers are much less likely to be enrolled in clinical trials than children.⁵⁹ Adolescents' needs also differ from those of both children and adults. There are special issues relating to self-image, independence, sexuality, education, career development and compliance with treatment.⁵⁹ There is now progress in cancer centers in Europe and North America towards establishing specialist "teenage cancer units", which are able to provide specialized medical, nursing and psychosocial treatments.

ACUTE MYELOID LEUKEMIA

Prognosis

In contrast to ALL, the outlook for childhood AML remains less encouraging, with cure rates between 35 percent and 50 percent.¹ Children treated with Australasian protocols have demonstrated comparatively high overall survival rates of 56 percent, with disease-free survival of 50 percent.⁶⁰ Initial chemotherapy will achieve remission in more than 90 percent of patients, but is extremely myelosuppressive and requires high quality supportive care. Interestingly, children with Down's syndrome and AML have a prognosis for cure of 80 to 90 percent when treated with chemotherapy alone.⁶¹

There is no convincing evidence for substitution of daunorubicin with other anthracyclines, nor evidence for using high-dose cytarabine during induction in childhood AML. Rather, a 3 + 10 regimen with total daunorubicin 180 mg/m² and cytarabine 100 to 200 mg/m² for 10 days appears to yield the best results. The most important component of the postremission chemotherapy continues to

be several courses of high dose cytarabine.¹ Despite these improvements in chemotherapy, allogeneic BMT from a matched family donor remains the best option for most patients [excluding Down's syndrome, acute promyelocytic leukemia, and possibly those with inv(16)]. Newer prognostic markers of interest include FLT3/ITD and minimal residual disease at the end of induction therapy.

Conventional Cytogenetics

Nonrandom clonal chromosome aberrations (i.e. reciprocal translocations, inversions, insertions, deletions, trisomies and monosomies) are found in the leukemic blasts of approximately 55 percent of patients with AML, and pretreatment karyotype has long been recognized as the most important independent predictor of clinical outcome in this disease.⁶² In addition, differential treatment of certain cytogenetic subgroups has resulted in markedly improved prognosis.⁶³⁻⁶⁵ As a consequence, chromosome banding analysis has become a part of routine diagnostics,⁶⁶ and several cytogenetic abnormalities [i.e., t(8;21) (q22;q22), inv(16) (p13q22) t(16;16) (p13;q22), t(15;17) (q22;q11~21), and abn (11q23)] are considered in the recent WHO classification of AML.^{67,68} Importantly, despite continuous improvements in cytogenetic methodology and the systematic application of molecular cytogenetic techniques, such as fluorescence *in situ* hybridization,⁶⁹ approximately 45 percent of AML patients lack chromosome abnormalities,⁶² and the identification of pathogenetically relevant genetic lesions as well as the discrimination between prognostically different subsets of patients within this group remain major challenges.⁷⁰

Acute Promyelocytic Leukemia

Acute promyelocytic leukemia (APL) deserves special attention among the subtypes of AML for several important reasons. First, the disease has become the most curable of all the subtypes of AML. With current therapy, including ATRA and anthracycline based induction, anthracycline based consolidation and maintenance, 70 to 80 percent of patients are alive and free of disease at 5 years. Second, the disease is associated with unique genetic features including the t(15;17) translocation and the formation of the PML-RAR fusion transcript. The fusion transcript permits precise diagnosis and provides the marker for the identification of minimal residual or recurrent disease. Third, insights into the mechanism of leukemogenesis and resistance in APL serve as a paradigm for other AMLs. Fourth, treatment with ATRA based regimens demonstrates that the novel strategy of differentiation therapy can be highly effective. Finally, the curability of APL reflects what can be accomplished from the union of progress in both laboratory science and well-designed clinical trials. Acute promyelocytic leukemia represents approximately 10 to 15

percent of AMLs. There appears to be an increased incidence among hispanic patients (20 to 30%).⁷¹

Molecular Genetics and Pathogenesis

The leukemic cells from virtually every patient with APL have a balanced reciprocal translocation, t(15;17). This translocation leads to a fusion of two otherwise disparate genes, the promyelocytic (PML) gene on chromosome 15 and the retinoic acid receptor (RAR α) on chromosome 17. The presence of the PML-RAR fusion protein inhibits myeloid differentiation.

As a result of the fusion of the RAR to the PML gene, there is increased affinity for the nuclear repressor protein complex. The formation of this protein complex attracts histone deacetylase which alters chromatin conformation and therefore inhibits transcription.⁷² The presence of retinoic acid functions in part, at least, by inducing release of the nuclear co-repressor complex with histone deacetylase. This leads to normal chromatin conformation and normal transcription (Fig. 3). A model for the interactions of APL fusion proteins with the N-Co-R-mSin3-histone deacetylase complex.⁷³

Bone Marrow Transplantation

Bone marrow transplantation from a matched sibling donor for patients in first complete remission is now established as the treatment of choice for high risk AML.⁷⁴ The cytogenetic profile of the leukemic cells at diagnosis is important in defining high and low risk subgroups. For most children with standard-risk AML in first remission without a fully matched sibling donor, either autologous transplantation or further intensive postremission chemotherapy is used. Some studies have shown a survival advantage for patients undergoing autologous transplantation. However, several recent studies have shown that intensive chemotherapy is just as effective, with the issue remaining unresolved.⁷⁵ Unrelated allogeneic transplants result in lower relapse rates but higher treatment related mortality, making this option suitable for high risk patients only.

Targeted Therapy

The focus of research in AML has shifted to the development of targeted therapy. The antigen CD33 has been the focus of intensive investigation. This has been an attractive target because it is expressed on most myeloid blasts but is absent from normal hematopoietic stem cells and other tissues. The drug gemtuzumab ozogamicin (mylotarg, wyeth) has been developed as an immunoconjugate of an anti-CD33 antibody and calicheamicin — an extremely potent cytotoxic agent that cleaves double-stranded DNA.⁷⁶ Phase 1 and 2 trials in adults and children with relapsed AML have shown responses in 30 percent of patients.⁷⁷

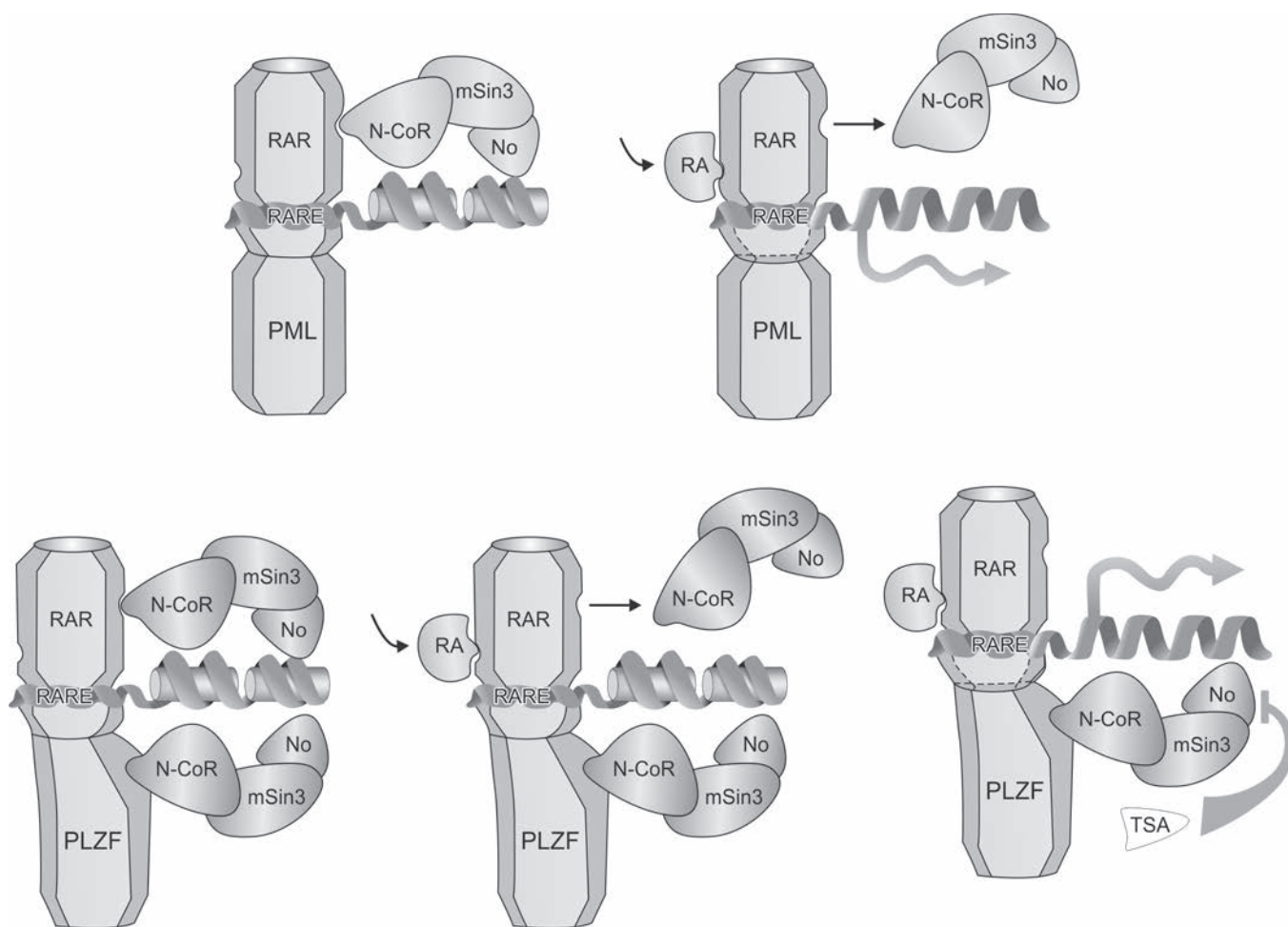


Fig. 3: A model for the interactions of APL fusion proteins with the N-Co-R-mSin3-histone deacetylase complex

CONCLUSION

Much has changed over the past decade in front-line treatment, identifying relapse risk and in our understanding of leukemogenesis. The genome revolution, molecular drug targeting and computer aided drug design techniques will reshape this field yet again over the next decade in ways which may allow for further individualization of therapy to enhance efficacy and reduce toxicity.

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Pediatric Oncology: Journey from Nihilism to Cautious Optimism

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The recent understanding and advances in the total management of pediatric cancers forms one of the most exciting chapters in the entire field of oncology. With increasing control of infectious disease, eradication of malnutrition and the rapid strides of the pediatric surgeons in correcting benign surgical problems, more children are now going to be affected by cancer. In US cancer is second to accidents as a cause of mortality in children beyond first year of life.¹ Even in developing countries like India, cancer is gradually assuming an important place as a cause of childhood mortality.^{2,3}

Cancer in children as compared to adults is clinically distinct. All pediatric cancers are considered as potentially curable. Also its sociologic impact in terms of disruption of family life, loss of productive years of life and generation of sympathy for its victims is far greater than cancer in the adults. There has been phenomenal progress in the field of pediatric oncology over last three decades. A disease with an in-variably fatal outcome in the past now enjoys a 5-year survival (equivalent to cure) of more than 70 percent and is one of the most gratifying illnesses to treat,⁴ (Fig. 1). Looking back at this success, It is clear that we started with Nihilism; the denial of the existence of any basis for curability of childhood cancers 25 years ago and we have come a long way to a state of optimism wherein nearly 50 percent of all children in India with cancer who manage to get optimum therapy are expected to be cured. Although this is definitely inferior to success of 75 percent and above in developed countries, we have an obligation to strive for improvement and provide these children with, if not the best, at least a reasonable chance for cure. This optimism is shared with a note of caution. Clinicians have learnt to appreciate that this success has come at cost of both short and long-term morbidity of treatment. In the ensuing paragraphs we narrate this success story, the consequent responsibilities of taking

care of survivors, the barriers to optimal development of pediatric oncology in India and the remedial measures needed for achieving the goal of optimally treating every child with cancer.

BURDEN OF CHILDHOOD CANCERS IN INDIA

Childhood cancer in India constitutes 2.1 to 6.2 percent of all cancers compared to 2 percent in developed countries.⁵ Globally, it is estimated that 10 to 12 children (less than 15 years) per 100,000 population per year develop cancer.⁷ The age-adjusted incidence of childhood cancer in India varies from 3.2/lakh in Barshi to 14.1/lakh in Delhi

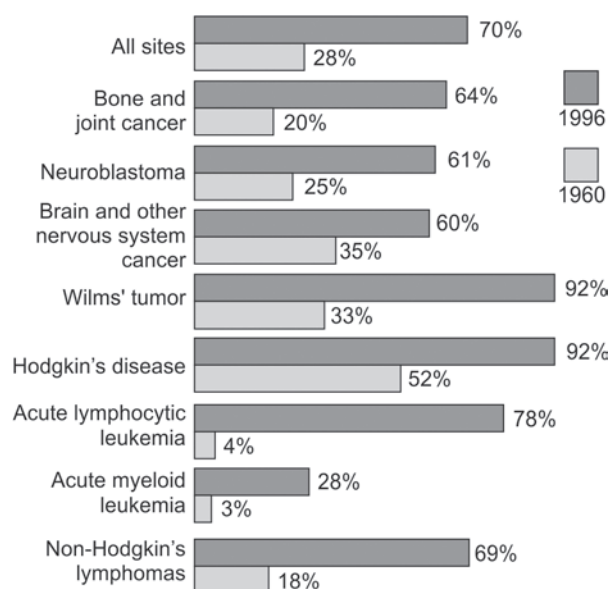


Fig. 1: Five years survival rates for childhood cancer
Source: American Cancer Society, Cancer facts and figures 1996

PBCR^{5,6} (Table 1). In India, with 36 percent population formed by children, approximately 30 to 40,000 new to cases of cancer would occur in children annually. The risk of cancer appears to be slightly higher in males compared to females.⁶

The relative frequency of various childhood malignancies in India is shown in Table 1. Leukemias and lymphomas comprise nearly half of pediatric cancers followed by tumors of the central nervous system, sympathetic nervous system, soft tissues, kidney, bone, eye liver and germ cells. The incidence of most pediatric hematological malignancies as well as solid tumors in India seems to be lower than most of developed countries. Compared to western countries, India has a higher frequency of retinoblastoma, T-cell lymphoma/leukemia, and mixed cellularity hodgkin's disease.^{5,6}

THE JOURNEY FROM NIHILISM TO CAUTIOUS OPTIMISM

The journey from nihilism to cautious optimism has been a long one with incremental advances made by multidisciplinary approach executed through carefully orchestrated combined modality team comprising of a pediatric oncologist, a pediatric surgeon, a radiation oncologist, diagnostic specialists and supportive care services. Burchenal succinctly characterized the basic tenet of multidisciplinary approach by stating, "the pride of discipline must be put aside". All the experts should work together, keeping well-being of the child as the central issue. We detail below the evolution of treatment in major childhood cancers in the past few decades worldwide and at Tata Memorial Hospital (TMH).

Hematological Malignancies

Acute Lymphoblastic Leukemia

The progress made in the treatment of acute lymphoblastic leukemia (ALL) of childhood is one of the true success stories of modern medicine. During the past 50 years, ALL

has gone from a uniformly fatal disease to one with an overall cure rate of more than 75 percent.⁸ This extraordinary therapeutic progress began with identification of single agent chemotherapy in 1940s followed by development of combination chemotherapy and maintenance chemotherapy in 1950s to 60s. After implementation of effective cranial prophylaxis in 1970s, continued gradual improvement occurred through 1990s by using additional information gained from cytogenetics, immunophenotype, molecular cytogenetics and evaluation of early treatment response.⁹ This helped to tailor the therapy allowing for more aggressive therapy for high-risk group and less aggressive therapy for low-risk group. The present focus is to decrease the long-term side effects, increase cure rates and improve the short-term convenience and economics. Advances in genomics are fuelling the future progress in ALL. In India too, the improvement in the treatment of ALL has been the most dramatic events in pediatric oncology. The disease free survival (DFS) of patients treated between 1982 and 83 was a poor 35 percent (in complete responders).¹⁰ The crowning glory of pediatric oncology in India is the implementation of a uniform protocol (MCP-841) for acute lymphoblastic leukemia (ALL) in many large centers all over the country. Over last 20 years, it has improved the 5-year event free survival (EFS) from < 20 to 50 to 60 percent all over the country. In addition, it has helped understand the biology of ALL in our country.¹¹ The EFS of patients treated with MCP-841 protocol at our institution has successively improved from 49 percent (1986 to 93) to 60 percent (1994 to 2000).^{11,12}

Acute Myeloid Leukemia

The survival of acute myeloid leukemia (AML) in early 1960s was dismal with virtually no survivors. In past 3 decades, despite the steady improvement in the treatment of children with AML, EFS continues to be less than 50 percent in most large series. The principal reasons for this therapeutic failure being development of multidrug resistance and treatment related mortality. Initial treatment for AML, which was modelled on ALL pattern with induction and maintenance produced less than 10 percent EFS. Later use of more intensive pulses of non-cross resistant agents leading to transient aplastic marrow improved the long-term EFS to 25 to 30 percent in 1980s.¹³ Subsequently, further dose intensification with autologous and allogenic bone marrow transplantation has produced 45 to 50 percent EFS in the recent years.¹⁴ At TMH, the 3-year EFS of patients treated between 1975 and 85 was abysmal at 8.5 percent which has increased to 45 percent 2-year-EFS in the recent analysis.^{15,16}

Hodgkin's Disease

The dominant treatment of Hodgkin's Disease (HD) in 1950s was radiotherapy, which produced 30 to 40 percent

Table 1: Frequency of types of cancer/hospital-based data*

Type of cancer	% of all pediatric cancers
Leukemia	28.6%
Lymphoma	13.2%
CNS	12.4%
Wilms' tumor	10.1%
Neuroblastoma	5.7%
Gonadal tumors	5.6%
Retinoblastoma	5.9%
Soft tissue tumors	5.3%
Bone	6.1%
Others	6.9%

*Computed from data from six cancer units/centers from India

CR rates in localized disease but was associated with unacceptable long-term morbidity. The discovery of nitrogen mustard and subsequent incorporation in MOPP protocol in 1964 improved the cure rates to more than 50 percent albeit at the cost of gonadal toxicity and second malignancies. Advent of ABVD regimen in 1970s provided excellent cure rates with limited toxicity. Presently use of chemotherapy alone in low-risk patients and use of chemo-radiotherapy in high-risk patients has led to more than 90 percent cure rates with minimal long-term morbidity.^{17,18} At TMH, a recent retrospective analysis showed an overall survival of 94 percent at 3 years for Hodgkin's Disease patients.¹⁹

Non-Hodgkin's lymphoma

Before 1970, the survival of Non-Hodgkin's lymphoma (NHL) patients was very poor with 5-year survival in the range of 5 to 20 percent. The only treatment available was surgery with or without RT in highly localised stage-I tumors. Use of pulsed chemotherapy regimens, e.g. COMP produced more than 20 percent 5-year EFS in early 1970s. Later, use of intensive regimens designed for ALL (LSA2L2) in NHL improved the survival further.²⁰ Subsequent identification of two biologic subgroups of NHL, the lymphoblastic requiring ALL like therapy and non-lymphoblastic requiring short intensive regimens has allowed better risk stratification of these patients leading to more than 80 percent EFS in this group.²¹ At TMH, the actuarial survival of NHL patients treated from 1976 to 1982 was 39 percent.²² Recently, after the introduction of short-duration pulse-intensive protocol called MCP-842, the 5-year-EFS of the whole group has increased to 58 percent lymphoblastic subset to 41 percent and Non-lymphoblastic subset to 68 percent.²³

Solid Tumors

Neuroblastoma

This most common extracranial solid tumor of childhood remains a challenge despite the advances seen in all other tumors. 50 percent of these patients have high-risk disease with survival of less than 40 percent even with best treatment. In past 30 years there has been significant improvement in the outcome of both infants and older children with local or regional disease. Indeed, some improvement has also occurred in the survival of older children with metastases after using intensive chemotherapy, autologous BMT and use of biological response modifiers. Furthermore, there have been advances in the prognostication with identification of novel clinico-biologic factors apart from age and stage. Overall the survival has improved from 25 percent in 1960s to 60 percent in 1990s.^{8,24} At TMH, we have observed a lower number of infants and low risk patients and an overall DFS of 58 percent at 3.5 years of follow up. Furthermore, the disease free survival

of infants has increased from 47 to 75 percent in the last decade.^{25,26}

Wilms' Tumor

In 1950s less than 30 percent children of Wilms' tumor were long-term survivors with the use of surgery alone. Gradually, the use of multidisciplinary approach has resulted in a striking improvement in survival to more than 90 percent in last decade.⁸ The primary objective of the recent clinical trials has shifted towards refinement of therapy for children with low-risk tumors so that they can be spared from unwanted long-term side effects without compromising the excellent cure rates. At the same time, novel strategies are being identified including treatment intensification to improve the outlook of high-risk tumors.²⁷ At TMH, the EFS of adequately treated patients between 1980 and 86 were 56 percent. This has improved in the recent analysis (1990-01) to 74 percent at a follow-up of 4-years.²⁸

Soft Tissue Sarcomas

Soft tissue sarcomas are a heterogeneous group of neoplasms of mesenchymal origin, constituting 8 percent of all childhood tumors. Sixty percent of these tumors in children are rhabdomyosarcoma (RMS); others include Ewing sarcoma (ES) and osteogenic sarcoma (OGS). The cure rate of RMS has dramatically improved from 25 percent in 1970s to 70 percent at present.^{8,29} This paradigm change was brought about by the formation of Intergroup Rhabdomyosarcoma Study Group (IRSG) in 1972 to stream-line the treatment and improve the biologic understanding of the disease. In last decade, the 5-year-EFS of these patients has improved from 55 percent in IRS-I to 71 percent in IRS III and IV.²⁹

In bony tumors (ES and OGS) the survival with surgery alone was less than 20 percent in 1960s. With the increasing use of neoadjuvant chemotherapy in both tumors and RT in Ewing's sarcoma, the survival has gradually climbed up to the present level of 65 to 70 percent at 5 years.^{30,31} Additionally, biologic understanding has improved with the identification of t (11:22) involving EWS:FLI1 fusion transcript in virtually all Ewing Sarcoma patients.³¹ In our center over the years, we have shown improvement in the DFS in the round cell sarcomas (RMS and ES) with treatment intensification and addition of newer chemotherapy agents like ifosfamide and etoposide. Our first study (1984-1988) showed less than 20 percent survival with vincristine, adriamycin and cyclophosphamide (VAC) regimen. With the addition of etoposide and cisplatin (RCT-I protocol), it improved to 32 percent during 1989 to 92. Later in the subsequent RCT-II protocol (1992 to 2001) the survival of rhabdomyosarcoma has improved to 54 percent and Ewing's Sarcoma to 46 percent at 5 years.^{32,33} Presently we have moved on to more intensive IRS IV protocol for RMS and EFT 2001 for Ewing's Sarcoma, which are likely to improve the results further.

Germ Cell Tumors

The outlook of malignant germ cell tumors (GCT's) was generally poor before the advent of effective chemotherapy, with only 10 to 20 percent survival after treatment with surgery and or radiotherapy. The introduction of chemotherapy regimens such as VAC and BEP (Bleomycin, Etoposide, and Cisplatin) has improved the survival rate of these patients beyond 90 percent and established GCT's as the paradigm of curable cancers.³⁴ At our institution, between 1984 to 1988, the survival of patients was 30 percent at 5 years with PVB-M (Cisplatin, vinblastine, bleomycin and methotrexate) chemotherapy, which after 1988 has improved to 80 percent with the use of BEP.³⁵ In the recently analysed data (1988 to 2000) the long-term EFS is 97 percent, 87 percent and 78 percent in testicular, ovarian and extragonadal germ cell tumors respectively.³⁶

PERPETRATORS OF NIHILISM IN INDIA

Social Roadblocks

Morbidity and mortality in childhood in a country is a direct function of average per capita income and the health expenditure by the government of that country.³⁷ In this regard, 28.6 percent of Indians live below the national poverty line and 34.7 percent of the population lives on less than 1\$ a day³⁸ (international extreme poverty line). In addition, the public and private health expenditure is a meagre 0.9 percent and 4.7 percent of GDP respectively⁴¹ (compared to 6.2 and 7.7 percent in USA). This huge economic gap is one of the major reasons why, in developing countries, including India, only 1 out of 10 children with cancer gets some form of reasonable treatment.³⁹

Also, the literacy rate in a country has a critical impact on the health care practices of that population because of its effect on the income and lifestyles as well as the manner in which treatment is sought. The average literacy rate in India is 61 percent.³⁸ Illiteracy acts a strong roadblock to the widespread dissemination of knowledge about the disease in the population. Lack of knowledge about cancer promotes late presentation of children with cancer to the health facility. On top of this all, majority of our population (including the educated) still consider cancer to be an incurable illness. Hence, the motivation on part of the patient's family to get treatment is lacking. In rural areas a large segment of population still resorts to traditional and some times irrational healing practices before bringing the child to the hospital. These factors contribute to half-hearted and delayed efforts to treat a child with cancer.

Limited Resources

There is great paucity of trained pediatric oncologists in our country as well as limited number of similarly trained nurses and supporting staff. In addition, the comprehensive diagnostic capabilities (imaging, microbiology and

oncopathology) are still limited to tertiary care centers. The supportive care like blood-banking facilities (particularly platelet concentrates) also need to be more widely available. It is estimated that, like most other developing countries, only 50 percent of the need of blood products is actually met in our country.⁴⁰ The family dislocation for cancer treatment to a new city, cost of to and fro travel, added financial burden of treatment, loss of the livelihood of the parents and problem of care of other siblings make the compliance to treatment a real challenge.

COMORBIDITIES

A significant number (47%) of Indian children suffer from malnutrition,³⁸ and micronutrient deficiency (such as anemia and vitamin-A deficiency). This might add to the poor tolerance of chemotherapy, higher toxicity and increased need for supportive care, which compromises their outcome.^{41,42} Along with poor hygiene and sanitation, this leads to increased incidence of bacterial and fungal sepsis during the treatment. Additionally, the high prevalence of infectious illnesses like tuberculosis, malaria and measles in India causes significant morbidity in immunocompromised cancer patients. The seroprevalence of hepatitis B (5%) and C (1.6%) in our population is much higher than the west, which increases the incidence of viral hepatitis related problems in children with cancer.⁴³

HOW CAN WE FACILITATE THIS JOURNEY?

Capacity Building

The best way of capacity building for India is to optimize utility of the existing infrastructure by creation of pediatric cancer units (PCU) at tertiary care centers including university hospitals and regional cancer centers.^{39,44} An ideal PCU should have a full time pediatric oncology specialist and other allied specialists such as pediatric surgeon. The mandate of such units would be to create infrastructure, train manpower, conduct research, develop indigenous protocols tailored for the local population and follow standards of care with respect to diagnosis, treatment and supportive care. There should also be an inbuilt mechanism for internal audit and step-wise improvement.⁴⁴

Protocol-based Care and Locally-appropriate Research

Blind transposition of western protocols to our country may not always be appropriate.²⁹ This could be because of differences in the biology of disease, pharmacogenomics and comorbidities in our population. Hence, concerted efforts are to be made to treat all patients on indigenously developed protocols. Such protocol-based care has the potential to impart high quality care, give better outcome as well as collect information in a systematic way. Established PCU's can act as nodal centers for design and

coordination of these regionally relevant clinical trials that pay particular attention to simplicity, economy, short duration treatment, and safety.⁵¹ An example in this regard is the nationwide usage of the MCP-841 protocol for ALL. This has not only contributed immensely to our understanding of biology of Indian ALL but also has improved the outcome of the disease.^{11,12}

Resource Augmentation

Active participation of pediatricians (shared care) from the country is our best bet for the delivery of care to children with cancer. In shared care model, the pediatrician's involvement is at the level of early diagnosis, timely referral, as well as the follow-up care of the child. This systematic decentralization process decreases the load on the PCU as well as is beneficial to parents (it decreases the direct and indirect cost of treatment). Training and exchanging qualified staff with the peripheral hospitals and dispensaries³⁹ can further refine this model. In addition, a national program could be undertaken for the identification of regional PCU's in our country and training of the requisite professionals. A highly successful National Training Program in Practical Pediatric Oncology (NTP-PPO) has been initiated by Pediatric Hematology Oncology (PHO) chapter of Indian Academy of Pediatrics (IAP) to impart hands on training to clinicians in practical aspects of pediatric oncology.⁴⁵ No effort is complete without imparting the basic knowledge about pediatric cancers to the practitioners at the grass root level as well as in the community. This could be accomplished with help of print, media, and hands on workshops, visits by health workers to the local communities, dissemination of information by the regional health authorities and inclusion of appropriate material in the school and university curricula.

Financial input is critical for the sustenance of a pediatric oncology facility. To this end, an important step is to create an association of parents, volunteers, physicians, and other health professionals known as 'alliance of the stakeholders' or 'therapeutic alliance'.⁴⁶ This parento-volunteer interface is important for sensitizing society, influencing the health policy decisions and help mobilizing the resources and energies at a national and international level.

National and International Collaboration

Internationally, the paradigm shift in the outcome of pediatric cancers was possible only from the randomized controlled trials conducted by the large national or international study groups. This is particularly important in pediatric oncology due to the limited number of cases seen in individual institutions. Hence, it is pertinent to form national cooperative groups in India. The formation and success of the Indian Cooperative Oncology Network (ICON) is an example for others to follow.

Furthermore, global long-term alliances with international institutions need to be built, also known as 'twinning'.⁴⁷ It is a symbiotic relationship that helps in the training of manpower, exchange of knowledge and local PCU development to international standards. This concept has been utilized by TMH in collaborating with National Cancer Institute, Bethesda, USA, International Network for Cancer Treatment and Research (INCTR), Brussels and MD Anderson Cancer Center, USA.

BIOLOGICAL CURE IS NOT THE END OF JOURNEY

Presently more than 70 percent of children diagnosed with cancer survive at least 5 years and most survivors are cured.^{1,4} Consequent to this success arise challenges inherent in co-coordinating life long health care for a high risk group of patients predisposed to a variety of cancer related complications. It has been estimated that in USA, the prevalence of childhood cancer survivors is expected to increase from 1 in 900 among young adults to 1:250 persons by 2010.⁴⁸ Though similar figures are not available from India. Approximately 30 to 40,000 cases of childhood cancer occur in our country annually. Even with conservative estimates of 10 to 20 percent long-term cure, approximately 3.5 to 7,000 survivors are added to our population each year.^{5,6} This is 8 to 10 times the annual number of survivors in UK.⁴⁹ Two-third of survivors are known to have at least one chronic or late occurring complications of their cancer therapy and of these, one-third have serious or life-threatening complications.⁵⁰ The incidence of most late effects increases with age often becoming clinically apparent decades after therapy.⁵¹

As there is a burgeoning population of vulnerable aging adult survivors, there is a pressing need to study the delayed effects of childhood cancer and adverse health outcomes in the context of organ senescence. An awareness of the potential long-term complications is important not only for optimizing health care of the current survivors but also for modifying future treatment protocols to avoid therapies that are associated with unacceptable morbidity and mortality. Many of the potential late effects can be ameliorated by prevention or by early diagnosis with therapeutic intervention. Hence, a specialized and structured plan for life long surveillance and prevention based on risks inherent to primary cancer, cancer therapy, genetics, life-style and co morbidities is required for each survivor. Creation of nationwide after completion of therapy (ACT) clinics' with tight linkage to primary care providers would be the right beginning.^{52,53} Further-more, there is a urgent need for national and international prospective multicenter studies, national population cohort studies, and randomized clinical trials designed to evaluate not only the survival and long-term toxicities but more importantly therapies or interventions to prevent, treat or modify late effects in our young survivors.

It is time; all health care workers involved in the care of pediatric oncology patients realize that 'biological cure is not enough'. We should all strive towards 'meaningful cure, i.e. complete restoration of physical, mental and social well-being and not mainly absence of disease.'

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Childhood Acute Lymphoblastic Leukemia: Current Perspective

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Childhood cancer is rare but its incidence has been slowly increasing since 1975.¹ Survival has improved dramatically in children and adolescents with cancer.¹ In last three decades, childhood cancer mortality has decreased by more than 50 percent. For childhood acute lymphoblastic leukemia (ALL), the 5-year survival rate has increased over the same time from 60 to 89 percent.¹

INCIDENCE AND EPIDEMIOLOGY

Acute lymphoblastic leukemia (ALL) is the most common cancer diagnosed in children and represents 23 percent of cancer diagnoses among children. ALL occurs at an annual rate of approximately 30 to 40 per million.² A sharp peak in ALL incidence is observed among children aged 2 to 3 years (>80 per million per year), with rates decreasing to 20 per million for ages 8 to 10 years.

Risk Factors for Developing ALL

Few factors associated with an increased risk of ALL have been identified. The primary accepted risk factors for ALL include the following:

- Prenatal exposure to X-rays.
- Postnatal exposure to high doses of radiation (e.g. therapeutic radiation as previously used for conditions such as tinea capitis and thymus enlargement).
- Down syndrome and other genetic conditions.
- Inherited genetic polymorphisms.

Children with Down syndrome have an increased risk of developing both ALL and acute myeloid leukemia (AML),³ with a cumulative risk of developing leukemia of approximately 2.1 percent.³ Approximately one-half to two-thirds of cases of acute leukemia in children with Down syndrome are ALL. While the vast majority of cases of AML in children with Down syndrome occur before the age of 4 years (median age, 1 year),⁴ ALL in children with

Down syndrome has an age distribution similar to that of ALL in non-Down syndrome children, with a median age of 3 to 4 years.⁵ Increased occurrence of ALL is also associated with other genetic conditions, including neurofibromatosis,⁶ Shwachman syndrome,⁷ Bloom syndrome,⁸ and ataxia telangiectasia.⁹

Some cases of ALL have a prenatal origin. Evidence in support of this comes from the observation that the immunoglobulin or T-cell receptor antigen rearrangements that are unique to each patient's leukemia cells can be detected in blood samples obtained at birth.^{10,11} Similarly, in ALL characterized by specific chromosomal abnormalities, data exist to support that patients had blood cells carrying the abnormalities at the time of birth with additional cooperative genetic changes acquired postnatally.¹⁰⁻¹² In one study, 1 percent of neonatal blood spots (Guthrie cards) tested positive for the TEL-AML1 translocation, far exceeding the number of cases of TEL-AML1 ALL in children.¹³ This may support the hypothesis that additional genetic changes are needed for the development of this type of ALL. Genetic studies of identical twins with concordant leukemia further support the prenatal origin of some leukemias.¹⁴

Overall Outcome for ALL

Among children with ALL, more than 95 percent attain remission and 75 to 85 percent survive free of leukemia recurrence at least 5 years from diagnosis with current treatments that incorporate systemic therapy (e.g. combination chemotherapy) and specific central nervous system preventive therapy (e.g. intrathecal chemotherapy with or without cranial radiation).¹⁵⁻¹⁹

PROGNOSTIC FACTORS AND RISK STRATIFICATION

Children with acute lymphoblastic leukemia (ALL) are usually treated according to risk groups defined by both

clinical and laboratory features. The intensity of treatment required for favorable outcome varies substantially among subsets of children with ALL. Risk-based treatment assignment is utilized in children with ALL so that patients with favorable clinical and biological features who are likely to have a very good outcome with modest therapy can be spared more intensive and toxic treatment, while a more aggressive, and potentially more toxic, therapeutic approach can be provided for patients who have a lower probability of long-term survival.²⁰⁻²² For children with ALL, a number of clinical and laboratory features have demonstrated prognostic value, some of which are described below.²³

PATIENT CHARACTERISTICS AT DIAGNOSIS

Age at Diagnosis

Age at diagnosis has strong prognostic significance, reflecting the different underlying biology of ALL in different age groups.²⁴ Young children (aged 1–9 years) have a better disease-free survival (DFS) than older children, adolescents, or infants.^{20,24,25}

Infants with ALL have a particularly high risk of treatment failure. Treatment failure is most common in infants younger than 6 months and in those with extremely high presenting leukocyte counts and/or a poor response to a prednisone prophase.²⁶⁻²⁹

White Blood Cell (WBC) Count at Diagnosis

Patients with B-precursor ALL and high white blood cell (WBC) counts at diagnosis have an increased risk of treatment failure compared with patients with low initial WBC counts. A WBC count of 50,000/ μ L is generally used as an operational cut point between better and poorer prognosis.²⁰

CNS Involvement at Diagnosis

The presence or absence of CNS leukemia at diagnosis has prognostic significance. Patients who have a nontraumatic diagnostic lumbar puncture may be placed into one of three categories according to the number of WBC/ μ L and the presence or absence of blasts on cytopsin as follows:

- *CNS1*: Cerebrospinal fluid (CSF) that is cytopsin negative for blasts regardless of WBC count.
- *CNS2*: CSF with fewer than five WBC/ μ L and cytopsin positive for blasts.
- *CNS3 (CNS disease)*: CSF with five or more WBC/ μ L and cytopsin positive for blasts.

Compared with patients classified as CNS1 or CNS2, children with ALL who present with CNS disease (i.e. CNS3) at diagnosis are at a higher risk of treatment failure (both within the CNS and systemically).³⁰ The adverse prognostic significance associated with CNS2 status, if any, may be overcome by the application of more intensive intrathecal therapy, especially during the induction

phase.^{30,31} A traumatic lumbar puncture (≥ 10 erythrocytes/ μ L) that includes blasts at diagnosis appears to be associated with increased risk of CNS relapse and indicates an overall poorer outcome.^{30,32}

Down Syndrome (Trisomy 21)

Outcome in Down syndrome children with ALL has generally been reported as somewhat inferior to outcomes observed in non-Down syndrome children.³³⁻³⁶ The lower event-free survival (EFS) and overall survival (OS) of children with Down syndrome appear to be related to higher rates of treatment-related mortality and the absence of favorable biological features.³³⁻³⁷

Gender

In some studies, the prognosis for girls with ALL is slightly better than it is for boys with ALL.³⁸⁻⁴⁰ One reason for the better prognosis for girls is the occurrence of testicular relapses among boys, but boys also appear to be at increased risk of bone marrow and CNS relapse for reasons that are not well understood.³⁸⁻⁴⁰ However, in clinical trials with high 5-year EFS rates ($>80\%$), outcomes for boys are closely approaching those of girls.⁴¹

LEUKEMIC CELL CHARACTERISTICS AT DIAGNOSIS

Immunophenotype

The World Health Organization (WHO) classifies ALL as either B lymphoblastic leukemia or T lymphoblastic leukemia. B lymphoblastic leukemia is subdivided by the presence or absence of specific recurrent genetic abnormalities (t(9;22)), MLL rearrangement, t(12;21), hyperdiploidy, hypodiploidy, t(5;14), and t(1;19).⁴²

Precursor B-cell ALL (WHO B Lymphoblastic Leukemia)

Precursor B-cell ALL, defined by the expression of cytoplasmic CD79a, CD19, HLA-DR, and other B-cell-associated antigens, accounts for 80 to 85 percent of childhood ALL. Approximately 90 percent of precursor B-cell ALL cases express the CD10 (formerly known as common ALL antigen [cALLa]) surface antigen. Absence of CD10 is associated with MLL translocations, particularly t(4;11), and a poor outcome.⁴³ It is not clear whether CD10-negativity has any independent prognostic significance in the absence of an MLL gene rearrangement.⁴⁴

T-cell ALL

T-cell ALL is defined by expression of the T cell-associated antigens (cytoplasmic CD3, with CD7 plus CD2 or CD5) on leukemic blasts and is frequently associated with a constellation of clinical features, including male gender, older age, leukocytosis, and mediastinal mass.⁴¹ With appropriately intensive therapy, children with T-cell ALL have an outcome similar to that of children with B-lineage ALL.⁴¹

Ambiguous Lineage

Less than 5 percent of cases of acute leukemia in children are of ambiguous lineage, expressing features of both myeloid and lymphoid lineage.⁴⁵⁻⁴⁷ Leukemias of mixed phenotype comprise two groups of patients: (1) bilineal leukemias in which there are two distinct population of cells, usually one lymphoid and one myeloid, and (2) biphenotypic leukemias where individual blast cells display features of both lymphoid and myeloid lineage. Biphenotypic cases represent the majority of mixed phenotype leukemias.⁴⁵ B-myeloid biphenotypic leukemias lacking the ETV6-RUNX1 fusion have a lower rate of complete remission and a significantly worse EFS compared with patients with B-precursor ALL.⁴⁵ Some studies suggest that patients with biphenotypic leukemia may fare better with a lymphoid, as opposed to a myeloid, treatment regimen,⁴⁶⁻⁴⁸ although the optimal treatment for patients remains unclear.

Cytogenetics

A number of recurrent chromosomal abnormalities have been shown to have prognostic significance, especially in B-precursor ALL. Some chromosomal abnormalities, such as high hyperdiploidy (51–65 chromosomes) and the ETV6-RUNX1 fusion, are associated with more favorable outcomes, while others, including the Philadelphia chromosome (t[9;22]), rearrangements of the MLL gene (chromosome 11q23), and intrachromosomal amplification of the AML1 gene (iAMP21), are associated with a poorer prognosis.⁴⁹

RESPONSE TO INITIAL TREATMENT

The rapidity with which leukemia cells are eliminated following onset of treatment is associated with long-term outcome, as is level of residual disease at the end of induction. Because treatment response is influenced by the drug sensitivity of leukemic cells and host pharmacodynamics and pharmacogenomics,⁵⁰ early response has strong prognostic significance. Various ways of evaluating the leukemia cell response to treatment have been utilized, including the following:

Day 7 and Day 14 Bone Marrow Responses

Patients who have a rapid reduction in leukemia cells to less than 5 percent in their bone marrow within 7 or 14 days following initiation of multiagent chemotherapy have a more favorable prognosis than do patients who have slower clearance of leukemia cells from the bone marrow.⁵¹

Peripheral Blood Response to Steroid Prophase

Patients with a reduction in peripheral blast count to less than 1,000/ μ l after a 7-day induction prophase with

prednisone and one dose of intrathecal methotrexate (a good prednisone response) have a more favorable prognosis than do patients whose peripheral blast counts remain above 1,000/ μ l (a poor prednisone response).²⁵

Induction Failure

The vast majority of children with ALL achieve complete morphologic remission by the end of the first month of treatment. The presence of greater than 5 percent lymphoblasts at the end of the induction phase is observed in up to 5 percent of children with ALL. Patients at highest risk of induction failure include those with T-cell phenotype (especially without a mediastinal mass) and patients with B-precursor ALL with very high presenting leukocyte counts and/or the Philadelphia chromosome.^{52,53} Induction failure portends a very poor outcome.⁵² In the French FRALLE 93 study, the 5-year OS rate for patients with initial induction failure was 30 percent.⁵³

Minimat Residual Disease Determination

Morphologic assessment of residual leukemia in blood or bone marrow is often difficult and is relatively insensitive. Traditionally, a cutoff of 5 percent blasts in the bone marrow (detected by light microscopy) has been used to determine remission status. This corresponds to a level of 1 in 20 malignant cells. If one wishes to detect lower levels of leukemic cells in either blood or marrow, specialized techniques such as PCR assays, which determine unique Ig/TCR gene rearrangements, fusion transcripts produced by chromosome translocations, or flow cytometric assays, which detect leukemia-specific immunophenotypes, are required. With these techniques, detection of as few as 1 leukemia cell in 100,000 normal cells is possible, and MRD at the level of 1 in 10,000 cells can be detected routinely.⁵⁴

Multiple studies have demonstrated that end-induction MRD is an important, independent predictor of outcome in children and adolescents with ALL.⁵⁵⁻⁵⁷

PROGNOSTIC GROUPS

Since 2000, risk stratification on BFM protocols has been based almost solely on treatment response criteria. In addition to prednisone prophase response, treatment response is assessed via MRD measurements at two time points, end induction (week 5) and end consolidation (week 12). Patients who are MRD negative at both time points are classified as standard risk, those who have positive MRD at week 5 and low MRD ($<10^3$) at week 12 are considered intermediate risk, and those with high MRD ($\geq 10^3$) at week 12 are high risk.

Patients with a poor response to the prednisone prophase are also considered high risk, regardless of subsequent MRD. Phenotype, leukemic cell mass estimate, also known as BFM risk factor, and CNS status at diagnosis

do not factor into the current risk classification schema. However, patients with either the t(9;22) or the t(4;11) are considered high risk, regardless of early response measures.

TREATMENT OPTION OVERVIEW

Treatment of childhood acute lymphoblastic leukemia (ALL) typically involves chemotherapy given for 2 to 3 years. Since myelosuppression and generalized immunosuppression are anticipated consequences of both leukemia and chemotherapy treatment, patients must be closely monitored at diagnosis and during treatment. Approximately 1 to 3 percent of patients die during induction therapy and another 1 to 3 percent die during the initial remission from treatment-related complications.^{58,59} Treatment for children with ALL is typically divided as follows:

- Remission induction (at the time of diagnosis)
- Postinduction therapy (after achieving complete remission)
 - Consolidation/intensification therapy
 - Maintenance or continuation therapy.

RISK-BASED TREATMENT ASSIGNMENT

Risk-based treatment assignment is an important therapeutic strategy utilized for children with ALL. This approach allows children who historically have a very good outcome to be treated with modest therapy and to be spared more intensive and toxic treatment, while allowing children with a historically lower probability of long-term survival to receive more intensive therapy that may increase their chance of cure.

Allogeneic bone marrow transplantation was once considered to be the treatment of choice for children with t(9;22) Philadelphia chromosome-positive (Ph+) ALL, especially those with high-risk clinical features (age >10 years or high initial leukocyte count) or poor early treatment response.^{60,61} However, a COG study demonstrated a 3-year EFS rate of 80.5 percent in Ph+ patients treated with concurrent intensive chemotherapy and a tyrosine kinase inhibitor (imatinib) given daily during pre-maintenance therapy.⁶² While longer follow-up is necessary to determine if this treatment regimen indeed improves cure rates or merely prolongs the duration of disease-free survival, these results suggest that the presence of the Philadelphia chromosome should no longer be considered an absolute indication for transplantation in first remission.

Treatment of Sanctuary Sites (Central Nervous System, Testes)

Successful treatment of children with ALL requires the control of systemic disease (e.g. marrow, liver and spleen, lymph nodes), as well as the prevention or treatment of

extramedullary disease, particularly in the central nervous system (CNS). Approximately 3 percent of patients have detectable CNS involvement by conventional criteria at diagnosis (cerebrospinal fluid specimen with ≥ 5 WBC/ μ l with lymphoblasts and/or the presence of cranial nerve palsies). However, unless specific therapy is directed toward the CNS, the majority of children will eventually develop overt CNS leukemia. Therefore, all children with ALL should receive systemic combination chemotherapy together with some form of CNS prophylaxis. Therapies that may be used for CNS prophylaxis include intrathecal chemotherapy and cranial radiation. CNS-penetrant systemic chemotherapy (such as intravenous methotrexate and high-dose cytarabine) and other drugs, including dexamethasone and asparaginase, may contribute to CNS prophylaxis as well. At present, most newly diagnosed children with ALL are treated without cranial radiation; many groups administer cranial radiation only to those patients considered to be at highest risk for subsequent CNS relapse, such as those with documented CNS leukemia at diagnosis (as defined above) (>5 WBC/ μ l with blasts; CNS3) and/or T-cell phenotype with high presenting WBC count.⁶³

CNS-directed therapy is provided during pre-maintenance chemotherapy by all groups. Some protocols provide ongoing intrathecal chemotherapy during maintenance (COG, St. Jude Children's Research Hospital [SJCRH], and Dana-Farber Cancer Institute), while others do not (Berlin-Frankfurt-Muenster).

Overt testicular involvement at the time of diagnosis occurs in approximately 2 percent of males. In early ALL trials, testicular involvement at diagnosis was an adverse prognostic factor. With more aggressive initial therapy, however, the prognostic significance of initial testicular involvement is unclear.^{64,65} The role of radiation therapy for testicular involvement is also unclear. A study from SJCRH suggests that a good outcome can be achieved with aggressive conventional chemotherapy without radiation.⁶⁴

PROGNOSIS OF RELAPSED ALL

The prognosis for a child with acute lymphoblastic leukemia (ALL) whose disease recurs depends on the time from diagnosis to relapse and site of relapse, as well as cytogenetics and immunophenotype.⁶⁶⁻⁷⁹ For patients with relapsed B-precursor ALL, early relapses fare worse than later relapses, and marrow relapses fare worse than isolated extramedullary relapses. For instance, survival rates after marrow relapse range from less than 20 percent for patients with marrow relapses occurring within 18 months from diagnosis to 40 to 50 percent for those whose relapses occur more than 36 months from diagnosis.^{70,78} For patients with isolated central nervous system (CNS) relapses, the overall survival (OS) rates for early relapse (<18 months from diagnosis) are 40 to 50 percent

and are 75 to 80 percent for those with late relapses (>18 months from diagnosis).^{78,80} No evidence exists that early detection of relapse by frequent surveillance (complete blood counts or bone marrow tests) in off-therapy patients improves outcome.⁸¹

Patients who have combined marrow/extramedullary relapses fare better than those with isolated marrow relapses.^{70,78} The Berlin-Frankfurt-Muenster (BFM) group has also reported that high peripheral blast counts at the time of relapse (>10,000/ μ l) were associated with inferior outcomes in patients with late marrow relapses.⁷⁵ Immunophenotype is an important prognostic factor at relapse. Patients with T-cell ALL who experience a marrow relapse (isolated or combined) at any point during treatment or post-treatment have a very poor prognosis.⁷⁰

Patients with marrow relapses who have persistent morphologic disease at the end of the first month of reinduction therapy have an extremely poor prognosis, even if they subsequently achieve a second remission (CR2).⁸² Minimal residual disease (MRD) levels after the achievement of CR2 are of prognostic significance in relapsed ALL.⁸² High levels of MRD at the end of reinduction and at later time points have been correlated with an extremely high risk of subsequent relapse.

INDIAN SCENARIO

Recent review of data from India shows remission induction rates of 87 to 92 percent, overall survival rates of 60 to 74 percent, event free survival of 50 to 56 percent and disease free survival of 54 to 68 percent.^{83,84}

Second, regarding poor survival, sepsis is a major barrier to improving survival in childhood ALL.⁸⁵ Lost to follow up (LFU) and treatment abandonment are other major causes of poor outcomes.^{86,87} Prevalence of TEL-AML1 fusion gene in ALL from India is reported 0 to 11 percent which is lower compared to western data probably contributing to the inferior outcomes.⁸⁸

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Management of Leukemia: The Future

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INTRODUCTION

The leukemias are a group of malignant diseases, characterized by unregulated clonal proliferation of hematopoietic cells which have a growth advantage over normal cellular elements. These are the most common malignant neoplasms in childhood, accounting for about 41 percent of all malignancies that occur in children <15 years of age. Acute lymphoblastic leukemia (ALL) accounts for about 77 percent of cases of childhood leukemia, acute myelogenous leukemia (AML) for about 11 percent, chronic myelogenous leukemia (CML) for 2 to 3 percent, and juvenile myelomonocytic leukemia (JMML) for 1 to 2 percent. The remaining cases consist of a variety of acute and chronic leukemias that do not fit classic definitions for ALL, AML, CML or JMML.¹

ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)

Acute Lymphoblastic Leukemia (ALL) is a heterogeneous disease with distinct biologic and prognostic groupings. Considerable progress has been made in understanding the biology of ALL and has led to more precise disease prognostication and treatment strategies tailored to specific disease subgroups. This has resulted in dramatic improvements in the outcomes of children with ALL, with cure rates up to 80 percent.

EPIDEMIOLOGY

Approximately 2,000 children <15 years of age are diagnosed with ALL in the USA each year. It peaks between 2 and 6 years of age and occurs more frequently in boys than in girls.² It is commonly seen in white populations and in advanced socioeconomic class of people.

ETIOLOGY

The etiology of ALL is unknown, although several genetic and environmental factors are associated with childhood leukemia (Table 1).

Table 1: Factors predisposing to childhood leukemia

<i>Genetic conditions</i>	<i>Environmental factors</i>
Down syndrome	Ionizing radiation
Fanconi syndrome	Drugs
Bloom syndrome	Alkylating agents
Diamond-Blackfan anemia	Nitrosourea
Shwachman syndrome	Epipodophyllotoxin
Klinefelter syndrome	Benzene exposure
Turner syndrome	Advanced maternal age
Neurofibromatosis type 1	Viruses
Ataxia-telangiectasia	
Severe combined immune deficiency	
Paroxysmal nocturnal hemoglobinuria	
Li-Fraumeni syndrome	

PATHOGENESIS

Genetic changes are central to the development of leukemia. The dysregulation of genes encoding transcription factors and the resulting subversion of transcriptional pathways that regulate hemopoietic cell homeostasis provides a mechanistic explanation for leukemogenesis. Hemopoiesis can also be altered by the dysregulated activity of tyrosine kinases, as in the case of the *BCR – ABL1* fusion gene or by activating mutations in tyrosine kinase receptors for growth factors which confers a growth advantage to leukemic cells, e.g. mutations of *FLT3*. Activating mutations of *NOTCH1*, a gene encoding a transmembrane receptor that regulates normal T-cell development, are frequently detected in T-cell ALL. A recent large-scale study of DNA single-nucleotide polymorphism (SNP) analysis examined 242 cases

of pediatric B-cell precursor ALL and identified lesions in genes encoding key regulators of B-cell differentiation in 40 percent of the cases. Most prominent were deletions and cryptic translocations involving the *PAX5* gene, which was altered in almost one-third of cases and which would be predicted to block normal B – progenitor cell differentiation prior to immunoglobulin heavy-chain gene rearrangement. Other mutated genes were found in concert with several of the more common translocation-induced chimeric oncogenes, such as *TCF3 – PBX1* and *ETV6 – RUNX1*, including the essential B-cell developmental genes *TCF3*, *EBF*, *LEF1*, *IKZF1* (Ikaros) and *IKZF3* (Aiolos).³ A subsequent study showed deletion of *IKZF1* in 83.7 percent of *BCR – ABL1*-positive ALL.⁴

CLASSIFICATION

The classification of ALL depends on characterizing the malignant cells to determine the morphology, phenotypic characteristics as measured by cell membrane markers, and cytogenetic and molecular genetic features.

Morphology

Is usually adequate to establish a diagnosis, but the other studies are essential for disease classification, which may have a major influence on both the prognosis and the choice of appropriate therapy. Morphologic classification by French-American-British (FAB) system divides ALL into three subtypes L1, L2 and L3 among which the recognition of L3 subtype (Burkitt leukemia) is important as it requires a different therapeutic approach.

Flowcytometric Immunophenotyping

Using surface markers show that about 85 percent of cases of ALL are derived from progenitors of B cells, about 15 percent are derived from T cells, and about one percent are derived from B-cells. Immunophenotypically, ALL has following types:

Early Pre-B ALL

Leukemic blast cells of early pre-B ALL resemble normal marrow B-cell precursors. The leukemic cells always express CD19, cytoplasmic CD22 and CD79 α ; surface CD22 expression is also evident in most cases. CD10 and terminal deoxynucleotidyltransferase (TdT) are expressed in 90 percent of cases, and CD34 in more than 75 percent of cases. The CD20 antigen is present on a minor proportion of blast cells in half of cases but its intensity might increase during treatment. Early pre-B ALL cells lack expression of surface and cytoplasmic immunoglobulins. ALL with rearrangement of the *MLL* gene typically has an early pre-B ALL (Pro-B) phenotype with distinctive features such as expression of CD15, CD65 and absence of CD10.

Pre-B ALL

The pre-B immunophenotype is defined by the accumulation of cytoplasmic immunoglobulin μ heavy chains with no detectable surface immunoglobulins and is found in approximately 20 to 25 percent of cases. Pre-B ALL expresses CD19, CD22 and CD79 α and, usually, CD10 and TdT but only two-thirds express CD34 (Fig. 1). In many cases of pre-B ALL, surface CD20 is absent or is weakly expressed.

B-cell ALL

In 2 to 4 percent of childhood ALL cases, cells express surface immunoglobulin μ heavy chains plus either κ or λ light chains. Commonly, cells have L3 morphology according to the FAB classification and express CD19, CD22, CD20 and frequently CD10; CD34 is negative (Fig. 1).

T-lineage ALL

T-lineage ALL cells express CD7 and CD3, the latter most commonly only in the cytoplasm. Other markers commonly expressed include CD2, CD5 and TdT; CD1a, surface CD3, CD4 and CD8 are detected in fewer than 45 percent of cases. HLA – DR expression is uncommon, and 40 to 45 percent of cases are positive for CD10 and/or CD21. CD79 α is also weakly expressed in approximately one-third of cases (Fig. 2). T-lineage ALL has been divided into three stages of immunophenotypic differentiation: early (CD7 +, cCD3 +, surface CD3 –, CD4 – and CD8 –), mid or common (cCD3 +, surface CD3 –, CD4 +, CD8 + and CD1a +) and late (surface CD3 +, CD1a – and either CD4 + or CD8 +). T-cell receptor (TCR) proteins are heterogeneously expressed in T-lineage ALL. In approximately two-thirds of cases, membrane CD3 and TCR proteins are absent. In half of these cases, however, TCR proteins (TCR- β , TCR- α , or both) are present in the cell cytoplasm. Most cases with membrane CD3 and TCR chains express the $\alpha\beta$ form of the TCR, whereas a minority express TCR $\gamma\delta$ proteins. One of the recently identified subtype of T – ALL is known as early thymic precursor (ETP) ALL. These leukemias are positive for CD7 and CD3, lack CD1a and CD8 expression, have weak or absent CD5 and CD2 expression and express at least one stem cell or myeloid-associated antigen (e.g. CD34, CD117, CD13, CD33, CD11b). These cases are characterized by a dismal response to therapy and a high rate of relapse.

Immunophenotypes often correlate to disease manifestations (Table 2).

Chromosomal Abnormalities

Standard karyotype analysis frequently is complemented with molecular analysis of known predictive chromosomal abnormalities using fluorescence *in situ* hybridization (FISH) and other molecular techniques. Both numerical and structural abnormalities of the chromosomes in ALL are associated with prognosis and influence selection of

Dot plots shows a blast cluster (arrow) with low SSC. These cells express CD 79a, CD19, CD10, CD20, CD34, tdt, CD58 and CD38. They are negative for cMPO, cCD3, CD117, CD14, CD64, CD33, CD4, CD5, CD7, CD2 and CD8

B Tube

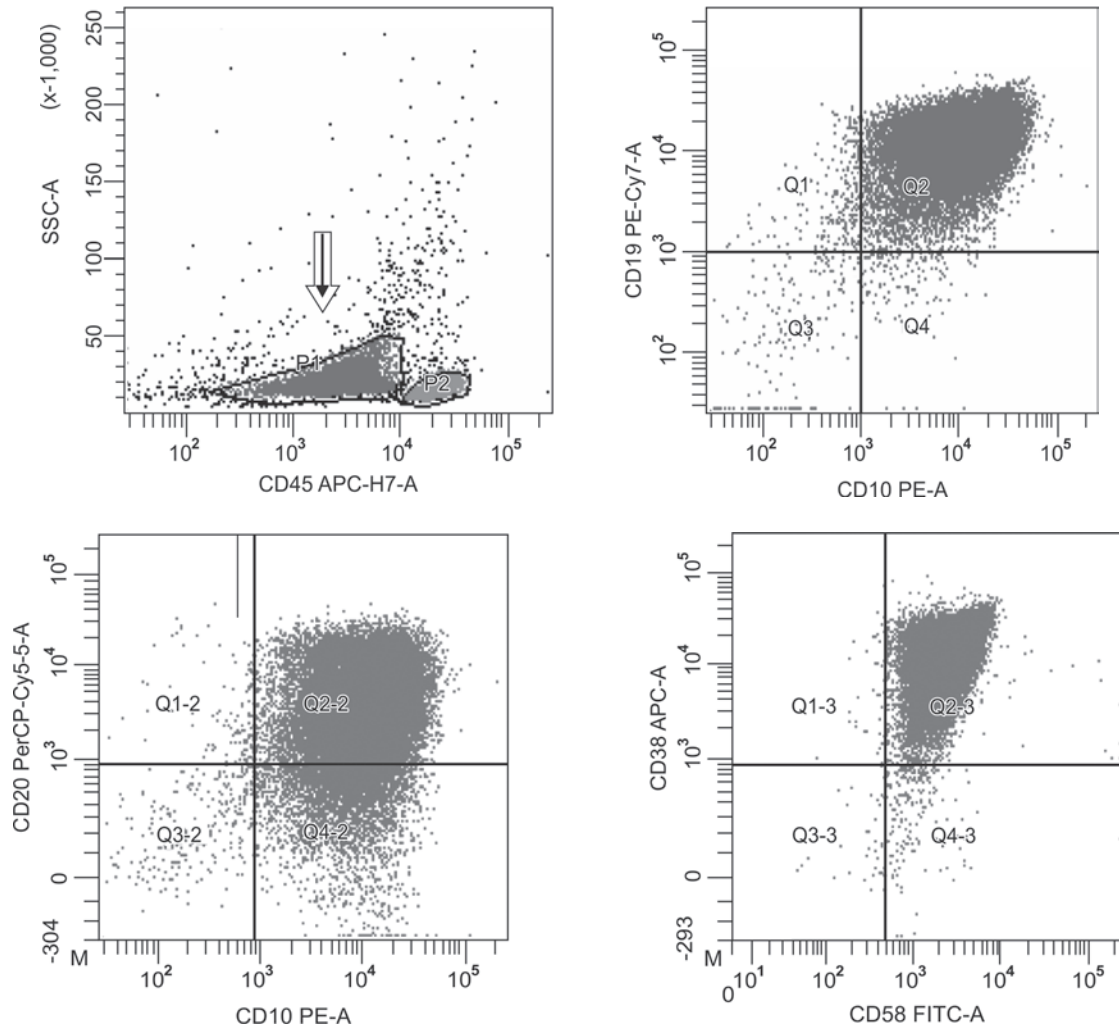


Fig. 1: Flow cytometric immunophenotyping of B-cell ALL

treatment.⁵ The following is a summary of these abnormalities.

Hyperdiploid ALL

In approximately half of ALL cases, leukemic cells are hyperdiploid. Hyperdiploid cases with a chromosome number of 51 to 65 represent a distinct biological subset of B-lineage ALL with an excellent prognosis. Leukemic lymphoblasts with this karyotype have a marked propensity to undergo apoptosis, and accumulate greater quantities of methotrexate and its active polyglutamate metabolites. Among chromosomes that are over-represented, only the trisomies of chromosome 4, 10 and 17 were associated with a favorable prognosis in some studies.⁶

Hypodiploid ALL

Hypodiploidy (<45 chromosomes) occurs in less than 2 percent of ALL cases and is associated with a poor outcome.⁷

ALL with TEL – AML 1 (ETV 6 – RUNX 1) Rearrangements

The t(12;21)(p12;q22) translocation brings together the 5' portion of the *TEL* (*ETV6*) gene and the nearly complete *AML1* (*RUNX1*) gene.⁸ This translocation can usually be detected only by fluorescence *in situ* hybridization (FISH) or reverse-transcriptase polymerase chain reaction (RT-PCR). This gene fusion is found in approximately 20 percent of ALL cases. In most studies, it is defined as a

T Tube

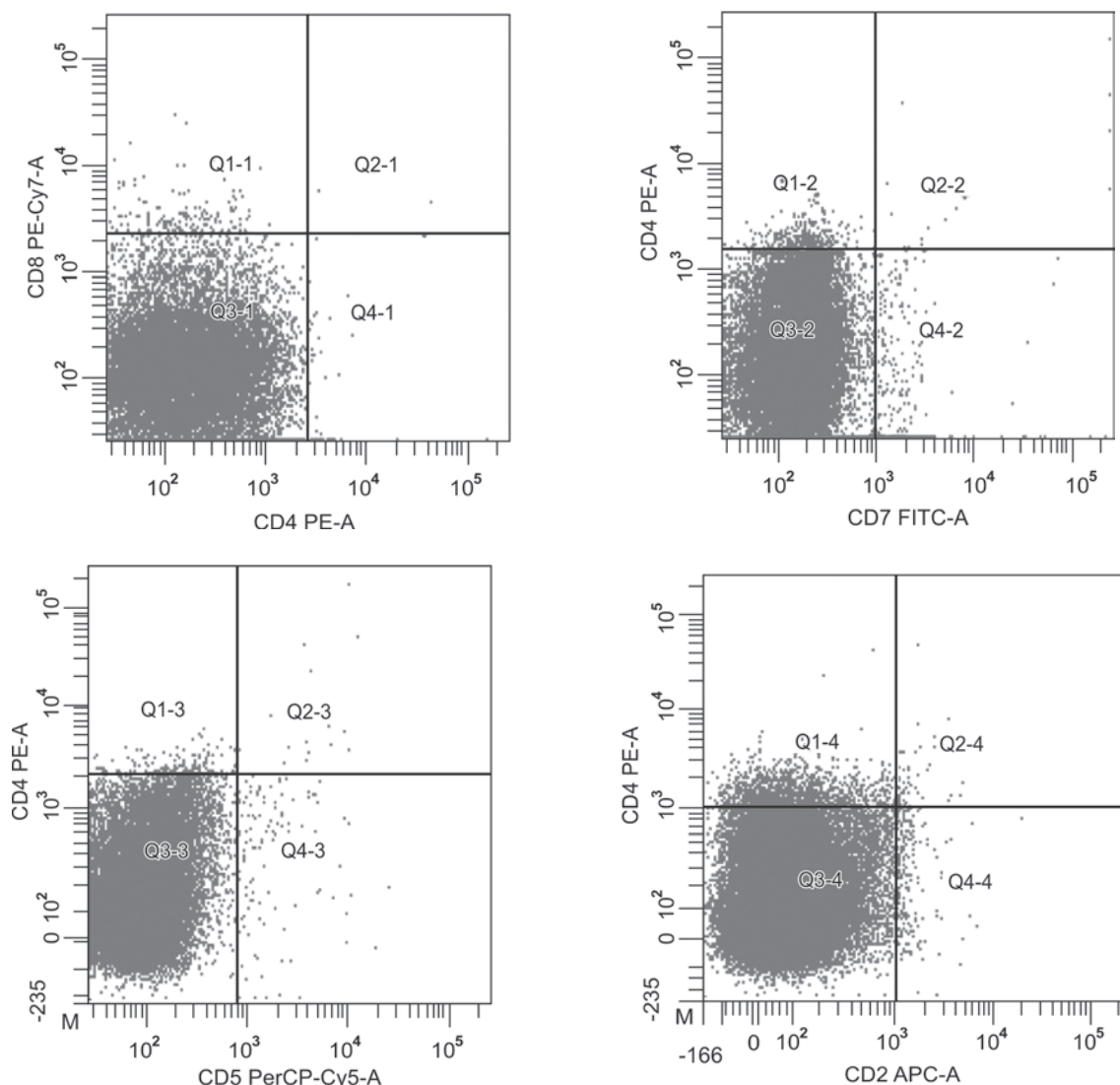


Fig. 2: Flow cytometric immunophenotyping of T cell ALL

subgroup with excellent prognosis. ALL cells bearing this abnormality reportedly have increased *in vitro* sensitivity to L-asparaginase, as well as to doxorubicin, etoposide, amsacrine and dexamethasone. Similar to T-cell ALL, blast cells with ETV6 – RUNX1 accumulate significantly lower levels of methotrexate polyglutamates than do those with other genetic abnormalities, suggesting that patients with this leukemia subtype might benefit from an increased dose of methotrexate.

ALL with E2A – PBX 1 (TCF 3 – PBX 1) Rearrangements

Approximately 20 to 25 percent of pre-B ALL cases have the t(1;19) (q23;p13) translocation abnormality that

juxtaposes the *E2A* (*TCF3*) gene on chromosome 19 and the *PBX1* gene on chromosome 1.⁹ The t(1;19) abnormality was associated with an unfavorable outcome in earlier trials. With contemporary treatment protocols, however, patients with this leukemia subtype have excellent response to initial therapy, and a favorable overall outcome although they still have increased risk of leukemia relapse in the CNS.

ALL with MLL Gene Rearrangements

Structural alterations involving band 11q23 of chromosome 11 are the most frequent cytogenetic abnormality in infant ALL. In most cases, the target is the *MLL* gene (for mixed-lineage leukemia). The most common 11q23

Table 2: Correlation of immunophenotype with clinical characteristics

	<i>Pro-B, CD10–</i>	<i>Early Pre-B, CD10+</i>	<i>Pre-B</i>	<i>Mature B</i>	<i>T-cell</i>
No. patients	52	635	156	39	124
Sex (% male)	39	53	50	85	75
Age (years)					
<1 (%)	33	1	6	3	1
1–<10 (%)	50	82	80	64	62
≥10 (%)	17	17	14	33	37
Leukocyte count <100×10 ⁹ /L					
Median	38	33	42	77	87
≤20 (%)	38	75	53	69	23
>50 (%)	44	11	21	5	57
Platelet count <100 × 10 ⁹ L (%)	77	75	81	56	56
Hemoglobin ≤8 g/dL (%)	58	40	60	21	15
Splenomegaly (%)	50	34	46	28	57
Hepatomegaly (%)	56	46	48	36	61
Mediastinal mass (%)	0	0	1	0	72
Lymphadenopathy	35	36	41	54	78
CNS disease	10	1	1	0	11

From Nathan DG, Orkin SH, Ginsburg D, et al (eds). *Nathan and Oski's Hematology of Infancy and Childhood*, 6th ed. Philadelphia: WB Saunders;2003.p.1139.

abnormality in ALL is t(4;11)(q21;q23), which produces a chimeric protein that contains the N-terminal portion of *MLL* linked to the C-terminal portion of *AFF1*. Treatment outcome of ALL with an *MLL* gene rearrangement differs by age group, with infants having the worst outcome.¹⁰

ALL with BCR – ABL 1 Rearrangements

The t(9;22)(q34;q11) translocation encodes a chimeric gene consisting of the 5' portion of BCR fused to the 3' portion of *ABL1*. It occurs in 3 to 4 percent of childhood ALL. In ALL, breaks tend to occur in the minor breakpoint cluster regions, forming a 190-kDa BCR–ABL. This alteration results in a constitutively active ABL tyrosine kinase that induces aberrant signaling and activates multiple

cellular pathways. Genome-wide analysis of BCR–ABL1 ALL samples revealed deletions of *IKZF1* in 84 percent of cases whereas deletions were not found in chronic-phase CML samples.⁴ BCR – ABL1 ALL has poor prognosis with standard chemotherapy. The development of the tyrosine kinase inhibitor imatinib mesylate has provided a way to disable the molecular mechanisms that drive leukemic cell growth, and patients with BCR–ABL1 ALL show dramatic responses. In a recent report, combination chemotherapy together with imatinib yielded an excellent 3-year event-free survival (EFS) exceeding 80 percent in childhood cases. The development of resistance due to the outgrowth of clones with mutations in the BCR – ABL1 kinase domain led to the development of newer and more potent inhibitors, such as nilotinib and dasatinib.

ALL with t(8;14)

t(8;14) MYC/IGH translocation is associated with mature B-cell ALL with FAB L3 morphology. This translocation is present in one percent of ALL patients.¹¹

Genetic Abnormalities in T-cell ALL

Genes that are dysregulated in T-cell ALL include *SCL* (*TAL-1*), *LMO1* (*TTG-1*), *LMO2* (*TTG-2*) and *HOX11*. In a small fraction of cases, *SCL* (a gene involved in early hemopoiesis located on chromosome 1) is inserted into the TCR- δ locus on chromosome 14. Much more frequent (approximately 25% of cases) is the internal deletion in the 5' untranslated region of *SCL*, which juxtaposes a locus called *SIL* with the *SCL* coding region, resulting in the expression of a fused *SIL* – *SCL* transcript that encodes a normal *SCL* protein. *LMO1* is inserted into the TCR- α/δ locus in t(11;14)(p15;q11), while *LMO2* is inserted into this locus in t(11;14)(p13;q11). An additional alteration found in T-cell ALL is the deletion from chromosome 9p21 of the *CDKN2A* (*INK4A*) and *CDKN2B* (*INK4B*) genes, which encode p16INK4a and p15INK4b, inhibitors of the Cdk4 cyclin D-dependent kinase. This locus, which is deleted in more than 50 percent of T-lineage cases, also encodes another important regulator of cell cycle and apoptosis, p19ARF. Levels of *HOX11*, *TAL1* and *LYL1* mRNA expression have been used to recognize distinct subtypes of T-ALL. Over-expression of *LMO1* or *LMO2* was observed in most samples also over-expressing *TAL1*, and high levels of *LMO2*, but not *LMO1*, were found in cases with high *LYL1* expression.¹²

CLINICAL MANIFESTATIONS

The initial presentation of ALL usually is nonspecific and relatively brief. Anorexia, fatigue, and irritability often are present, as is an intermittent, low-grade fever. Bone or, less often, joint pain, particularly in the lower extremities, may be present. As the disease progresses, signs and symptoms of bone marrow failure become more obvious with

the occurrence of pallor, fatigue, bruising, or epistaxis, as well as fever, which may be caused by infection.

On physical examination, findings of pallor, listlessness, purpuric and petechial skin lesions, or mucous membrane hemorrhage may reflect bone marrow failure. The proliferative nature of the disease may be manifested as lymphadenopathy, splenomegaly, or, less commonly, hepatomegaly. In patients with bone or joint pain, there may be exquisite tenderness over the bone or objective evidence of joint swelling and effusion. Rarely, patients show signs of increased intracranial pressure that indicate leukemic involvement of the central nervous system (CNS). Patients may have cranial nerve palsies. Respiratory distress usually is related to anemia but may occur in patients with an obstructive airway problem due to a large anterior mediastinal mass (e.g. in the thymus or nodes). This problem is most typically seen in adolescent boys with T-cell ALL, especially with higher leukocyte count. CNS symptoms are seen at presentation in five percent of patients and testicular in 20 percent.

DIAGNOSIS

Peripheral blood abnormalities: Most children with ALL have anemia and/or thrombocytopenia with either normal or depressed WBC counts and lymphoblasts on peripheral smear. The lymphoblast count has to exceed 20 percent of leukocytes in peripheral blood and/or bone marrow. Approximately 50 percent of children have WBC counts $<10,000/\mu\text{L}$, and 20 percent have an initial leukocyte count $>50,000/\mu\text{L}$.¹³ These findings suggest the need for bone marrow examination, which should be performed for the following indications:

- Atypical cells in the peripheral blood
- Unexplained depression of more than one peripheral blood element
- Unexplained lymphadenopathy or hepatosplenomegaly associated with cytopenias.

The initial laboratory evaluation also includes assessment for possible disease complications. As an example, patients with a high tumor burden may have increased serum uric acid concentration, which can cause uric acid nephropathy and renal failure if not addressed before chemotherapy is started. The initial laboratory evaluation should include a complete blood count with manual differential, PT, PTT, electrolytes, uric acid, and renal and liver function tests. Baseline viral titers, including cytomegalovirus, Epstein-Barr virus, human immunodeficiency virus, hepatitis B virus, and varicella zoster virus often are included. Several abnormalities, including hepatic dysfunction, coagulation abnormalities, hypercalcemia, hypocalcemia, hyperkalemia, and hyperphosphatemia, may be noted.¹³

Flowcytometric immunophenotyping together with cytogenetics and molecular testing provides the prognostic information and influences selection of treatment.

DIFFERENTIAL DIAGNOSIS

Acute lymphoblastic leukemia must be differentiated from acute myelogenous leukemia (AML) other malignant diseases that invade the bone marrow and cause marrow failure include neuroblastoma, rhabdomyosarcoma, Ewing sarcoma, and retinoblastoma; and causes of primary bone marrow failure, such as aplastic anemia (congenital, acquired) and myelofibrosis. Failure of a single cell line, as in transient erythroblastic anemia, immune thrombocytopenia, and congenital or acquired neutropenia, sometimes produces a clinical picture that is difficult to distinguish from ALL and that may require bone marrow examination. A high index of suspicion is required to differentiate ALL from infectious mononucleosis in patients with acute onset of fever and lymphadenopathy and from rheumatoid arthritis in patients with fever and joint swelling. It may also mimic osteomyelitis and hypereosinophilic syndrome. These presentations also may require bone marrow examination.

PROGNOSIS

Presenting Features

Presenting clinicobiological features are commonly used to define subtypes of ALL with different risk of relapse. Presenting age and leukocyte count have prognostic strength in B-lineage but not T-lineage ALL. However, as many as 20 percent of patients with B-lineage ALL who are considered at lower risk of relapse by these criteria (e.g. age 1–9 years with leukocyte count more than $50 \times 10^9/\text{L}$) may relapse. Moreover, cases with a very high risk of relapse cannot be reliably distinguished by these criteria. For unclear reasons, boys have worse outcome than girls in many treatment protocols. As discussed earlier, primary genetic abnormalities of leukemic cells are excellent predictors of outcome but correlations are not perfect. For example, as many as 15 percent of children with favorable genetic features (*ETV6* – *RUNX1* fusion and hyperdiploidy >50 chromosomes) will eventually relapse, while approximately one-third of those with unfavorable genetic abnormalities (*BCR* – *ABL1* or *MLL* – *AF4*) can be cured with chemotherapy alone. It was shown that among patients with *BCR* – *ABL1*-positive ALL, age over 10 years or a high leukocyte count was associated with a poor outcome; in those with *MLL* – *AF4*-positive ALL, infant age group (<12 months) conferred a particularly poor outcome. Patients with ETP ALL have a dismal outcome with contemporary therapy irrespective of other presenting features.¹⁴

Minimal Residual Disease

A slow reduction of the leukemic cell burden by remission induction therapy is associated with a poor treatment outcome. Response to therapy, as assessed by morphological examination of bone marrow and peripheral blood smears, has limited sensitivity and accuracy. The advent of methods for detecting minimal residual disease (MRD), which are at least 100 times more sensitive than conventional morphological techniques, has introduced a profoundly new way to monitor response to treatment. The most reliable methods for measuring MRD include flow cytometric profiling of aberrant immunophenotypes, PCR amplification of fusion transcripts and chromosomal breakpoints, and PCR amplification of antigen receptor genes. The prognostic importance of MRD in childhood ALL has been unequivocally established by the results of numerous correlative studies. Investigators of the International Berlin – Frankfurt – Münster (I-BFM) Study Group found that the combined information about MRD on days 33 and 78 could identify three groups of patients with a significantly different outcome: 10-year EFS was 93 percent for patients who were MRD negative at both time points, 16 percent for patients with MRD of 0.1 percent or more at both time points, and 74 percent for the remaining patients. Investigators of the Children's Oncology Group reported that the presence of MRD (0.01% or higher) at the end of remission induction (day 29) was the strongest prognostic indicator, superior to other commonly used prognostic parameters in childhood ALL, and predicted both early and late relapses.¹⁵

Pharmacogenetic Variables

Mutations and polymorphisms of genes encoding several drug-metabolizing enzymes have been associated with response to therapy.¹⁶ The best-established association regards the thiopurine S-methyltransferase gene, which encodes the enzyme that catalyses the inactivation of mercaptopurine. Approximately 1 in 300 patients have an inherited homozygous deficiency of thiopurine S-methyltransferase and are therefore extremely sensitive to mercaptopurine. Both homozygous and heterozygous deficiencies are associated with a better EFS, likely due to higher dose intensity of mercaptopurine, but they also carry the increased risk of acute toxicities and a higher rate of irradiation – induced brain tumors and therapy-related acute myeloid leukemia. Hence, mercaptopurine dosages must be carefully adjusted in these patients, an approach that abrogated the clinical impact of these mutations. The null genotype for the glutathione S-transferase genes *GSTM1* or *GSTT1* and for *GSTP1* V105/V105 is also associated with increased treatment-related toxicity and a lower risk of relapse, perhaps because of reduced detoxification of cytotoxic chemotherapy. In one study, 16 polymorphisms in genes involved in drug metabolism,

including *GSTM1* and *TYMS* (thymidylate synthetase), were associated with treatment outcome, while polymorphisms in genes involved in folate metabolism, including those for methylenetetrahydrofolate reductase (*MTHFR*) and methionine synthase reductase (*MTRR*), affected methotrexate sensitivity *in vitro*. A study comparing the polymorphisms of 16 genes with functions related to treatment response to MRD levels on day 8 in blood and on day 28 in bone marrow found that the G allele of a common polymorphism in the gene for the chemokine receptor 5 (*CCR5*) was associated with better MRD clearance than the A allele; the molecular mechanisms underlying this association are unclear. Another study identified 102 SNPs associated with MRD, including 21 in genes associated with anti-leukemic drug disposition and five in the *IL15* gene. The mechanisms linking alterations in *IL15* and poor response to chemotherapy are also unclear but recall findings that *IL15* over-expression is associated with increased CNS involvement at diagnosis and CNS relapse in childhood ALL. Significantly higher concentrations of methylmercaptopurine nucleotides were found in patients with a non-functional allele of the gene for inosine triphosphate pyrophosphatase, which were associated with a higher probability of severe febrile neutropenia.

TREATMENT

Overview

The more successful contemporary clinical trials for children with newly diagnosed ALL have resulted in 5-year EFS rates ranging from 75 to 87 percent. The general treatment approach relies on three main phases: remission induction, intensification (consolidation) therapy, and continuation treatment along with the supportive treatment. In patients with mature B-cell ALL, regimens of intensive chemotherapy are typically shorter and based primarily on cyclophosphamide, methotrexate and cytarabine, resulting in cure rates of 74 to 87 percent. All patients require treatment for subclinical leukemia of the CNS, which should be initiated early in the form of intrathecal therapy.¹⁴

Remission Induction

Rates of complete remission (i.e. absence of leukemic cells detectable morphologically and restoration of normal hemopoiesis) currently range from 96 to 99 percent. Remission induction regimens typically include a glucocorticoid (prednisone, prednisolone or dexamethasone), vincristine and asparaginase, with or without one or more additional drugs (e.g. an anthracycline, cyclophosphamide). Intensification of induction therapy may achieve a more effective clearance of leukemic cells but it might not be necessary for patients lacking unfavorable

prognostic features and having a good early response, particularly if they receive post-induction intensification therapy. Intensified induction therapy may increase early morbidity and mortality. Because of its reported longer half-life and increased penetration into CSF, dexamethasone may be more effective than prednisone or prednisolone. Its use yielded an improved outcome in some trials but resulted in excessive life-threatening infections and septic deaths in another study. A small randomized study showed that an increased dose of prednisone produced results comparable to those achieved with dexamethasone in the context of other intensive treatment, suggesting dose rather than type of glucocorticoid influences treatment outcome. Most remission induction regimens include asparaginase. However, clinical trials limiting that use of asparaginase to the post-induction period yielded low morbidity (especially in terms of thrombotic complications) and excellent overall outcome. The currently available asparaginase for newly diagnosed patients is derived from *Escherichia coli* and there is a polyethylene glycol-bound form of the *E. coli* product (pegaspargase); asparaginase derived from *Erwinia chrysanthemi* is typically used in patients who have hypersensitivity reactions to *E. coli* product. Each type has a different half-life, pharmacokinetics and immunogenicity. In terms of antileukemic activity, the key issue is the amount of asparagine depletion achieved. Because of lower immunogenicity and less frequent administration, pegaspargase has become the first-line treatment in the USA and is also increasingly used in other childhood ALL trials worldwide.¹⁴

Intensification (Consolidation)

Patients who achieve remission typically receive intensification (also called consolidation) therapy. This consists of the same drug scheme used in the remission induction regimen or of a combination of drugs not previously used. Patients with different subtypes of leukemia may respond particularly well to certain intensification regimens. For example, patients with *ETV6 – RUNX1* had an especially good outcome in clinical trials featuring intensive postremission treatment with glucocorticoids, vincristine and asparaginase, while a very high dose of methotrexate (5 g/m²) improved treatment outcome of patients with T-cell ALL. Other regimens have not proven to be advantageous, such as high-dose intravenous mercaptopurine and high-dose cytarabine. Delayed intensification (or reinduction) is a widely used approach consisting of a repetition of the first remission induction therapy 3 months after the end of remission induction. Investigators at the Children's Cancer Group and of the Associazione Italiana Ematologia ed Oncologia Pediatrica (AIEOP) group reported that double delayed intensification improved patient outcome in patients with

intermediate risk. Extended and stronger intensification therapy also significantly benefited patients with high-risk ALL and slow response to initial induction therapy. While reinduction or delayed intensification therapy is probably beneficial to all patients, double or prolonged intensification appears to be beneficial primarily to those with features predicting a higher risk of relapse.¹⁴

Continuation Therapy

With the exception of patients with B-cell (surface immunoglobulin positive) ALL, all children with ALL require prolonged continuation treatment, which typically lasts for 2 to 2.5 years. Attempts to shorten its duration have led to inferior outcomes. Continuous uninterrupted therapy appears to be more effective than high-dose pulse therapy with prolonged rest periods to recover from myelosuppression. The classical components of continuation therapy are methotrexate and mercaptopurine, administered weekly and daily, respectively. Low systemic exposure to methotrexate and low dose intensity of mercaptopurine have been associated with an inferior outcome. Conversely, administration of doses gauged to produce the lowest tolerable neutrophil counts reportedly improved outcomes. Mercaptopurine is most effective when it is given orally daily and in the evening. In some studies, thioguanine appeared to have a superior antileukemic effect than mercaptopurine but its use at a daily dose above 40 mg/m² was associated with a higher rate of toxicities, such as profound thrombocytopenia and hepatic veno-occlusive disease. Studies have shown that adding intermittent pulses of vincristine and a glucocorticoid (prednisone or dexamethasone) to the methotrexate/mercaptopurine combination is beneficial.¹⁴

Prevention and Therapy of CNS Leukemia

The infiltration of the leptomeninges by leukemic cells poses a challenge because the blood-brain barrier provides a pharmacological sanctuary for leukemic cells and protects them from systemic therapy. Hence, cranial irradiation (12–24 Gy) and methotrexate administered intrathecally after induction of complete remission as a prophylactic measure to prevent CNS leukemia has become a key feature of childhood ALL treatment since the 1970s. Cranial irradiation can cause serious side effects and a reduction of the radiation dose to a less harmful 12 Gy appeared to provide adequate protection against CNS relapse. A recent study at St Jude Children's Research Hospital tested the feasibility of total omission of prophylactic cranial irradiation.¹⁷ The 5-year survival rate for the 498 patients enrolled was 93.5 percent and the cumulative risk of an isolated CNS relapse rate was only 2.7 percent, demonstrating that cranial irradiation can be avoided in the context of effective risk-adapted intrathecal and

systemic chemotherapy. Intensive systemic and intrathecal treatment, without cranial irradiation, appears to provide adequate CNS prophylaxis. Therefore, most investigators now treat infants without cranial irradiation. Importantly, patients with an isolated CNS relapse have a very high retrieval rate if they did not receive cranial irradiation as CNS prophylaxis. Systemic treatment including high-dose methotrexate, intensive asparaginase, and dexamethasone as well as optimal intrathecal therapy are essential to control CNS leukemia. Intrathecal therapy should be intensified in patients with detectable ALL blasts in the CSF (even because of traumatic lumbar puncture) as this finding carries an increased risk of CNS relapse and inferior overall outcome.

Allogeneic Hemopoietic Stem Cell Transplantation

Patients with the *BCR-ABL1* gene fusion, ETP ALL, poor early response or early hematological relapse are the more frequent candidates for transplantation. Nevertheless, the indications for transplantation should be continuously reviewed as treatment improves and new agents become available. For example, the use of imatinib and other tyrosine kinase inhibitors has dramatically improved early treatment response in patients with *BCR-ABL1*-positive ALL, questioning whether transplantation in first remission should be recommended in these cases.

Transplantation has not been shown to improve outcome of other subtypes of very high risk leukemia, including infant cases and those with *MLL* rearrangement. Levels of MRD prior to transplant predict the risk of relapse after transplant. In patients receiving T-cell-depleted grafts, high levels of MRD PCR positivity (0.1–1%) before transplant were consistently associated with relapse after transplant, and patients with lower levels of MRD had a 2-year EFS of 35 to 50 percent compared with 70 percent for MRD-negative patients.¹⁴

Treatment Sequel

Improvements in supportive care have reduced the early death rate to less than 2 percent. Remission induction therapy including prednisone, vincristine and asparaginase causes hyperglycemia in 10 to 20 percent of patients, particularly adolescents and patients with obesity, a family history of diabetes mellitus or Down syndrome. The same induction regimen can also lead to a hypercoagulable state in 3 to 5 percent of patients, promoting cerebral and/or peripheral vein thromboses. The intensified use of methotrexate and glucocorticoids has been associated with an increased frequency of neurotoxicity and osteonecrosis. High cumulative doses of anthracyclines can produce severe cardiomyopathy, especially in young children. Cranial irradiation may cause second neoplasms within the irradiated field, as well as neuropsychological deficits and endocrine

abnormalities, leading to obesity, short stature, precocious puberty and osteoporosis.

Relapse

Leukemia relapse may occur during or after treatment, usually within 2 years after cessation of therapy but occasionally later. The bone marrow remains the most common site of relapse, while the frequency of relapse in extramedullary sites, such as the CNS and testes, has steadily decreased. Even when extramedullary relapse appears to be an isolated event, it is often associated with submicroscopic residual disease in the bone marrow. Bone marrow relapse, with or without extramedullary involvement, is associated with a poor outcome. Paradoxically, patients with isolated bone marrow relapse generally do worse than those with combined bone marrow and extramedullary relapse. In children with relapsed ALL, adverse risk factors include short initial remission, T-cell immunophenotype, *BCR-ABL1* ALL, presence of circulating blast cells or a high leukocyte count at relapse. The presence of MRD at the end of second remission induction is a strong adverse prognostic indicator. Chemotherapy may be sufficient to induce prolonged second remissions in patients without high-risk features but allogeneic hemopoietic stem cell transplantation is a reasonable treatment option for the remaining patients, particularly those who experience hematological relapse during therapy or shortly thereafter, those with T-cell ALL, and those with persistent MRD.¹⁴

Concluding Remarks

The current cure rates for children with ALL demonstrate the remarkable progress that has been made in treating this disease through improvements in risk classification, chemotherapy, transplantation and supportive care. Classification of ALL into prognostically meaningful subtypes defined by clinical presenting features and genetic abnormalities of the leukemic cells is well established. The uncovering of new genetic lesions in leukemic lymphoblasts using novel screening techniques and the definition of their prognostic significance should further improve risk classification. Genome-wide expression profiling studies may also facilitate the discovery of molecules that critically influence drug resistance. The development of robust MRD assays and the understanding of the clinical significance of MRD have opened a new approach to monitoring the response to treatment and have introduced a new concept of 'remission'. MRD assays have been incorporated into many major treatment protocols and are now an integral part of the modern management of childhood ALL. Simplification of MRD methods should widen the application of this powerful prognostic parameter, and extend its potential benefits to most patients, including

those living in areas with limited resources. Further progress in optimizing intensity of treatment for each patient is coming from a better understanding of the relation between pharmacogenomic features and responses to chemotherapy, which should lead to significant refinements of treatment schedules and dosages. Despite these remarkable improvements, standard chemotherapy still produces low cure rates for patients with some subtypes of ALL, such as infants with *MLL* rearrangement and those with ETP ALL; for these patients, substantial improvements can only come from the development of new treatment modalities. Imatinib mesylate and other ABL kinase inhibitors are the paradigm of molecular therapy of leukemia. Other novel agents include inhibitors of *FLT3*, farnesyl transferase, proteasome, DNA methylation and histone deacetylase. Nucleoside analoges of more recent generation, such as gemcitabine, clofarabine and nelarabine, have shown promise. The application of gene expression-based drug screening might facilitate the identification of new effective compounds, while the detailed understanding of the cooperating genetic abnormalities associated with ALL could identify new targets.

Immunotherapeutic options are progressively emerging. Rituximab (anti-CD20), alemtuzumab (anti-CD52) and epratuzumab (anti-CD22) have already been incorporated into some clinical trials. In the context of hemopoietic stem cell transplantation, donors can be selected so that their natural killer (NK) cells can exert maximum cytotoxicity against the leukemic cells of the host, and infusions of haploidentical NK cells are being evaluated.

For many decades, oncologists have been familiar with the concept that pharmacological sanctuaries (e.g. the CNS) contribute to protect leukemic cells from chemotherapy. More recent evidence indicates that the bone marrow microenvironment can also antagonize the effects of chemotherapy. For instance, bone marrow mesenchymal cells protect ALL cells from asparaginase cytotoxicity by forming an asparagines rich microenvironment, suggesting a scenario whereby ALL cells that reside in mesenchymal cell niches become relatively resistant to chemotherapy. Because agents that interfere with the interaction between ALL and mesenchymal cells are available for clinical use, it should be possible to design protocols that attempt to improve chemotherapy effectiveness by mobilizing ALL cells.¹⁴

MYELOID LEUKEMIAS IN CHILDREN

The myeloid leukemias in childhood represent a spectrum of hematopoietic malignancies. More than 90 percent of myeloid leukemias are acute and the remainder includes chronic and/or subacute myeloproliferative disorders such as CML and JMML. Myelodysplastic syndromes represent less than five percent of myeloid malignancies in children.

ACUTE MYELOGENOUS LEUKEMIA

Epidemiology

AML accounts for 11 percent of the cases of childhood leukemia in the USA, with approximately 370 children diagnosed with AML annually. Several chromosomal abnormalities associated with AML have been identified, but no predisposing genetic or environmental factors can be identified in most patients. Nonetheless, a number of risk factors have been identified, including ionizing radiation, chemotherapeutic agents (e.g. alkylating agents, epipodophyllotoxin), organic solvents, paroxysmal nocturnal hemoglobinuria, and certain syndromes: Down syndrome, Fanconi anemia, Bloom syndrome, Kostmann syndrome, Shwachman-Diamond syndrome, Diamond-Blackfan syndrome, Li-Fraumeni syndrome, and neurofibromatosis type 1.

Classification

World Health Organization (WHO) Classification System

In 2008, WHO expanded the number of cytogenetic abnormalities linked to AML classification, and for the first time included specific gene mutations (*CEBPA* and *NPM* mutations) in its classification system. Such a genetically based classification system links AML class with outcome and provides significant biologic and prognostic information.¹⁸

WHO Classification of AML

- AML with recurrent genetic abnormalities:
 - AML with t(8;21)(q22;q22), *RUNX1-RUNX1T1* (*CBFA/ETO*)
 - AML with inv (16)(p13;q22) or t(16;16)(p13;q22), *CBFB-MYH11*
 - Acute promyelocytic leukemia with t(15;17)(q22;q11-12), *PML-RARα*
 - AML with t(9;11)(p22;q23), *MLLT3-MLL*
 - AML with t(6;9)(p23;q34); *DEK-NUP214*
 - AML with inv(3)(q21;q26.2) or t(3;3)(q21;q26.2), *RPN1-EVI1*
 - AML (megakaryoblastic) with t(1;22)(p13;q13), *RBM15-MKL1*
 - AML with mutated *NPM1*
 - AML with mutated *CEBPA*
- AML with myelodysplasia-related features
- Therapy-related myeloid neoplasms
- AML, not otherwise specified:
 - AML with minimal differentiation
 - AML without maturation
 - AML with maturation
 - Acute myelomonocytic leukemia
 - Acute monoblastic and monocytic leukemia
 - Acute erythroid leukemia
 - Acute megakaryoblastic leukemia
 - Acute basophilic leukemia

- Acute panmyelosis with myelofibrosis
- Myeloid sarcoma
- Myeloid proliferations related to Down syndrome:
 - Transient abnormal myelopoiesis
 - Myeloid leukemia associated with Down syndrome.
- Blastic plasmacytoid dendritic cell neoplasm.

Immunophenotypic Classification

Various lineage-specific monoclonal antibodies that detect antigens on AML cells should be used at the time of initial diagnostic workup, along with a battery of lineage-specific T-lymphocyte and B-lymphocyte markers to help distinguish AML from ALL and bilineal (as defined above) or biphenotypic leukemias. The expression of various CD proteins that are relatively lineage-specific for AML include CD33, CD13, CD14, CDw41 (or platelet antigen glycoprotein IIb/IIIa), CD15, CD11b, CD36, and antigen glycoprotein A (Fig. 3). Lineage-associated B-lymphocytic antigens CD10, CD19, CD20, CD22, and CD24 may be present in 10 to 20 percent of AMLs, but monoclonal surface immunoglobulin and cytoplasmic immunoglobulin heavy chains are usually absent; similarly, CD2, CD3, CD5, and CD7 lineage-associated T-lymphocytic antigens are present in 20 to 40 percent of AMLs.¹⁹ The aberrant expression of lymphoid-associated antigens by AML cells is relatively common but generally has no prognostic significance.¹⁹

Immunophenotyping can also be helpful in distinguishing some FAB subtypes of AML. Testing for the presence of HLA-DR can be helpful in identifying APL. Overall, HLA-DR is expressed on 75 to 80 percent of AMLs but rarely expressed on APL. The absence of HLA-DR, CD11b, CD11c pattern is highly suggestive of APL. Testing for the presence of glycoprotein Ib, glycoprotein IIb/IIIa, or Factor VIII antigen expression is helpful in making the diagnosis of M7 (megakaryocytic leukemia). Glycophorin expression is helpful in making the diagnosis of M6 (erythroid leukemia).

CYTOGENETIC EVALUATION AND MOLECULAR ABNORMALITIES

Chromosomal analyses of leukemia should be performed on children with AML because chromosomal abnormalities are important diagnostic and prognostic markers.²⁰ Clonal chromosomal abnormalities have been identified in the blasts of about 75 percent of children with AML and are useful in defining subtypes with particular characteristics (e.g. t(8;21) with M2, t(15;17) with M3, inv(16) with M4 Eo, 11q23 abnormalities with M4 and M5, t(1;22) with M7). Leukemias with the chromosomal abnormalities t(8;21) and inv(16) are called core-binding factor leukemias; core-binding factor (a transcription factor involved in hematopoietic stem cell differentiation) is disrupted by each of these abnormalities.

Molecular probes and newer cytogenetic techniques (e.g. fluorescence *in situ* hybridization (FISH) can detect cryptic abnormalities that were not evident by standard cytogenetic banding studies. This is clinically important when optimal therapy differs, as in APL.

Specific Recurring Cytogenetic and Molecular Abnormalities

- *t(8;21)*: In leukemias with t(8;21), the *AML1 (RUNX1, CBEA2)* gene on chromosome 21 is fused with the *ETO* gene on chromosome 8. The t(8;21) translocation is associated with the FAB M2 subtype and with granulocytic sarcomas. Adults with t(8;21) have a more favorable prognosis than adults with other types of AML. Several reports describe a more favorable outcome for children with t(8;21) AML compared with children with AML characterized by normal or complex karyotypes.²¹
- *inv(16)*: In leukemias with inv(16), the *CBF* beta gene at chromosome band 16q22 is fused with the *MYH11* gene at chromosome band 16p13. The inv(16) translocation is associated with the FAB M4Eo subtype. Inv(16) confers a favorable prognosis for both adults and children with AML.²¹
- *t(15;17)*: AML with t(15;17) is invariably associated with APL, a distinct subtype of AML that is treated differently than other types of AML because of its marked sensitivity to the differentiating effects of all-trans retinoic acid. The t(15;17) translocation leads to the production of a fusion protein involving the retinoid acid receptor alpha and PML.²² Other much less common translocations involving the retinoic acid receptor alpha can also result in APL (e.g. t[11;17] involving the *PLZF* gene).²³ Identification of cases with the t(11;17) is important because of their decreased sensitivity to all-trans retinoic acid.²³
- *MLL gene rearrangements*: Translocations of chromosomal band 11q23 involving the *MLL* gene are associated with monocytic differentiation (FAB M4 and M5). The most common translocation, representing approximately 50 percent of *MLL*-rearranged cases in the pediatric AML population, is t(9;11)(p22;q23) in which the *MLL* gene is fused with the AF9 gene.²⁴ However, more than 50 different fusion partners have been identified for the *MLL* gene in patients with AML. The median age for 11q23/*MLL*-rearranged cases in the pediatric AML setting is approximately 2 years and most translocation subgroups have a median age at presentation of less than 5 years.²⁴

As the *MLL* gene can participate in translocations with many different fusion partners, the specific fusion partner appears to influence prognosis for e.g. t(1;11)(q21;q23) is associated with favorable prognosis, t(10;11) and t(6;11)(q27;q23) are associated with

Myeloid-1

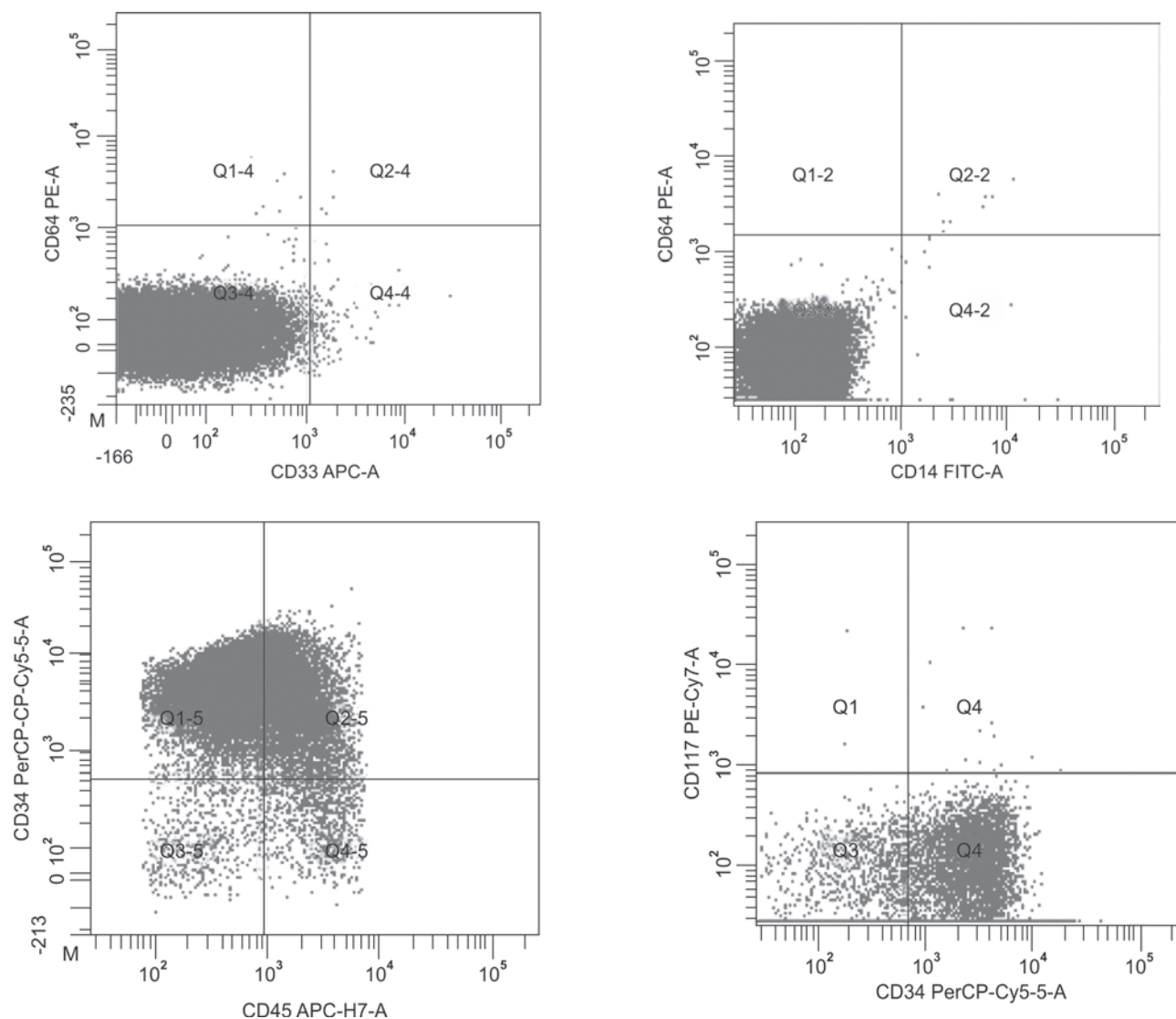


Fig. 3: Flow cytometric immunophenotyping of acute myeloid leukemia

inferior survival while as studies on t(9;11) have given variable results.

- *t(6;9)*: Leads to the formation of a leukemia-associated fusion protein DEK-NUP214.²⁵ This subgroup of AML has been associated with a poor prognosis.²⁵
- *Abnormalities with chromosomes 3, 5, and 7*: Chromosomal abnormalities associated with poor prognosis in adults with AML include those involving chromosome 7 (monosomy 7), chromosome 5 (monosomy 5 and del[5q]), and the long arm of chromosome 3 (inv[3][q21;q26] or t[3;3][q21;q26]).²⁶ These cytogenetic subgroups are also associated with poor prognosis in children with AML, though abnormalities of the long arm of chromosomes 3 and 5 are extremely rare in pediatric patients.²⁶

- *t(1;22)*: The t(1;22)(p13;q13) translocation is restricted to AMKL and occurs in as many as one-third of AMKL cases in children.²⁷ Most AMKL cases with t(1;22) occur in infants, and the translocation is uncommon in children with Down syndrome who develop AMKL. In leukemias with t(1;22), the OTT (*RBM15*) gene on chromosome 1 is fused to the *MAL* (*MLK1*) gene on chromosome 22. In the small number of children reported, the presence of the t(1;22) appears to be associated with poor prognosis, though long-term survivors have been noted following intensive therapy.
- *12p abnormalities*: The presence of 12p abnormalities has been reported to be associated with a significantly worse prognosis.²⁸

- *FLT3 mutations*: Presence of a *FLT3* internal-tandem duplication (ITD) mutation appears to be associated with poor prognosis in adults with AML,²⁹ particularly when both alleles are mutated or there is a high ratio of the mutant allele to the normal allele. *FLT3*-ITD mutations also convey a poor prognosis in children with AML. The frequency of *FLT3*-ITD mutations in children is lower than that observed in adults, especially for children younger than 10 years, for whom 5 to 10 percent of cases have the mutation (compared with approximately 30 percent for adults). Activating point mutations of *FLT3* have also been identified in both adults and children with AML, though the clinical significance of these mutations is not clearly defined. *FLT3*-ITD and point mutations occur in 30 to 40 percent of children and adults with APL.³⁰ Presence of the *FLT3*-ITD mutation is strongly associated with the microgranular variant (M3v) of APL and with hyperleukocytosis.³⁰ It remains unclear whether *FLT3* mutations are associated with poorer prognosis in patients with APL who are treated with modern therapy that includes all-trans retinoic acid.
- *RAS and other tyrosine kinase receptor mutations (e.g. c-KIT)*: Although mutations in *RAS* have been identified in approximately 25 percent of patients with AML, the prognostic significance has not been clearly shown. A report in adults has suggested that AML characterized by *RAS* mutations has increased sensitivity to cytarabine and benefits more from higher cytarabine doses than does wild-type *RAS*.³¹ Mutations in *c-KIT* occur in less than five percent of AML, but in 10 to 40 percent of AML with core-binding factor abnormalities. The presence of activating *c-KIT* mutations in adults with this subgroup of AML appears to be associated with a poorer prognosis compared with core-binding factor AML without *c-KIT* mutation.³² The prognostic significance of *c-KIT* mutations occurring in pediatric core-binding factor AML remains unclear.³³
- *GATA1 mutations*: *GATA1* mutations are present in most, if not all, Down syndrome children with either transient myeloproliferative disease or AMKL. *GATA1* mutations are not observed in non-Down syndrome children with AMKL or in Down syndrome children with other types of leukemia. *GATA1* is a transcription factor that is required for normal development of erythroid cells, megakaryocytes, eosinophils, and mast cells. *GATA1* mutations confer increased sensitivity to cytarabine by down-regulating cytidine deaminase expression, possibly providing an explanation for the superior outcome of children with Down syndrome and M7 AML when treated with cytarabine-containing regimens.³⁴
- *Nucleophosmin (NPM1) mutations*: *NPM1* is a protein that has been linked to ribosomal protein assembly and transport as well as being a molecular chaperone involved in preventing protein aggregation in

the nucleolus. Immunohistochemical methods can be used to accurately identify patients with *NPM1* mutations by the demonstration of cytoplasmic localization of *NPM*. Mutations in the *NPM1* protein that diminish its nuclear localization are primarily associated with a subset of AML with a normal karyotype, absence of CD34 expression, and an improved prognosis in the absence of *FLT3*-ITD mutations in adults and younger adults.³⁵ Preliminary studies of children with AML suggest a lower rate of occurrence of this mutation in children compared with adults with normal cytogenetics.³⁶ *NPM1* mutations have been reported to occur in approximately 8 percent of pediatric patients with AML and are associated with a favorable prognosis.

- *CEBPA mutations*: Mutations in the CCAAT/Enhancer Binding Protein Alpha gene (*CEBPA*) occur in a subset of children and adults with cytogenetically normal AML. *CEBPA* mutations occur in approximately 5 percent of children with AML and have been preferentially found in the cytogenetically normal subtype of AML; approximately 80 percent of pediatric patients have double mutant alleles and these mutations have been shown to predict a significantly improved survival, similar to adult studies.³⁷
- *WT1 mutations*: *WT1*, a zinc-finger protein regulating gene transcription, is mutated in approximately 10 percent of cytogenetically normal cases of AML in children.³⁸ In univariate analyses, *WT1* mutations are predictive of poorer outcome in pediatric patients, but the independent prognostic significance of *WT1* mutation status is unclear because of its strong association with *FLT3*-ITD.³⁸ The largest study of *WT1* mutations in children with AML observed that children with *WT1* mutations in the absence of *FLT3*-ITD had outcomes similar to that of children without *WT1* mutations, while children with both *WT1* mutation and *FLT3*-ITD had survival rates less than 20 percent.³⁸

PROGNOSTIC FACTORS IN CHILDHOOD ACUTE MYELOID LEUKEMIA

Prognostic factors in childhood AML have been identified and can be categorized as follows:

- *Age*: Several reports published since 2000 have identified older age as being an adverse prognostic factor.³⁹ The age effect is not large, but there is consistency in the observation that adolescents have a somewhat poor outcome than younger children.
- *Race/Ethnicity*: In both the Children's Cancer Group (CCG) CCG-2891 and COG-2961 (CCG-2961) studies, Caucasian children had higher overall survival (OS) rates than African American and Hispanic children.⁴⁰
- *Down syndrome*: For children with Down syndrome who develop AML, outcome is generally favorable.

The prognosis is particularly good (event-free survival exceeding 80%) in children aged 4 years or younger at diagnosis, the age group that accounts for the vast majority of Down syndrome patients with AML.⁴¹

- *Body mass index (BMI):* In the COG-2961 study, obesity (BMI more than 95th percentile for age) was predictive of inferior survival.⁴²
- *White blood cell (WBC) count:* WBC count at diagnosis has been consistently noted to be inversely related to survival.⁴³
- *FAB subtype:* Associations between FAB subtype and prognosis have been more variable. The M3 (APL) subtype has a favorable outcome in studies utilizing all-trans retinoic acid in combination with chemotherapy.⁴⁴ Some studies have indicated a relatively poor outcome for M7 (megakaryocytic leukemia) in patients without Down syndrome,⁴⁵ though reports suggest an intermediate prognosis for this group of patients when contemporary treatment approaches are used.⁴⁶ The M0, or minimally differentiated subtype, has been associated with a poor outcome.⁴⁷
- *CNS disease:* The presence of CNS disease at diagnosis has not been shown to affect OS; however, it may be associated with an increased risk of isolated CNS relapse.⁴⁸
- *Cytogenetic and molecular characteristics:* Cytogenetic and molecular characteristics are also associated with prognosis as given in Table 3.
- *Response to therapy/minimal residual disease (MRD):* Early response to therapy, generally measured after the first course of induction therapy, is predictive of outcome and can be assessed either by standard morphologic examination of bone marrow, by cytogenetic analysis or by more sophisticated techniques to

identify minimal residual disease (MRD).⁴⁹ Multiple groups have shown that the level of MRD after one course of induction therapy is an independent predictor of prognosis.⁴⁹

Risk Classification Systems Under Clinical Evaluation

While the optimal manner in which to utilize MRD to risk stratify treatment has not been determined, the next COG trial for newly diagnosed patients with AML will use the combination of MRD status as well as cytogenetic and molecular information to risk stratify patients into two groups. Thus, the low-risk AML group will include mutations involving *CBF*, *CEBPA*, *NPM*, and those with no MRD at end of induction therapy; this group of patients represents about 73 percent of patients and has a predicted OS of approximately 75 percent. In contrast, the high-risk AML group represents the remaining 27 percent of patients and has a predicted OS less than 35 percent; this group includes patients with adverse cytogenetic abnormalities, such as monosomy 7, del(5q)-, -5, high *FLT3*-ITD to wild-type allelic ratio, or MRD at the end of induction. The high-risk group of patients will be offered transplantation in first remission with the most appropriate available donor. Patients in the low-risk group will only be offered transplantation in second complete remission.⁵⁰

CLINICAL MANIFESTATIONS

The production of symptoms and signs of AML, as in ALL, is due to replacement of bone marrow by malignant cells and to secondary bone marrow failure. Thus, patients with AML may present with any or all of the findings associated with marrow failure in ALL. In addition, patients with AML present with signs and symptoms that are uncommon in ALL, including subcutaneous nodules or “blueberry muffin” lesions, infiltration of the gingiva, signs and laboratory findings of disseminated intravascular coagulation (especially indicative of acute promyelocytic leukemia), and discrete masses, known as chloromas or granulocytic sarcomas. These masses may occur in the absence of apparent bone marrow involvement and typically are associated with the M2 subcategory of AML with a t(8;21) translocation. Chloromas also may be seen in the orbit and epidural space. CNS symptoms are more common in AML than ALL.

DIAGNOSIS

Analysis of bone marrow aspiration and biopsy specimens of patients with AML typically reveals the features of a hypercellular marrow consisting of a rather monotonous pattern of blast cells with features that permit FAB subclassification of disease. Diagnosis of AML requires 20 percent blasts or less than 20 percent in case of t(8;21), Inv16 or t(15;17). Special stains assist in identification of myeloperoxidase-containing cells, thus confirming both

Table 3: Risk stratification based on cytogenetic and molecular characteristics

Risk Status	Cytogenetics	Molecular Abnormalities
Better risk	Inv 16 t(8;21) t(15;17)	Normal cytogenetics: with <i>NPM1</i> mutation or isolated <i>CEBPA</i> mutation in the absence of <i>FLT3</i> t(8;21), inv(16) with <i>c-kit</i> mutation Normal cytogenetics: with <i>FLT3</i> -ITD mutation in the absence of <i>NPM1</i> mutation
Intermediate risk	Normal cytogenetics +8 t(9;11) other nondefined	
Poor risk	Complex (≥3 abnormal clones) -5, 5q-, -7, 7q- 11q23-non t(9;11) Inv(3) t(6;9) t(9;22)	

the myelogenous origin of the leukemia and the diagnosis. Then the chromosomal abnormalities and molecular genetic markers define the specific subtypes of disease.

TREATMENT OF NEWLY DIAGNOSED ACUTE MYELOID LEUKEMIA

Overall survival (OS) rates have improved over the past three decades for children with AML, with 5-year survival rates now in the 55 to 65 percent range.⁵¹ Overall remission induction rates are approximately 85 to 90 percent, and event-free survival (EFS) rates from the time of diagnosis are in the 45 to 55 percent range.⁵¹ Treatment is ordinarily divided into two phases:

1. induction (to attain remission)
2. post-remission consolidation/intensification

Induction Chemotherapy

Contemporary pediatric AML protocols result in 85 to 90 percent complete remission rates.⁵² Of those patients who do not go into remission, about one-half have resistant leukemia and one-half die from the complications of the disease or its treatment. To achieve a complete remission (CR), inducing profound bone marrow aplasia (with the exception of the M3 APL subtype) is usually necessary. Because induction chemotherapy produces severe myelosuppression, morbidity and mortality from infection or hemorrhage during the induction period may be significant.

The two most effective drugs used to induce remission in children with AML are cytarabine and an anthracycline. Commonly used pediatric induction therapy regimens use cytarabine and an anthracycline in combination with other agents such as etoposide and/or thioguanine.⁵² The anthracycline that has been most used in induction regimens for children with AML is daunorubicin, though idarubicin and the anthracenedione mitoxantrone have also been used.

Central Nervous System Prophylaxis for Acute Myeloid Leukemia

Although the presence of CNS leukemia at diagnosis (i.e. clinical neurologic features and/or leukemic cells in cerebrospinal fluid on cytocentrifuge preparation) is more common in childhood AML than in childhood acute lymphoblastic leukemia (ALL), survival is not adversely affected.⁵³ This finding is perhaps related to both the higher doses of chemotherapy used in AML (with potential crossover to the CNS) and the fact that marrow disease has not yet been as effectively brought under long-term control in AML as in ALL. Children with M4 and M5 AML have the highest incidence of CNS leukemia (especially those with inv[16] or 11q23 chromosomal abnormalities). The use of some form of CNS-directed treatment

(intrathecal chemotherapy with or without cranial irradiation) is now incorporated into most protocols for the treatment of childhood AML and is considered a standard part of the treatment for AML.

GRANULOCYTIC SARCOMA CHLOROMA

Granulocytic sarcoma (GS) (chloroma), describes extramedullary collections of leukemia cells. These collections can occur, albeit rarely, as the sole evidence of leukemia. The patient who presents with an isolated tumor, without evidence of marrow involvement, must be treated as if there is systemic disease. Patients with isolated GS have a good prognosis if treated with current AML therapy. Many of these patients have t(8;21) with orbital myeloblastomas. The use of radiation therapy does not improve survival in patients with GS who have a complete response to chemotherapy, but may be necessary if the site(s) of GS do not show complete response to chemotherapy, or for disease that recurs locally.⁵⁴

Post-remission Therapy for Acute Myeloid Leukemia

A major challenge in the treatment of children with acute myeloid leukemia (AML) is to prolong the duration of the initial remission with additional chemotherapy or hematopoietic stem cell transplantation (HSCT). In practice, most patients are treated with intensive chemotherapy after remission is achieved, as only a small subset have a matched-family donor (MFD). Such therapy includes the drugs used in induction and often includes high-dose cytarabine. Studies in adults with AML have demonstrated that consolidation with a high-dose cytarabine regimen improves outcome compared with consolidation with a standard-dose cytarabine regimen, particularly in patients with inv(16) and t(8;21) AML subtypes.⁵⁵ Randomized studies evaluating the contribution of high-dose cytarabine to postremission therapy have not been conducted in children, but studies employing historical controls suggest that consolidation with a high-dose cytarabine regimen improves outcome compared with less intensive consolidation therapies. The optimal number of post-remission courses of therapy remains unclear, but appears to require at least three courses of intensive therapy, including the induction course.⁵⁶

The use of HSCT in first remission has been under evaluation since the late 1970s. Prospective trials of transplantation in children with AML suggest that 60 to 70 percent of children with HLA-matched donors available who undergo allogeneic HSCT during their first remission experience long-term remissions.⁵⁷ Prospective trials of allogeneic HSCT compared with chemotherapy and/or autologous HSCT have demonstrated a superior outcome for patients who were assigned to allogeneic transplantation based on availability of a family 6/6 or 5/6 HLA-matched donor.⁵⁷ Several large cooperative group clinical

trials for children with AML have found no benefit for autologous HSCT over intensive chemotherapy.⁵⁷

Because of the improved outcome in patients with favorable prognostic features receiving contemporary regimens, it is now recommended that this group of patients receive an MFD HSCT only after first relapse and the achievement of a second complete remission (CR).⁵⁸ While there is a clear movement away from CR1 transplantation using matched family donors in pediatric patients with AML that has favorable prognostic features, there is evidence suggesting an advantage for allogeneic HSCT in patients with intermediate-risk characteristics. A large intent-to-treat analysis of 472 young adults treated on Bordeaux Grenoble Marseille Toulouse (BGMT) studies showed a survival benefit from allogeneic HSCT in intermediate-risk patients (all patients not favorable or unfavorable), while patients with favorable risk disease [M3, t(8;21), or inv(16)] did not appear to benefit. Of note, there were insufficient numbers in the study to determine whether patients with unfavorable-risk disease [complex karyotype (≥ 5 cytogenetic findings), del(5q), monosomy 5 or 7, 3q rearrangements, t(9;22), t(6;9), or 11q23 rearrangements, except t(9;11)] benefit from this approach.⁵⁹ Because definitions of high-, intermediate-, and low-risk patients are evolving due to the ongoing association of molecular characteristics of the tumor with outcome (i.e. *FLT-3* internal tandem duplications, *WT1* mutations, etc.), further analysis of subpopulations of patients treated with allogeneic HSCT will be an ongoing need in current and future clinical trials. Based on a published retrospective study of 95 children who received unrelated cord blood (UCB) transplantation for AML, the Eurocord Group is recommending UCB transplantation for children who have very poor prognosis AML and who lack an HLA-identical sibling. Poor-risk AML was defined as that having cytogenetics with any of the following abnormalities: monosomy 5 and 7, del(5q), 11q23 abnormalities other than t(9;11), abnormal 3q, t(6;9), or complex karyotypes.⁶⁰

Maintenance chemotherapy has been shown to be effective in the treatment of acute promyelocytic leukemia (APL).⁶¹ In other subtypes, there are no data that demonstrate that maintenance therapy given after intensive post-remission therapy significantly prolongs remission duration.

ACUTE PROMYELOCYTIC LEUKEMIA

The characteristic chromosomal abnormality associated with APL is t(15;17) which leads to production of the promyelocytic leukemia/retinoic acid receptor alpha (PML/RARA) fusion protein. Clinically, APL is commonly characterized by a severe coagulopathy often present at the time of diagnosis. Mortality during induction (with cytotoxic agents) due to bleeding complications is more common in this subtype. Because of the extremely low incidence of

central nervous system disease in patients with APL, a lumbar puncture is not required at the time of diagnosis and prophylactic intrathecal chemotherapy is not administered.

APL in children is generally similar to APL in adults, though children have a higher incidence of hyperleukocytosis (defined as white blood cell [WBC] count higher than $10 \times 10^9/L$) and a higher incidence of the microgranular morphologic subtype. Similar to adults, children with WBC count less than $10 \times 10^9/L$ at diagnosis have significantly better outcome than patients with higher WBC count.

The leukemia cells from patients with APL are especially sensitive to the differentiation-inducing effects of all-trans retinoic acid (ATRA). The basis for the dramatic efficacy of ATRA against APL is the ability of pharmacologic doses of ATRA to overcome the repression of signaling caused by the PML/RARA fusion protein at physiologic ATRA concentrations. Restoration of signaling leads to differentiation of APL cells and then to postmaturation apoptosis. Most patients with APL achieve a complete remission (CR) when treated with ATRA, though single-agent ATRA is generally not curative. For children with APL, survival rates exceeding 80 percent are now achievable using treatment programs that prescribe the rapid initiation of ATRA and appropriate supportive care measures.⁶²

Molecular variants of APL produce fusion proteins that join distinctive gene partners (e.g. PLZF, NPM, STAT5B, and NuMA) to RARA. Recognition of these rare variants is important as they differ in their sensitivity to ATRA and to arsenic trioxide. The PLZF-RARA variant has been associated with a poor prognosis and does not usually respond to ATRA or to arsenic trioxide. The rare APL variants with NPM-RARA (t[5;17][q35;q21]) or with NuMA-RARA (t[11;17][q13;q21]) translocations are responsive to ATRA.

The standard approach to treating children with APL utilizes induction therapy with ATRA, in conjunction with standard-dose cytarabine and daunorubicin, followed by consolidation therapy with ATRA and daunorubicin. Maintenance therapy, includes ATRA plus 6-mercaptopurine and methotrexate; this combination showed an advantage over ATRA alone in randomized trials in adults. European clinical trials groups (Gruppo Italiano Malattie Ematologiche Maligne dell' Adulto–Associazione Italiana Ematologia ed Oncologia Pediatrica [GIMEMA–AIEOP] and Programa de Estudio y Tratamiento de las Hemopatías Malignas [PETHEMA]) have utilized idarubicin and ATRA without cytarabine for remission induction in children with APL.⁶³ Subsequent therapies for these groups include treatment courses with an anthracycline (idarubicin and mitoxantrone) plus ATRA (PETHEMA) or treatment courses with an anthracycline, ATRA, and other agents (GIMEMA–AIEOP), with both groups utilizing maintenance therapy as described above. Because of the favorable outcomes observed with chemotherapy plus

ATRA (EFS rates of 70–80%), hematopoietic stem cell transplantation (HSCT) is not recommended in first CR.

Arsenic trioxide has also been identified as an active agent in patients with APL. Approximately 85 percent of patients in relapse achieve morphologic remission following treatment with this agent.⁶⁴ Arsenic trioxide is well tolerated in children with relapsed APL. The combination of arsenic trioxide and ATRA might achieve quicker CR, but OS is not affected. A report on 19 children treated with arsenic alone for newly diagnosed APL showed EFS of 73 percent and OS of 84 percent at 5 years.

CHILDREN WITH DOWN SYNDROME

Children with Down syndrome have an increased risk of leukemia with a ratio of acute lymphoblastic leukemia to acute myeloid leukemia (AML) typical for childhood acute leukemia. The exception is during the first 3 years of life, when AML predominates and exhibits a distinctive biology.⁶⁵

In addition to increased risk for AML during the first 3 years of life, neonates with Down syndrome may also develop a transient myeloproliferative disorder (TMD) (also termed transient leukemia). This disorder mimics congenital AML, but typically improves spontaneously within the first 3 months of life, though TMD can remit as late as 20 months. Although TMD is usually a self-resolving condition, it can be associated with significant morbidity and may be fatal in 10 to 20 percent of affected infants; Infants with progressive organomegaly, visceral effusions, preterm delivery (less than 37 weeks gestation), bleeding diatheses, failure of spontaneous remission, laboratory evidence of progressive liver dysfunction (elevated direct bilirubin), and very high white blood cell count are at particularly high risk for early mortality.⁶⁶ Therapeutic intervention is warranted in patients in whom severe hydrops or organ failure is apparent. Several treatment approaches have been used, including exchange transfusion, leukapheresis, and low-dose cytarabine. *GATA1* mutations (a transcription factor that controls megakaryopoiesis) are present in blasts from patients with Down syndrome who have transient myeloproliferative disease and also in those with leukemia.

The mean time for the development of AML in the 10 to 30 percent of children who have a spontaneous remission of TMD but then develop AML, has been reported to be 16 months with a range of 1 to 30 months. Thus, most infants with Down syndrome and TMD who later develop AML will do so within the first 3 years of life. Patients with Down syndrome who develop AML with an antecedent TMD have superior event-free survival (EFS) ($91\% \pm 5\%$) compared with such children without TMD ($70\% \pm 4\%$) at 5 years. While TMD is generally not characterized by cytogenetic abnormalities other than trisomy 21, the presence of additional cytogenetic findings may connote an increased risk for developing subsequent AML.

The AML which develops in children with Down syndrome is acute megakaryoblastic leukemia, the outcome of which is generally favorable. The prognosis is particularly good (EFS exceeding 80%) in children aged 4 years or younger at diagnosis, the age group that accounts for the vast majority of Down syndrome patients with AML. Patients with Down syndrome demonstrate a remarkable sensitivity to methotrexate and other antimetabolites, which can result in substantial toxicity if standard doses are administered. After induction therapy, these patients require less intensive therapy to achieve better results. Appropriate therapy for these children is less intensive than current AML therapy, and hematopoietic stem cell transplant is not indicated in first remission.

MYELODYSPLASTIC SYNDROMES

Childhood myelodysplastic syndromes (MDS) is recognized as an entity of its own in the current version of the WHO classification. It accounts for less than five percent of all hematological neoplasms in children less than 14 years of age. In comparison to adult MDS, childhood MDS commonly has neutropenia and thrombocytopenia more than anemia, hypocellular marrow in 75 percent patients and refractory cytopenias of childhood. RARS and del5q are rare. RAEBs are more stable. Monosomy 7 is the most common cytogenetic abnormality and the hematopoietic stem cell transplant is the only curative option.

CHRONIC MYELOGENOUS LEUKEMIA

Chronic myelogenous leukemia (CML) is a clonal disorder of the hematopoietic tissue that accounts for 2 to 3 percent of all cases of all childhood leukemias. It is characterized by a specific translocation, $t(9;22)(q34;q11)$, producing the classical Philadelphia chromosome with bcr-abl fusion gene. The disease is characterized by an initial chronic phase in which the malignant clone produces an elevated leukocyte count with a predominance of mature forms but with increased numbers of immature granulocytes. The spleen often is greatly enlarged. This phase terminates 3 to 4 year after onset, when the CML moves into the accelerated or “blast crisis” phase. At this point, the blood counts rise dramatically and cannot be controlled with drugs such as hydroxyurea.

Imatinib mesylate, an agent designed specifically to inhibit the BCR-ABL tyrosine kinase, has been used in adults and has shown an ability to produce major cytogenetic responses in over 70 percent of patients. Limited experience in children suggests it can be used safely with results comparable to those seen in adults. While waiting for a response with imatinib, disabling or threatening signs and symptoms of CML can be controlled during the chronic phase with hydroxyurea, which will gradually return the leukocyte count to normal. Prolonged morphologic and

cytogenetic responses are expected, but the opportunity for cure is enhanced by allogeneic stem cell or marrow transplant, with up to 80 percent of children achieving a cure. Second line tyrosine kinase inhibitors like dasatinib, nilotinib are alternative options for imatinib resistant CML.

JUVENILE MYELOMONOCYTIC LEUKEMIA

Juvenile myelomonocytic leukemia (JMML) is a rare hematopoietic malignancy of childhood accounting for less than one percent of all childhood leukemias. Its incidence is 1.3 per million children 0 to 14 years of age per year. Seventy-five percent cases occur under 3 years of age. Children with neurofibromatosis 1 (NF1) and Noonan syndrome are at increased risk for developing JMML. Approximately 75 percent of JMML cases harbor one of three mutually exclusive mutations leading to activated RAS signaling, including direct oncogenic RAS mutations (approximately 20%), NF1 inactivating mutations (approximately 15% to 25%), or protein tyrosine phosphatase, non-receptor type 11 (PTPN11) (SHP-2) mutations (approximately 35%). Mutations of the E3 ubiquitin ligase CBL are observed in 10 to 15 percent of JMML cases. Patients with this disease do not have the Philadelphia chromosome that is characteristic of CML. They present with rashes, lymphadenopathy, and splenomegaly. The WHO 2008 diagnostic criteria are as follows.

1. Peripheral blood monocytosis $>1 \times 10^9/L$.
2. Blasts (including promonocytes) are <20 percent of the leukocytes.
3. No Ph chromosome or *bcr-abl1* fusion gene.
4. Plus two or more of the following
 - Hb F increased for age
 - Immature granulocytes in the peripheral blood
 - WBC count $>10 \times 10^9/L$.
 - Clonal chromosomal abnormality (may be monosomy 7)
 - GM-CSF hypersensitivity of myeloid progenitors *in vitro*.

Historically, more than 90 percent of patients with JMML died despite the use of chemotherapy, but with the application of hematopoietic stem cell transplant (HSCT), survival rates of approximately 50 percent are now reported.⁶⁷ Children aged 2 years or older and high blood fetal hemoglobin levels at diagnosis are predictors of poor outcome.

The role of conventional chemotherapy in the treatment of JMML is not defined. Among the agents that have shown antileukemia activity against JMML include etoposide, cytarabine, thiopurines (thioguanine and 6-mercaptopurine), and isotretinoin. Acute myeloid leukemia (AML) induction chemotherapy can induce remissions in children with JMML, but resistant disease is much more common for JMML than for *de novo* AML and the role of AML-type therapy in the treatment of JMML is not clear.

INFANT LEUKEMIA

About two percent of cases of leukemia during childhood occur before the age of 1 year. In contrast to older children, the ratio of ALL to AML is 2:1. Some cases may be due to maternal exposure to naturally occurring DNA topoisomerase II inhibitors. Several unique biologic features and a particularly poor prognosis are characteristic of ALL during infancy. More than two thirds of the cases demonstrate rearrangements of the *MLL* gene, found at the site of the 11q23 band translocation; this subset of patients largely accounts for the very high relapse rate. These patients often present with hyperleukocytosis and extensive tissue infiltration producing organomegaly, including CNS disease. Subcutaneous nodules, known as leukemia cutis, and tachypnea due to diffuse pulmonary infiltration by leukemic cells are observed more often in infants than in older children. The leukemic cell morphology is usually that of large irregular lymphoblasts (FAB L2), with a phenotype negative for the CD10 (cALLa) marker.

Very intensive chemotherapy programs including stem cell transplantation are being explored in infants with rearrangement of *MLL* in band 11q23, but none has yet proved satisfactory. Infants with leukemia who lack the 11q23 rearrangements have a prognosis similar to that of older children with ALL. Infants with AML often present with CNS or skin involvement and have the FAB M4 subtype. The treatment may be the same as that for older children with AML. Meticulous supportive care is necessary because of the young age and aggressive therapy needed in these patients.

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Hemophagocytic Lymphohistiocytosis

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The hemophagocytic lymphohistiocytosis (HLH), whether familial or acquired, share one common feature, namely a highly stimulated but ineffective immune response that threatens the life of the patient and may lead to death unless arrested by appropriate treatment.

CLINICAL SYMPTOMS OF HLH ARE CHARACTERISTIC BUT NONSPECIFIC

The cardinal symptoms of HLH are prolonged high fever, hepatosplenomegaly and cytopenias. Lymphadenopathy, icterus, or neurological symptoms such as cranial nerve palsies or seizures may also be present. Characteristic laboratory findings include high triglycerides, ferritin, transaminases, bilirubin and decreased fibrinogen. Hemophagocytosis, although it has given the disease its name, is found at presentation in only the minority of cases, but usually develops as the disease progresses. A hallmark of HLH is impaired or absent function of natural killer (NK) cells and cytotoxic T-cells (CTL). For more detailed information the reader is referred to recent reviews.¹⁻³ While many of these cardinal symptoms are found in immune-competent patients in response to an infectious organism, they are more pronounced in patients with HLH.

In particular, the progression of organomegaly, blood count changes and biochemical parameters should alert the physician that this could be an unusual response to an infectious agent. Without treatment, the uncontrolled inflammatory response leads to sustained neutropenia and death from bacterial or fungal infections as well as from cerebral dysfunction.

UNDERLYING CONDITIONS ASSOCIATED WITH OR PREDISPOSING TO HLH

Hemophagocytic lymphohistiocytosis (HLH) occurs in all age groups. It is not a single disease but can be encountered

in association with a variety of underlying conditions leading to the same hyperinflammatory phenotype (Table 1).

Genetic HLH is inherited in an autosomal recessive fashion and can be divided into 2 subgroups: familial HLH (FHLH) and the immune deficiencies Chédiak-Higashi syndrome (CHS), Griscelli syndrome (GS), and X-linked lymphoproliferative syndrome (XLP). Both genetic subgroups are associated with impaired NK cell function. In FHLH, originally described by Farquhar and Claireaux in 1952,⁴ the clinical syndrome of HLH is the primary and only manifestation. FHLH is estimated to occur with a frequency of 1 in 50,000 births. The onset of the disease is during the first year of life in 70 percent of the children. A symptom-free interval after birth is typical. CHS, GS,

Table 1: Classification and underlying conditions of hemophagocytic lymphohistiocytosis (HLH)

Genetic HLH

- Familial HLH (Farquhar disease*)
- Known gene defects (perforin, munc13-4, syntaxin 11)
- Unknown gene defects
- Immune deficiency syndromes
- Chédiak-Higashi syndrome (CHS)
- Griscelli syndrome (GS)
- X-linked lymphoproliferative syndrome (XLP)

Acquired HLH

- Exogenous agents (infectious organisms, toxins)
- Infection-associated hemophagocytic syndrome (IAHS)
- Endogenous products (tissue damage, metabolic products)
- Rheumatic diseases
- Macrophage activation syndrome (MAS)
- Malignant diseases

* Familial HLH was first described by Farquhar and Claireaux in 1952

and XLP are immune deficiencies with distinctive clinical features in which the development of HLH is sporadic, though frequent. HLH is often the presenting symptom but may also occur later during the course of disease. Patients with CHS show albinism and frequent pyogenic infections. Their white blood cells exhibit decreased chemotaxis and characteristic giant inclusion bodies (lysosomes). Patients with GS also have hypopigmentation and various degrees of neutrophil dysfunction but lack the giant granules. XLP is mainly characterized by a predisposition for Epstein-Barr virus (EBV)-associated HLH. XLP patients may develop lymphomas and dysgammaglobulinemia. There is no data about the incidence of acquired HLH in children or in adults. From numerous case reports and from our own experience, however, it appears that acquired HLH may be more common than previously believed. The clinical picture of HLH can be induced by a variety of infectious organisms, mostly viruses, but also bacteria, protozoa and fungi. The patients in the original report by Risdall and colleagues were mostly adults with a viral infection following organ transplantation.⁵ Subsequently it became clear that nonviral agents could trigger HLH, and the term virus-associated hemophagocytic syndrome (VAHS) was redesignated infection-associated hemophagocytic syndrome (IAHS). Whereas in the first report by Risdall et al the majority of cases had an acquired iatrogenic immune deficiency, most patients in subsequent reports had no known genetic or acquired immune defect. A review of the published cases in children diagnosed with IAHS before 1996, reported that more than half of them were from the far east. EBV was the triggering virus in 74 percent of the children in whom an infectious agent could be identified.² In this series, most patients received only supportive care and the mortality was 50 percent. The identification of an infectious organism does not help to differentiate FHLH from acquired HLH since the former is also usually triggered by infectious agents. This cannot be emphasized enough, since appropriate therapy should not be withheld when an infectious agent has been found.

HLH in association with malignant diseases, especially lymphomas (lymphoma-associated hemophagocytic syndrome; LAHS), is a well-known entity in adults but is rare in children. Cases formerly diagnosed as histiocytic medullary reticulosis or malignant histiocytosis included patients with LAHS, but also IAHS. Interestingly, in a recent review of patients with LAHS from Japan, the EBV genome was detected only rarely in patients with B-cell lymphoma but was demonstrated in more than 80 percent of patients with T/NK cell lymphoma.⁶ EBV-infected T/NK cells appear to play a major role in the development of LAHS as well as EBV-associated HLH without lymphoma,⁷ and both in LAHS and EBV-HLH the infected T/NK cells show a monoclonal or oligoclonal proliferation. Hemophagocytosis and symptoms of HLH have also been described in association with inborn errors of

metabolism, including lysinuric protein intolerance and multiple sulfatase deficiency. In such cases, it is not clear what role metabolic products may play as triggers to the immune response.

Genetic Defects in FHLH Elucidate the Pathophysiology of the Spectrum of HLH

The cytotoxic activity of NK cells and CTLs is mediated by the release of cytolytic granules (containing large amounts of perforin, granzymes and other serine like proteases) via the immunological synapse to the target cell. Several independent genetic loci related to this activity have been implicated in the pathophysiology of genetic HLH (Table 2). In 1999 mutations in the perforin gene at locus 10q24 were described in 8 patients with FHLH.⁸ The overall frequency of perforin mutations in FHLH is between 15 percent and 50 percent and depends on the geographical and ethnic origin of the patients.⁹ *UNC13D*, at locus 17q25, was the second gene associated with FHLH. The encoded protein (Munc13-4) is important for cytolytic granule exocytosis.¹⁰ *UNC13D* mutations do not affect docking of secretory vesicles (also known as lytic granules or secretory lysosomes) at the plasma membrane, but they impair priming of these vesicles and the subsequent release of cytolytic enzymes. The frequency of *UNC13D* mutations in FHLH was estimated to be around 30 percent.¹¹ Our group recently identified a third FHLH associated gene on chromosome 6q24 with mutations in *STX11*.¹² The encoded protein, t-SNARE syntaxin 11, also plays a role in intracellular trafficking, but its precise role is not known. The protein is strongly associated with intracellular membrane fractions and is detectable only in monocytes and not in lymphocytes. So far, mutations in the coding exon of syntaxin 11 seem to be restricted to patients from Turkey. Linkage analysis in 4 HLH families of Pakistani origin revealed a fourth putative disease gene for familial HLH on chromosome 9q21.3-22 but the gene has not yet been identified.¹³ In patients with GS type 2 (GS-2), immune dysfunction results from mutations in *RAB27A* on chromosome 15q21 (Table 2).¹⁴ Activated T cells of Rab27 α -deficient patients are unable to dock their secretory granules at the plasma membrane, thereby impairing secretion via the immunological synapse.¹¹ A direct interaction between Munc13-4 and Rab27 α has recently been demonstrated, and the complex seems to be an essential regulator of secretory granule fusion with the plasma membrane.¹⁵ CHS is caused by mutations in the *LYST* gene, located on chromosome 1q42.1-q42.2, which encodes a 3801 amino acid protein required, by an unknown mechanism, for the final steps of granule secretion.^{16,17} XLP results from mutations in the *SH2D1A* gene.¹⁸ *SH2D1A*(*SAP*) seems to be required for the signaling lymphocytic activating molecule (SLAM), which itself is important for signal transduction in immune cells and for activation of granule-mediated

cytotoxicity of NK cells and CTLs.¹⁹ Mutation screening in male patients with HLH may be useful as some of them harbor mutations in *SH2D1A*.²⁰

DEFECTIVE CYTOTOXIC FUNCTION IS CRUCIAL IN THE PATHOPHYSIOLOGY OF HLH

The clinical picture of HLH is due to an increased inflammatory response caused by hypersecretion of proinflammatory cytokines such as interferon- γ (IFN- γ), tumor

necrosis factor- α (TNF- α), interleukin (IL)-6, IL-10 and macrophage—colony-stimulating factor (M-CSF). These mediators are secreted by activated T-lymphocytes and histiocytes that infiltrate all tissues, and lead to tissue necrosis and organ failure. The pivotal role of IFN γ together with CD8+ T-cells for the development of HLH was demonstrated in a perforin knock-out mouse model.²¹ Inflammatory cytokines are responsible for the characteristic disease markers such as cytopenias, coagulopathy and high triglycerides. In spite of the excessive expansion and activation of cytotoxic cells, patients with HLH have severe impairment of the cytotoxic function of NK cells and CTLs. Impaired NK cell activity is seen in FHLH, GS, CHS and XLP as well as in acquired HLH. In the latter, impaired NK cell activity may be due in part to reduced numbers of NK cells and is usually transient. Defective cytolytic activity thus seems to be the common denominator that predisposes to HLH. NK cells and cytotoxic T-lymphocytes kill their targets through cytolytic granules containing perforin and granzyme. Upon contact between the effector killer cell and the target cell, an immunological synapse is formed and cytolytic granules have to traffic to the contact site, dock and fuse with the plasma membrane and release their contents.¹⁷ All known defects in HLH seem to be involved in this process (Fig. 1): *LYST* mutations impair granule secretion, *RAB27a* deficiency leads to impaired docking at the membrane, mutations in *UNC13D* do not impair docking but cause defective granule priming at the immunological synapse. Finally, lack of *PRF1* leads to loss of cytolytic activity. In XLP, granule-mediated cytotoxicity is defective through impaired lymphocyte activation. Syntaxin 11 mutations might

Table 2: Genetics defects in hemophagocytic lymphohistiocytosis			
Disease	Chromosome Location	Associated Gene	Gene function
FHLH-1	9q21.3-22	Not known	Not known
FHLH-2	10q21-22	PRF1	Induction of apoptosis
FHLH-3	17q25	UNC13D	Vesicle priming
FHLH-4	6q24	STX11	Vesicle transport; t-SNARE
GS-2	15q21	RAB27A	Vesicle transport, not further defined
CHS-1	1q42.1-q42.2	LYST	Vesicle transport; not further defined
XLP	Xq25	SH2D1A	Signal transduction and activation of lymphocytes

Abbreviation: FHLH, famillal hemophagocytic lymphohistiocytosis; GS: Griscelli syndrome; CHS: Chédiak-Higashi syndrome; XLP: X-linked lymphoproliferative syndrome

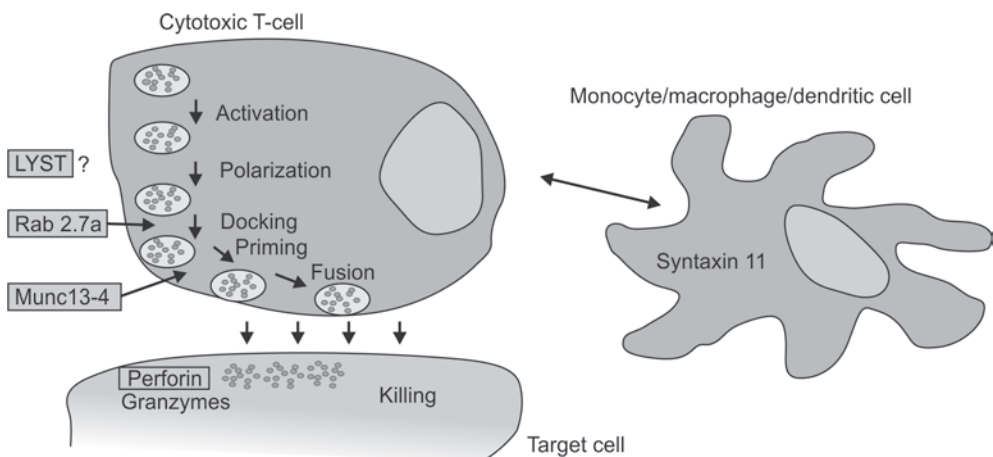


Fig. 1: Molecular mechanisms based on the identification of genetic defects associated with the clinical picture of familial hemophagocytic lymphohistiocytosis (FHLH), Griscelli syndrome (GS-2) and Chédiak-Higashi syndrome (CHS). Perforin is secreted via cytotoxic granules and leads to disruption of the target cell. Cytotoxic granule processing occurs by means of a complex that contains at least a Rab27 α /Munc13-4 complex and several other unknown proteins. The exact functions of *LYST* and syntaxin 11 are not known. In case of syntaxin 11, monocytes or macrophages/dendritic cells may interact with cytotoxic cells by an unknown mechanism.

theoretically impair cytolytic activity involving the interaction of dendritic and killer cells.²² The mechanisms leading to cytolytic defects in immune competent patients with acquired HLH are less clear. Viruses may interfere with CTL function by specific proteins,²³ and high levels of cytokines may have the same effect.²⁴ The prevalence of EBV-associated HLH in Asia suggests that a specific genetic susceptibility may result in an abnormal immune response to the virus. HLH cases associated with genetic defects in the granule exocytosis pathway demonstrate a critical role of the granule-dependent cytotoxic activity in T-lymphocyte homeostasis.¹¹ Activated NK-cells and CTLs can kill infected cells and antigen-presenting cells, thus reducing the antigen load; however, more complex mechanisms seem to be involved in the down-regulation of the immune response. Studies in mice indicate that NK cells and perforin-based systems play an important role in this process.²⁵

MACROPHAGE ACTIVATION SYNDROME IS CLOSELY RELATED TO HLH

The macrophage activation syndrome (MAS) occurs in children and adults with autoimmune diseases. It is most commonly seen in association with systemic onset juvenile arthritis (sJRA) or adult-onset Still's disease, but also occurs rarely with systemic lupus erythematosus or other entities.²⁶⁻²⁸ The clinical picture has all of the characteristic features of HLH including clinical symptoms, laboratory findings (especially very high ferritin levels), and hemophagocytosis.

Pronounced coagulopathy and severe cardiac impairment are common and potentially life-threatening.²⁷ Patients with MAS exhibit the defective NK cell function common to other patients with HLH. They may also have decreased expression of perforin or SAP, mimicking the defects associated with FHLH and XLP, respectively.²⁹⁻³¹ Furthermore, low NK cell function and perforin expression was found to distinguish patients with sJRA from those with other clinical forms of JRA.³² The overall incidence of MAS is not known, but about 100 cases have been published to date. It generally develops in the earlier and active phases of the underlying disease. Viruses have been identified as triggering factors, but other inciting factors that have been implicated include nonsteroidal anti-inflammatory drugs, methotrexate, and gold-salt injections. Mortality of patients with MAS is between 10 percent and 20 percent. It has been suggested by some rheumatologists that MAS be classified as a form of secondary HLH.^{33,34}

DIAGNOSTIC PROBLEMS IN HLH

Many patients with HLH present with mild signs of an upper respiratory or gastrointestinal infection and a high fever. The fever often subsides spontaneously and recurs

after some days to weeks. Transient improvements in cytopenias, especially thrombocytopenia, with unspecific measures such as antibiotics and transfusions are seen frequently. Organomegaly, anemia or other changes commonly persist. In babies, the initial suspicion often focuses on a metabolic disorder due to organomegaly, disturbed liver function or excessively high triglycerides. Severe, fulminant liver failure with coagulopathy or neurological symptoms may dominate the presentation and thereby delay the diagnosis of HLH. Several patients, including 2 with a novel perforin mutation, have been described with isolated CNS involvement mimicking chronic encephalitis and preceding systemic HLH by several months.³⁵⁻³⁷ The characteristic laboratory findings of high triglycerides and ferritin and a low fibrinogen may be absent; therefore, repeat studies are indicated when HLH is suspected.³⁸ A high lactate dehydrogenase may suggest a hemolytic anemia, but most patients with HLH characteristically have only moderately elevated reticulocytes in the presence of severe anemia, compatible with ineffective erythropoiesis. Highly activated immature-looking lymphocytes in lymph node biopsies may suggest a malignant process, and periportal infiltrates in a liver biopsy are often interpreted as viral hepatitis.

LABORATORY INVESTIGATIONS

When a patient presents with prolonged fever, hepatosplenomegaly and cytopenias, the diagnosis of HLH should be considered. Minimal diagnostic requirements are a complete blood count, liver enzymes, bilirubin, triglycerides, ferritin and a coagulation profile including fibrinogen. All patients should have a bone marrow aspirate; however, this test is insensitive. In the majority of cases, hemophagocytosis is not observed in the initial bone marrow aspirate and only increased monocytes and monohistiocytic cells may be present. A myelodysplastic syndrome is sometimes suspected due to marked dysplastic changes in the red cell precursors. Lumbar puncture is also indicated and more than half of the patients will have an elevated cell count or protein or both, even in the absence of clinical symptoms. Two highly diagnostic disease parameters are an increased plasma concentration of the α -chain of the soluble IL-2 receptor (sCD25) and impaired NK cell activity.³⁹ The latter is usually not available in time but should be measured in all patients. It is persistently decreased to absent in nearly all genetic cases. In acquired cases it usually reverts to normal, but some patients show prolonged impairment. In these patients genetic testing is recommended. The patients should be screened for an underlying disease like GS, XLP, CHS, autoimmune diseases or malignancy by detailed clinical history, physical examination and other appropriate studies. The search for a triggering infectious agent like EBV, cytomegalovirus (CMV), herpes simplex virus (HSV), adenovirus, varicella-zoster virus (VZV) and

Table 3: Diagnostic criteria for hemophagocytic lymphohistiocytosis (HLH)*

• Familial disease/known genetic defect
• Clinical and laboratory criteria (5/8 criteria)
Fever
Splenomegaly
Cytopenia ≥2 cell lines
Hemoglobin <90 g/L (below 4 weeks <120 g/L)
Neutrophils <1 × 10 ⁹ /L
Hypertriglyceridemia and/or hypofibrinogenemia
Fasting triglycerides ≥3 mmol/L
Fibrinogen <1.5 g/L
Ferritin ≥500 µg/L
sCD25 ≥ 2400 U/ml [§]
Decreased or absent NK-cell activity
*Hemophagocytosis in bone marrow, CSF or lymph nodes
[§] Supportive evidence are cerebral symptoms with moderate pleocytosis and/or elevated protein, elevated transaminases and bilirubin, LDH >1000 U/L

leishmania is important since most of these organisms are treatable. However, it should be emphasized that, with the possible exception of leishmaniasis, anti-infectious therapy alone is not sufficient to control HLH. Viral PCRs are more helpful than serology. Positive results are useful to follow during antiviral treatment. Expression of perforin by flow cytometry can identify patients with perforin defects and is also desirable in patients with MAS or other acquired forms of HLH in which data on perforin expression are still scant. In proven familial cases or in presumed familial cases with persistent or relapsing disease material for genetic analysis should be obtained.

DIAGNOSTIC CRITERIA

The revised criteria of the Histiocyte Society for the diagnosis of HLH are shown in Table 3. They are based primarily on the findings in familial cases but also apply to the diagnosis of infection-associated acquired HLH. For patients with systemic onset juvenile arthritis who develop MAS some criteria may not be relevant. For example, pre-existing inflammation is associated with a higher white blood count and platelets as well as fibrinogen. Accordingly, for MAS, other diagnostic criteria have recently been advocated that take the specific characteristics of these patients into account.⁴⁰

THERAPEUTIC OPTIONS AND PROBLEMS

The immediate aim in the treatment of any patient with HLH is to suppress the severe hyperinflammation that is responsible for the life-threatening symptoms. Another

aim is to kill pathogen-infected antigen-presenting cells and thus remove the stimulus for the ongoing but ineffective activation of T cells. It has to be specifically emphasized that pathogen-directed therapy is usually not sufficient to control hyperinflammation with the possible exception of leishmaniasis, in which most patients promptly respond to liposomal amphotericin B.

In genetic HLH the ultimate aim must be stem cell transplantation to exchange the congenitally defective immune system with normal functioning immune effector cells. In our experience treatment should be guided mainly by the severity of clinical symptoms, but age of the patient, presence of familial disease, underlying secondary disease, and the identification of an infectious organism also should be taken into account. Hyperinflammation can be treated with corticosteroids, which are cytotoxic for lymphocytes and inhibit expression of cytokines and differentiation of dendritic cells. Since dexamethasone crosses the blood brain barrier better than prednisolone it is the preferred corticosteroid. Cyclosporine A (CSA) prevents T-lymphocyte activation and immunoglobulin infusions probably act by providing cytokine and pathogen-specific antibodies. The cytostatic drug etoposide has high activity in monocytic and histiocytic diseases and it inhibits EBNA synthesis in EBV-infected cells. In patients with less severe symptoms, corticosteroids and immunoglobulin infusions are sometimes sufficient to control hyperinflammation and to reverse the clinical and laboratory symptoms. However, if symptoms progress, the treating physician should not hesitate to use therapy with dexamethasone, etoposide and CSA. The risk of etoposide, even if given for 8 weeks, is by far exceeded by the risk of losing a patient through inadequate treatment. Etoposide may be life-saving, especially in patients with HLH due to EBV infection. Mortality was 14 times higher for patients with EBV-associated HLH who did not receive etoposide within the first 4 weeks.⁴¹ Since initially mild cases may progress rapidly it is our opinion that the indication for the use of etoposide should be determined liberally. Several problems may arise during the initial treatment of patients with HLH. Although symptoms and laboratory abnormalities usually improve within 2 to 3 weeks of treatment, persistent cytopenias could indicate either nonresponse to therapy or myelosuppression by etoposide. A repeat bone marrow examination may be helpful. However, since uncontrolled hypercytokinemia also leads to bone marrow aplasia, at least 3-4 doses of etoposide should be given before a decision is made to interrupt the drug, while continuing with CSA and dexamethasone. The close monitoring of other parameters associated with disease activity is important in this situation. If there is no response to treatment after 4 weeks it is unlikely that the patient will have a benefit from continuing the same combination. There is no established salvage regimen; in single patients there has been

anecdotal evidence of transient responses to daclizumab or alemtuzumab. Antithymocyte globulin, which may be effective in initial treatment, rarely produces a response in patients with no response to an etoposide-containing combination. If a donor is available and the clinical condition is not prohibitive, stem cell transplant could be tried, although there is little experience proving its benefit in this situation. Reactivation during treatment is a frequent problem, either systemically or in the CNS. Immunosuppressive treatment should be reinforced in this situation. Intrathecal therapy with methotrexate +/- corticosteroids has been beneficial for some patients with recurrent CNS involvement and is recommended in view of the deleterious late effects of uncontrolled CNS disease.

Study HLH 94, which enrolled children up to the age of 15 years, used a combination of dexamethasone, CSA and etoposide for the initial treatment of HLH. Familial cases or patients with recurrences and therefore presumed genetic disease, subsequently received a bone marrow transplant from related or unrelated donors. Probability of survival at 3 years in 113 children was 55 percent for all cases and 51 percent for proven familial cases.⁴² Based on these data, patients with known familial disease, suspected genetic disease due to age below 1 year, or those with a severe clinical picture such as marked cytopenias, coagulation problems and CNS symptoms should receive treatment according to the present HLH protocol (*available at www.histio.org/society/protocols*). In familial cases or presumed familial cases (no complete resolution of symptoms, reactivations during or after cessation of therapy), active therapy should be continued until stem cell transplantation can be performed. A similar approach should be used for patients with the accelerated phase of CHS, GS or XLP, based on documented responses to HLH therapy. If a treatable infectious agent is identified, appropriate antimicrobial or antiviral therapy should be given.

The management of patients with MAS is usually based on the administration of high doses of corticosteroids. CSA has also proven effective in treating severe or corticosteroid resistant cases. Whereas immunoglobulin infusions failed in children with MAS, responses were observed in adult patients.²⁶ Limited experience exists with etoposide in MAS; however, similarities in pathophysiology between MAS and other forms of HLH⁴³ suggest that it might be beneficial in cases refractory to CSA and corticosteroids.

SUMMARY

HLH is a life-threatening disease characterized by uncontrolled hyperinflammation on the basis of a variety of inherited or acquired immune deficiencies. Awareness of its clinical symptoms and diagnostic criteria is important to starting prompt life-saving therapy. While HLH and its genetic defects have provided insight into the mechanisms of host defense, our understanding of its complex pathophysiology still remains incomplete.

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Abstract

Wilms' tumor constitutes 6 percent of all childhood malignancies. With improvement in multidisciplinary care and organized clinical trials the outcome of children with favorable histology and genetic features has improved considerably. The focus of current therapeutic strategies is to devise effective treatment for patient with poor histology and recurrent tumor along with minimizing late effects. This article reviews the epidemiology, biology, pathology and treatment of children with Wilms' tumor.

INTRODUCTION

Wilms' tumor or nephroblastoma, is the most common primary malignant renal neoplasm of childhood. Although relatively rare, this disease has served as a paradigm for multimodality management of childhood solid tumors. Developments in surgical techniques and postoperative care, recognition of the sensitivity of Wilms' tumor to irradiation, and the availability of several active chemotherapeutic agents led to a dramatic change in the prognosis for this disease. Studies of Wilms' tumor genetics have also laid the foundation for our understanding of tumor suppressor genes and genomic imprinting.

Epidemiology

Wilms' tumor is the second most common intra-abdominal malignant solid tumor accounting for 5 percent of all childhood malignancies. As per SEER statistics the annual incidence of Wilms' tumor is 8 cases per 1 million children younger than 15 years, representing 6.3 percent of cases of childhood and an estimated 500 new cases per year in the United States.¹ Girls have a slightly increased risk for Wilms' tumor, with a male-to-female ratio of 0.92 to 1.00.² The mean age at diagnosis is 44 months for unilateral disease and 31 months for bilateral disease.² According to the Knudson two-hit model of tumorigenesis, the earlier age at onset of bilateral Wilms' tumor represents a genetic predisposition to the disease. Wilms' tumor in the adult population is rare, although numerous cases have been

reported.^{3,4} Although results of older studies indicate that the prognosis for adult Wilms' tumor is unfavorable, recent reports demonstrate cure of both localized and advanced disease with treatment regimens similar to those used for children.^{5,6}

Familial Wilms' tumor is uncommon, occurring in only 1.5 percent of affected patients. Most cases of familial Wilms' tumor occur in distant relatives, rather than in parents or siblings. Sixteen percent of cases of familial Wilms' tumor are bilateral, compared with 7 percent of sporadic cases. Unlike retinoblastoma, familial Wilms' tumor is bilateral in only a small number of cases.⁶ Conversely, only a small proportion (3%) of cases of bilateral Wilms' tumor is familial. The mean ages at diagnosis of familial unilateral and bilateral disease are 35 months and 16 months, respectively.⁶

Tumor Biology

Wilms' tumor appears to result from changes in one or more of at least ten genes. The first Wilms' tumor gene identified was *WT1*, at chromosome 11p13 in 1990. Other loci for Wilms' tumor gene include *WT2* gene at chromosome 11p15, and two familial Wilms' tumor loci, *FWT1* at chromosome 17q and *FWT2* at chromosome 19q. *WT1* encodes a transcription factor that is critical to normal kidney and gonadal development and is a tumor suppressor gene.⁷ The *WT1* is associated with WAGR syndrome which also includes aniridia, genitourinary anomalies and

mental retardation. These patients are at high (greater than 30%) risk for development of Wilms' tumor. A gene that causes aniridia (PAX-6) is located near the *WT1* gene on chromosome 11p13 and deletions encompassing the *WT1* and aniridia genes explain the association between aniridia and WT.⁸⁻¹⁰ Patients with Denys-Drash syndrome characterized by ambiguous genitalia and diffuse mesangial sclerosis, are also associated with *WT1* gene mutation and has a 95 percent chance of developing WT.¹¹

Other Wilms' tumor-associated conditions include Beckwith-Wiedemann syndrome, which is an over growth disorder that manifests with high birth weight, macroglossia, organomegaly, hemihypertrophy, neonatal hypoglycemia, abdominal wall defects, and ear pits and creases. Patients with this syndrome have a 5 to 10 percent risk for development of Wilms' tumor but also are predisposed to the development of other malignant tumors, such as hepatoblastoma, adrenocortical carcinoma, neuroblastoma, and rhabdomyosarcoma.¹² Beckwith-Wiedemann syndrome maps to chromosomal band 11p15, sometimes called *WT2*, because loss of heterozygosity at this locus has been detected in Wilms' tumor. Although the precise *WT2* gene is undefined, molecular characterization of the *WT2* locus has revealed several genes that may play a role in tumorigenesis. These genes are imprinted, which means that they are preferentially expressed from one of the two parental alleles. Loss of imprinting, leading to aberrant messenger RNA and protein expression, has been postulated as a mechanism of tumor formation.^{13, 14}

Loss of heterozygosity at 1p and 16q has been found in 10 to 20 percent of Wilms' tumors. Loss at either or both loci is associated with adverse prognosis and is used for treatment stratification in the current children oncology group (COG) studies.¹⁵ Cytogenetic and loss of heterozygosity analyses have revealed recurrent abnormalities of 7p, but the clinical and biologic significance of these findings is unknown.¹⁶ Finally, mutations in the *TP53* gene are observed in most cases of anaplastic histological features of Wilms' tumor, implicating a role for this gene in progression from favorable to anaplastic histological type.^{17, 18}

Pathology

Classic Wilms' tumor pathology consists of variable proportions of blastemal, stromal, and epithelial elements, although tumors do not necessarily contain all three. Tumors that exhibit exclusively one pattern can present diagnostic difficulties. Monophasic blastemal tumors are highly invasive and have high risk of r' tumor often contains scattered cysts and sometimes may be associated with predominantly or purely cystic. Tumor without any solid nodular component but with immature nephrogenic component is designated as cystic partially differentiated nephroblastoma and with mature nephrogenic components classified as cystic nephroma. An important advance in the

care of patients with Wilms' tumor has been appreciation of the prognostic importance of anaplastic histological subtype. Approximately 6 percent of the Wilms' tumor specimens contained anaplasia, a term used to describe nuclear enlargement and atypia with irregular mitotic figures.¹⁹ The anaplasia may be focal or diffuse. Focal anaplasia is sharply confined to circumscribed region in renal parenchyma without any extrarenal spread. Diffuse anaplasia is defined as either unequivocal presence of anaplasia in one region along with extreme nuclear polymorphism in other regions or anaplasia in extra renal tissue or presence of anaplasia in random biopsy specimen. The presence of diffuse anaplasia is marker of resistance to chemotherapy and tumor aggressiveness and is associated with advanced stage and high risk of recurrence.^{20, 21}

The other facet of histology of kidney tumor is nephrogenic rests which are foci of embryonal kidney cells that persist abnormally into postnatal life. They are present in approximately 1 percent of newborn kidneys and usually regress or differentiate by early childhood.²² Nephrogenic rests are more commonly associated with WAGR, Deny-Drash and Beckwith-Wiedemann syndromes. Because nephrogenic rests are present in the kidneys of approximately 40 percent of patients with Wilms' tumor, it is presumed that the rests represent Wilms' tumor precursors.

Other rare childhood renal neoplasms that must be considered in the differential diagnosis for Wilms' tumor are clear cell sarcoma of the kidney, rhabdoid tumor of the kidney, congenital mesoblastic nephroma, renal cell carcinoma and soft-tissue sarcoma of the kidney. Clear cell sarcoma and rhabdoid tumor were initially considered to be variants of Wilms' tumor but are now recognized as separate entity.

- Congenital mesoblastic nephroma is the most common renal tumor in infants. It is generally curable by surgery but the cellular variant may recur, particularly in children over the age of 3 months. These tumors are characterized by the presence of a chromosomal translocation, t (12; 15) (p13; q25) which results in an *ETV6-NTRK3* gene fusion, which is also found in congenital infantile fibrosarcoma.²³ Accurate pathologic diagnosis is essential as these patients require radical surgical approach due to high chances of local recurrences.²⁴
- Clear cell sarcoma of the kidney is characterized by presence of widespread metastases, (specially to bone), when compared to Wilms' tumor and also by occurrence of late recurrences. Hence, patients with clear cell sarcoma should have skeletal surveys and bone scans as part of initial staging. Initially classified as an unfavorable histology tumor, the prognosis for patients with clear cell sarcoma has improved dramatically with

the addition of doxorubicin to therapy. Relapse free survival on NWT-4 is 72 percent at 8 years.²⁵ It is crucial to make the diagnosis of clear cell sarcoma so that patients with stage I and II disease are treated with doxorubicin. Such patients mistakenly treated as favorable histology Wilms' tumor without doxorubicin are at increased risk of relapse.²⁵

- Rhabdoid tumor of the kidney is the most aggressive tumor of infancy with survival rates of 20 to 25 percent. The atypical teratoid-rhabdoid tumors, a distinct category of primary CNS tumors occur in 10 to 15 percent of children with rhabdoid tumors of the kidney.²⁶ The two most important prognostic factors are stage and age. A review of the NWT-4 experience showed that patients with stage I/II tumors had an overall survival rate of 42 percent compared to 16 percent in stage III/IV. Patients less than 6 months of age had a 9 percent survival compared to 41 percent in children over 2 years of age.²⁶
- Renal cell carcinoma accounts for 2 to 6 percent of malignant childhood renal tumors. Mean age at diagnosis is approximately 15 years. Surgery remains the main stay of therapy and prognosis is dependent upon stage at diagnosis.²⁷ Patients with recurrent or unresectable disease have poor prognosis and do not respond to chemotherapy.

Clinical Manifestations and Patterns of Spread

Wilms' tumor typically presents as an asymptomatic abdominal mass discovered by a parent while bathing or dressing the child. Children with Wilms tumor are often asymptomatic in contrast to those with neuroblastoma, the other common abdominal tumor that must be clinically differentiated from Wilms' tumor. The mass is often smooth and firm, fixed in position and may extend across the midline. Abdominal pain, fever, anemia, hematuria and hypertension are other common features observed in 20 to 30 percent of children with Wilms' tumor.²⁸ Constitutional signs and symptoms (e.g. weight loss, cachexia, bone pain) are usually not present. Wilms' tumor can spread both locally and hematogenously. Local spread typically occurs into the renal hilar structures and may penetrate the renal capsule. These tumors also have a propensity to invade the renal vein and form thrombi in the inferior vena cava, sometimes progressing as far as the right atrium. Local and distant lymph node involvement can occur. The most common sites of hematogenous metastasis are the lungs and liver. A varicocele secondary to obstruction of the spermatic vein may be associated with the presence of a tumor thrombus in the renal vein or inferior vena cava. Persistence of the varicocele when the child is supine is highly suggestive of venous obstruction. It is important to include blood pressure, careful palpation of the abdomen, examination of lymph nodes (nodal metastases, especially

to the supraclavicular area, may suggest neuroblastoma), and a search for congenital abnormalities.

Laboratory and Radiologic Evaluation

The initial radiographic study is often an abdominal ultrasound examination. This demonstrates whether the abdominal mass is solid or cystic and may allow identification of the organ of origin and size of the mass. It is also adequate for determination of inferior vena cava patency.

Computed tomography (CT scan) provides detailed information regarding pelvic, abdominal structures as well as lymph nodes. CT is especially useful in detection of bilateral tumors. Intravenous pyelography and MRI typically are not necessary in the evaluation of Wilms' tumor, although MRI may facilitate differentiation between nephrogenic rests and Wilms' tumor.²⁹ Because Wilms' tumor metastasizes to the lungs, preoperative chest radiography is imperative. Plain radiographs of the chest are the traditional means of evaluation. Although chest CT is more sensitive than plain radiography in the detection of pulmonary metastasis, its role in initial evaluation for Wilms' tumor is controversial because CT is associated with false-positive findings and high inter-reader variability among radiologists.³⁰ Moreover, it is not clear whether the prognosis for patients with small pulmonary nodules detected only with chest CT is inferior to that for patients without detectable pulmonary metastasis by radiology.^{31,32} Imaging of the head or bones is usually reserved for patients with rhabdoid tumors of the kidney and clear cell sarcoma of the kidney.

PROGNOSTIC FACTORS

Wilms' tumor is a curable disease in the majority of affected children. Since the 1980's, the 5-year survival rate for Wilms' tumor has been consistently above 90 percent.³³ This favorable outcome occurred despite reduction in the length of therapy, dose of radiation, extent of fields irradiated, and the percentage of patients receiving radiation therapy.³⁴ The prognosis for patients with Wilms' tumor is related not only to the stage of disease at diagnosis, the histopathologic features of the tumor, patient age, and tumor size but also to the team approach provided to each patient by the pediatric surgeon, radiation oncologist and pediatric oncologist.

Staging

Two major staging systems are currently used: A prechemotherapy/up-front, surgery-based system developed by the National Wilms' Tumor Study Group (NWTSG) and a post chemotherapy-based system developed by the International Society of Pediatric Oncology (SIOP).^{35,36} The details of staging are listed in Table 1.

Table 1: Staging of Wilms' tumor

Stage	NWTSG (Before chemotherapy)	SIOP (After chemotherapy)
I.	<p>a. Tumor is limited to the kidney and completely excised</p> <p>b. The tumor was not ruptured before or during removal</p> <p>c. The vessels of the renal sinus are not involved beyond 2 mm</p> <p>d. There is no residual tumor apparent beyond the margins of excision</p>	<p>a. Tumor is limited to kidney or surrounded with fibrous pseudocapsule if outside of the normal contours of the kidney, the renal capsule or pseudocapsule may be infiltrated with the tumor but it does not reach the outer surface, and is completely resected (resection margins "clear")</p> <p>b. The tumor may be protruding into the pelvic system and "dipping" into the ureter (but it is not infiltrating their walls)</p> <p>c. The vessels of the renal sinus are not involved</p> <p>d. Intrarenal vessel involvement may be present</p>
II.	<p>a. Tumor extends beyond the kidney but is completely excised</p> <p>b. No residual tumor is apparent at or beyond the margins of excision</p> <p>c. Tumor thrombus in vessels outside the kidney is stage II if the thrombus is removed en bloc with the tumor</p> <p><i>Although tumor biopsy or local spillage confined to the flank were considered stage II by NWTSG in the past, such events will be considered stage III in upcoming COG studies.</i></p>	<p>a. The tumor extends beyond kidney or penetrates through the renal capsule and/or fibrous pseudocapsule into perirenal fat but is completely resected (resection margins "clear")</p> <p>b. The tumor infiltrates the renal sinus and/or invades blood and lymphatic vessels outside the renal parenchyma but is completely resected</p> <p>c. The tumor infiltrates adjacent organs or vena cava but is completely resected</p>
III.	<p>Residual tumor confined to the abdomen:</p> <p>a. Lymph nodes in the renal hilum, the periaortic chains or beyond, are found to contain tumor</p> <p>b. Diffuse peritoneal contamination by the tumor</p> <p>c. Implants are found on the peritoneal surfaces</p> <p>d. Tumor extends beyond the surgical margins either microscopically or grossly</p> <p>e. Tumor is not completely resectable because of local infiltration into vital structures</p>	<p>a. Incomplete excision of the tumor, which extends beyond resection margins (gross or microscopic tumor remains postoperatively)</p> <p>b. Any abdominal lymph nodes are involved</p> <p>c. Tumor rupture before or intraoperatively (irrespective of other criteria for staging)</p> <p>d. The tumor has penetrated through the peritoneal surface</p> <p>e. Tumor thrombi present at resection margins of vessels or ureter, transected or removed piecemeal by surgeon</p> <p>f. The tumor has been surgically biopsied (wedge biopsy) prior to preoperative chemotherapy or surgery</p> <p><i>Regional lymph node involvement was considered stage II in the previous SIOP staging system.</i></p>
IV.	Presence of hematogenous metastases or metastases to distant lymph nodes	Hematogenous metastases (lung, liver, bone, brain, etc.) or lymph node metastases outside the abdominopelvic region
V.	Bilateral renal involvement at the time of initial diagnosis	Bilateral renal tumors at diagnosis

Abbreviations: COG, Children's Oncology Group; NWTSG, National Wilms' Tumor Study Group; SIOP, International Society of Pediatric Oncology.

Treatment

The treatment of Wilms' tumor is one of the great success stories in oncology. Current excellent outcome of children with Wilms' tumor has been possible due to various systematic and coordinated trials by NWTSG and SIOP group. Although these two groups have generally used similar chemotherapeutic agents, their treatment approaches are fundamentally different in the way that NWTSG recommends up front surgery whereas SIOP advocates preoperative chemotherapy. Both approaches yield excellent

results for patients with favorable histology, whereas outcome for other patients are suboptimal.

Surgery

Surgical resection is the primary method for achieving local control and is usually performed at the time of initial presentation in NWTSG studies (which is now part of the Children's Oncology Group (COG), and after 6 weeks of neoadjuvant chemotherapy in SIOP studies. Wilms' tumor surgery should be performed by an experienced pediatric

Table 2: Treatment regimens for Wilms' tumor with favorable or standard histologic features from recently completed NWTSG and siop studies

Stage	NWTSG-5		SIOP93-01		
	Chemotherapy	Radiation Therapy	Chemotherapy		Radiation Therapy
			Preoperative	Postoperative	
I.	VA × 18 weeks	—	VA × 4 weeks	VA × 4 weeks	—
II.	VA × 18 weeks	—	VA × 4 weeks	VDA × 27 weeks	Node-negative: none Node-positive: 15 Gy
III.	VDA × 24 weeks	10.8 Gy	VA × 4 weeks	VDA × 27 weeks	15 Gy
IV.	VDA × 24 weeks	12 Gy lung (if lung metastasis) 10.8 Gy flank (if local stage III)	VDA × 6 weeks	CR after 9 weeks: VCA × 27 weeks	None if lung lesions disappear by week 9, otherwise 12 Gy No CR after 9 weeks: ICED × 34 weeks

Adapted from: Metzger ML, Dome JS. Current therapy for Wilms' tumor. *Oncologist* 2005;10:815

surgeon through a transverse abdominal incision. The tumor is removed en bloc with the kidney, hilar structures, and a generous segment of the ureter. The adrenal gland is included in the resection if the tumor is adherent to the gland or if the tumor originates in the upper pole of the kidney. Caution should be exercised to avoid capsular rupture and tumor spillage, which could adversely influence staging and alter therapy.³⁷ The peritoneal surface, liver and lymph nodes are inspected for tumor involvement. A lymph node sample should be obtained whether or not the node appears involved. Although the NWTSG group previously recommended inspection of the contralateral kidney, less than 0.3 percent of patients enrolled in NWTSG-4 had lesions detected during surgery that were not detected on preoperative imaging studies.³⁸ With the availability of modern imaging techniques, routine exploration of the contralateral kidney is no longer recommended. In the NWTSG approach, if a tumor is deemed inoperable owing to size or invasion of vital structures, biopsy is performed and adjuvant therapy is administered before definitive surgery.

Chemotherapy

Wilms' tumor is a systemic disease from onset; hence chemotherapy plays a crucial role in the treatment. Vincristine, dactinomycin, and doxorubicin form the backbone of most combinations for the treatment of Wilms' tumor. The recommended drugs and duration of favorable histology Wilms' tumor according to stage and intergroup studies are listed in Table 2.

Anaplasia, either diffuse or focal, adversely affects the outcome even after the administration of conventional chemotherapy with vincristine, dactinomycin, and doxorubicin. Addition of cyclophosphamide and etoposide improved the survival of patients with stage II-IV diffuse anaplasia.⁴³ In addition, the ongoing trial for these patients

will incorporate carboplatin in an attempt to improve the clinical outcome. For patients with stage I anaplasia, a more aggressive regimen that incorporates doxorubicin will be used. Patients with stage IV diffuse anaplasia continue to do extremely poorly with 4-year EFS of less than 35 percent, and novel investigational combinations including carboplatin, topotecan, and irinotecan are under investigation. The need for chemotherapy in patients less than 2 years of age with stage I favorable histology tumors who weigh less than 550 g is being evaluated in the current trial.

Lessons Learnt from NWTSG and SIOP Studies

Consecutive trials of the NWTSG beginning in the late 1960's provided critical insights into the role of adjuvant therapy for Wilms' tumor. NWTSG-1 and NWTSG-2 revealed that the combination of vincristine and actinomycin D is superior to treatment with either drug alone and that irradiation is not necessary in the care of patients with stage I disease. NWTSG-3 showed that patients with stage II tumors with favorable histologic features can be treated without abdominal irradiation if vincristine and actinomycin D are administered. This study also revealed that the addition of doxorubicin to the two-drug regimen improves outcome in stage III and IV disease with favorable histologic features. If doxorubicin is administered, radiation doses of 1000 cGy are sufficient to eliminate residual microscopic disease in the abdomen. NWTSG-3 also showed that addition of cyclophosphamide to the vincristine actinomycin D-doxorubicin regimen improved outcome for patients with stage II through IV tumors with anaplastic histologic features but not for those with tumors with favorable histologic features. NWTSG-4 compared the use of single-dose pulse-intensive actinomycin D and doxorubicin with the traditional divided-dose method of administration. The investigators found that pulse-intensive dosing was equally efficacious, less toxic, and more cost-effective than

the conventional regimen.⁴⁴ NWTSG-4 also revealed that 6 months of therapy for stage II through IV tumors with favorable histologic features was equivalent to 15 months of therapy. The NWTSG-5 study sought to capitalize on previous successes. The aim was to curtail therapy in low-risk groups, improve cure rates for high-risk groups, and identify novel prognostic markers.

SIOP-1 study showed that in stage I, II and III there was no difference in survival rate between the preoperative radiation therapy and immediate surgery groups. Significantly fewer tumor ruptures occurred in the pretreated group, and the recurrence-free survival rate was lower for patients who experienced intraoperative rupture. SIOP II showed that in stage I, II and III six months of postoperative treatment was as effective as 15 months in terms of event free and overall survival. SIOP-6 showed that treatment with vincristine and dactinomycin was as effective for 17 weeks as for 38 weeks in stage I and patients with negative lymph nodes who were assigned to receive no radiation therapy had a higher recurrence rate in stage II. SIOP-9 showed that for patients with negative lymph nodes in stage II, the rate of relapse was reduced by treatment with epirubicin without radiation therapy.

Pros and Cons of the NWTSG and SIOP Approaches

The NWTSG and SIOP approaches to Wilms' tumor treatment each have distinct advantages and disadvantages. The primary strength of the NWTSG approach is that up-front radical nephrectomy allows an accurate histological diagnosis and staging. On SIOP 93-01, approximately 5 percent of lesions in patients treated with chemotherapy were ultimately shown not to be Wilms' tumor and included 1.8 percent that were benign.³⁹ A research benefit of removing the tumor before chemotherapy is that it enables the collection of untreated tumor for biological studies and provides an unadulterated view of the tumor's molecular biology. The primary strength of the SIOP approach is that preoperative chemotherapy usually reduces the tumor volume, thereby decreasing the likelihood of spillage and helps in "downstaging" the tumor.⁴⁵ As a result, fewer patients received local irradiation on SIOP-9 than on NWTSG-5, although slightly more of the SIOP-9 patients receive anthracycline.⁴⁶ A second advantage of preoperative chemotherapy is that response to treatment may provide a valuable prognostic indicator.^{47,48} In the absence of a clear choice between up-front nephrectomy and preoperative chemotherapy, it is reasonable to base the timing of resection on factors such as tumor size, the patient's clinical condition, and the experience of the surgeon. Another difference between the NWTSG and SIOP studies is in the management of lung metastases. In the most recent NWTSG studies, computerized tomographic (CT) scan and chest X-ray were performed to determine the presence of lung metastases.

If the two imaging modalities yielded discordant results (usually in the form of "CT only" nodules), the disease stage was ultimately designated by the treating physician. Any patient deemed to have lung metastases was given whole-lung irradiation. The 2-year relapse-free survival estimate for patients with stage IV disease treated on NWTSG-4 was 81 percent.⁴⁹ In the SIOP studies, only chest X-ray was used to evaluate lung metastasis. If lung metastases completely disappeared with chemotherapy (or were completely resected), patients did not receive lung irradiation. With this approach, SIOP reported a 4-year EFS rate of 83 percent.⁵⁰ In contrast, the first Wilms' tumor study by the United Kingdom Children's Cancer Study Group reported a survival rate of only 65 percent when radiation therapy was not given to patients with lung metastases.⁵¹ This finding raises the question about the role of lung irradiation. Future COG trials will assess the necessity of lung irradiation for patients whose tumors have favorable biological and histological features and show rapid response to chemotherapy.

Radiotherapy

Radiation was an important treatment modality in preoperative and adjuvant settings in the earlier studies. With subsequent refinement in therapy with an aim of maximizing cure and reducing morbidity, there are now precise indications for adjuvant radiotherapy. The current standard of care includes flank/abdominal irradiation (10-8Gy in six fractions) for Stage III favorable-histology (FH) tumors and Stage II-III diffuse anaplastic WT.⁵²

The role and timing of lung irradiation in metastatic disease is controversial. The NWTSG continues to administer whole lung irradiation (12Gy in eight fractions) in patients with pulmonary metastases, while the SIOP group advocates omission of radiotherapy for patients whose lung metastases disappear completely after six weeks of prenephrectomy chemotherapy with vincristine, dactinomycin and doxorubicin. The role of pulmonary irradiation in children with pulmonary metastases visible on CT but not chest radiograph is still unclear. Use of conformal radiotherapy as well as IMRT has led to dose escalation without increase in morbidity.

Bilateral Wilms' Tumor

Bilateral Wilms' tumor occurs in approximately 5 to 10 percent of patients with Wilms' tumor. Usually these are synchronous, but may develop subsequently in the remaining kidney among 1 to 3 percent of children treated successfully for Wilms' tumor. The incidence of such metachronous bilateral Wilms' tumors was much higher in children whose original Wilms' tumor was diagnosed before age of 12 months and/or whose resected kidney contains nephrogenic rests. Periodic abdominal ultrasound is recommended for early detection of metachronous bilateral Wilms' tumor.^{53,54}

These children pose a therapeutic challenge because of difficulty in obtaining local control while sparing renal parenchyma. The approach to patients with bilateral Wilms' tumor is to administer preoperative chemotherapy to elicit tumor shrinkage and then to perform partial nephrectomy, whenever possible, or complete nephrectomy. Patients with tumors that cannot be resected with clear margins receive localized radiation therapy. The 4-year overall survival rate among patients with bilateral Wilms' tumor treated in NWTs-4 was 81.7 percent.⁵⁵ Compared with patients with unilateral Wilms' tumor, patients with bilateral tumors have an increased rate of renal failure, estimated to be 3.8 percent in NWTs-4.⁵⁵ The most common cause of renal failure in this patient group is tumor progression or recurrence necessitating nephrectomy, not therapy-related effects.

Recurrent Wilms' Tumor

Despite excellent outcome among most patients with Wilms' tumor, approximately 10 to 15 percent of patients with disease with favorable histologic features and 50 percent of patients with anaplastic disease experience primary progression or tumor recurrence. The most common sites of recurrence are the lungs, liver, opposite kidney, and intra-abdominal sites, including the original tumor bed. Wilms' tumor occasionally recurs in the brain, bone, and distant lymph nodes. Most relapses are diagnosed within the first 2 years after the original diagnosis. Factors associated with favorable prognosis after recurrence include favorable histologic features, initial treatment with only vincristine and actinomycin D, recurrent disease involving the lungs only, recurrent disease arising in the abdomen of a patient who did not receive abdominal irradiation and relapse more than 12 months after the original diagnosis.⁵⁶ With aggressive therapy, approximately 60 to 80 percent of patients with tumors with favorable prognostic features can be cured. Salvage regimens are not as successful for patients with tumors with at least one unfavorable prognostic feature. Salvage regimens include ifosfamide, cyclophosphamide, carboplatin, and etoposide.^{57,58} The overall 4-year survival rate after relapse for patients whose initial treatment regimen consisted of vincristine and actinomycin D was 81 percent after treatment with a regimen containing vincristine, doxorubicin, cyclophosphamide, and etoposide and radiation therapy.⁵⁸ For patients whose initial treatment regimen included agents in addition to vincristine and actinomycin D, the 4-year overall survival rate was 48 percent after treatment with cyclophosphamide, carboplatin, etoposide, and irradiation.⁵⁹ Several groups of investigators have used high-dose chemotherapy followed by autologous stem cell rescue in patients with recurrent Wilms' tumor.^{60, 61} Results are promising, but it is unclear whether high-dose therapy is superior to conventional-dose chemotherapy with modern agents.

Late Effects of Therapy

The late effects of Wilms' tumor treatment have received considerable attention because Wilms' tumor usually is curable and the number of long-term survivors is growing. Late complications can result from chemotherapy, radiation therapy or the surgery itself. Although most Wilms' tumor survivors have only one kidney, less than 1 percent of patients with unilateral Wilms' tumor treated in NWTs-1 through NWTs-4 were found to have renal failure.⁶² The median interval from diagnosis to onset of renal failure was 21 months. Renal failure is most prevalent in patients with bilateral Wilms' tumor. Another recognized long-term effect of Wilms' tumor therapy is congestive heart failure (CHF), which was found to have a cumulative frequency of 4.4 percent 20 years after diagnosis of Wilms' tumor in patients whose initial treatment regimen included doxorubicin.⁶³ Risk factors for CHF included increasing cumulative doxorubicin dose, female gender, and radiation to the lung and left hemiabdomen (but not right hemiabdomen). An analysis of pregnancy outcome among Wilms' tumor survivors revealed that women who received flank radiation therapy and their infants were at increased risk for fetal malposition, premature labor, low birth weight and occurrence of congenital malformations.⁶⁴ Finally, the cumulative incidence of second malignant neoplasms, including secondary AML in Wilms' tumor survivors was 1.6 percent 15 years after diagnosis of their initial tumor.^{65,66}

KEY MESSAGES

- Wilms' tumor is the most common primary kidney tumor of childhood.
- It is highly curable and requires multidisciplinary care.
- Treatment approach includes radical nephrectomy along with chemotherapy, with or without radiation.
- Both the NWTs and SIOP approaches though fundamentally different yield excellent results in terms of overall and event free survival and these trials have improved knowledge about tumor biology.
- Primary goal of current treatment is to minimize acute and long-term adverse effects without compromising outcome.

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CHAPTER 73

Childhood Brain Tumors

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INTRODUCTION

Central nervous system (CNS) tumors are the second most common childhood tumor after leukemia, constituting approximately 20 to 25 percent of all childhood malignancies and remain the leading form of cancer related deaths in children.

EPIDEMIOLOGY

The approximate incidence is 35 cases per million in children under 15 years of age. Unlike adults, the majority are infratentorial in location (60-70%) while as supratentorial tumors constitute approximately 30 to 40 percent.

The etiology is unknown but there is some predilection in the following conditions:

- Neurofibromatosis type 1 (NF-1)
- Turcot's syndrome
- Gorlin's syndrome
- Tuberous sclerosis
- von Hippel-Lindau syndrome
- Li-Fraumeni syndrome
- Previous cranial radiotherapy

CLASSIFICATION AND GRADING OF BRAIN TUMORS (ACCORDING TO WHO 2007)

Histological grading helps the clinician in choice of therapies and determining the prognosis of the tumor. In the recent WHO classifications of brain tumors, few additional entities have been incorporated (Table 1).

GENERAL SIGNS AND SYMPTOMS OF INTRACRANIAL TUMORS

The common signs and symptoms are grouped in Table 2. The signs and symptoms depend upon the size, location and growth rate of the tumor. Slow growing tumors are

usually large at presentation and on the other hand rapidly growing tumors present early when they are small. Suspicion should warrant need for imaging to rule out brain tumors.

DIAGNOSTIC STUDIES

Imaging

- *CT scan:* It is often the first imaging technique obtained because it is easily available. If performed using thin sections of 5 mm and with contrast, about 95 percent tumors can be detected. MRI scans are better for posterior fossa tumors, but CT scans are better to evaluate bony destruction and for calcifications.
- *MRI:* MRI offers far superior tumor localization because of the superior image contrast, and its multi-planar capabilities. Especially useful in posterior fossa and spinal tumors. MRI is recommended as the first line imaging of choice in pediatric brain tumors. MRI specificity is enhanced with the contrast agent gadolinium diethylenetriaminepentaacetic acid dimeglumine (Gd-DTPA), which should be used in the evaluation of childhood CNS tumors. For the diagnosis of spinal cord tumors or determination of leptomeningeal dissemination of tumors, spinal MRI has supplanted all other techniques, including myelography or CT studies. Another advantage is that there is no radiation exposure. The disadvantage being long imaging time.
- *Magnetic resonance spectroscopy:* This is newer imaging modality and very useful in distinguishing malignant and necrotic areas. This also distinguishes postoperative residual tumor from postoperative changes.
- *PET scan:* PET is most helpful in the determination of transformation of a lower-grade tumor (primarily glial) to a higher-grade neoplasm and the separation

Table 1: Recent WHO classification of brain tumors

<i>Tumors</i>	<i>Grade</i>	<i>Tumors</i>	<i>Grade</i>
Diffusely infiltrating astrocytocyctic tumors		Neuronal and mixed neuronal–glial tumors	
Diffuse fibrillary astrocytoma	II	Gangliocytoma	I
Gemistocytic astrocytoma	II	Ganglioglioma	I
Protoplasmic astrocytoma	II	Anaplastic ganglioglioma	III
Anaplastic astrocytoma	III	Desmoplastic infantile astrocytoma and ganglioglioma	I
Glioblastoma	IV	Central neurocytoma	II
• Giant cell glioblastoma			
• Gliosarcoma			
Circumscribed astrocytic tumors		Extraventricular neurocytoma	II
Pilocytic Astrocytoma	I	Cerebellar liponeurocytoma	II
• Pilomyxoid astrocytoma			
Subependymal giant cell astrocytoma	I	Paragangliomas of spinal cord	I
Pleomorphic xanthoastrocytoma	II	Papillary glioneuronal tumors	I
<i>Oligodendrogial tumors</i>		Rosette forming glioneuronal tumor of the fourth ventricle	I
Oligodendroglioma	II	<i>Embryonal tumors</i>	
Anaplastic oligodendroglioma	III	Medulloblastoma	IV
		• Classical	
		• Desmoplastic	
		• Medulloblastoma with extensive nodularity	
		• Anaplastic medulloblastoma	
		• Large cell medulloblastoma	
<i>Ependymal tumors</i>		CNS primitive neuroectodermal tumor	IV
		• CNS neuroblastoma	
		• CNS ganglioneuroblastoma	
		• Medulloepithelioma	
		• Ependymoblastoma	
Subependymoma	I	Atypical teratoid/rhabdoid tumor	IV
Myxopapillary ependymoma	I	<i>Germ cell tumors</i>	
Ependymoma	II	Germinoma	
• Cellular		Embryonal carcinoma	
• Papillary		Yolk sac tumor	
• Clear Cell		Choriocarcinoma	
• Tanacytic		Teratoma mature	
		• Immature	
		• With malignant transformation	
Anaplastic ependymoma	III	Mixed germ cell tumors	
<i>Choroid plexus tumors</i>		<i>Pineal tumors</i>	
Choroid plexus papilloma	I	Pineocytoma	I
Atypical choroid plexus papilloma	II	Pineal tumor of intermediate differentiation	II, III
Choroid plexus carcinoma	III	Pineoblastoma	IV
<i>Other neuroepithelial tumors</i>		Papillary tumor of pineal region	II, III
Astroblastoma	NA	<i>Other tumors</i>	
Chordoid glioma of the third ventricle	II	Tumors of cranial and paraspinal nerves	
Angiocentric glioma	I	Meningeal tumors	
		Sellar region tumors	
		Lymphomas	

Table 2: Common signs and symptoms of CNS tumors in children

- *Headache:* In young children headache can present as irritability. Often worse in the morning, and improves throughout the day.
- Vomiting (often early morning)
- Disturbances of gait and balance
- Cranial nerve abnormalities
- *Impaired vision:*
 - Diplopia (6th nerve palsy). In young children diplopia may present as frequent blinking or intermittent strabismus
 - Papilledema from increased ICP may present as intermittent blurred vision
 - Parinaud syndrome (failure of upward gaze and setting-sun sign, large pupils and decreased constriction to light)
- *Mental disturbances:* somnolence, irritability, personality or behavioral change, or change in school performance
- Seizures, usually focal
- *Endocrine abnormalities:* Midline supratentorial tumors may cause endocrine abnormalities due to effects on the hypothalamus or pituitary and visual field disturbances due to optic pathway involvement
- Cranial enlargement (characteristic of increased ICP in infants)
- Diencephalic syndrome can be seen in patients aged 6 months to 3 years with brain tumors who present with sudden failure to thrive and emaciation. The syndrome is caused by a hypothalamic tumor in the anterior portion of the hypothalamus or the anterior floor of the third ventricle
- *Spinal tumors:* Back pain, spinal deformity, gait disturbances, sensory abnormalities, muscle power/tone abnormalities, sphincter impairment.

of post-therapy, especially postradiation, treatment effects from tumor progression.

Immunohistochemistry

Immunohistochemical markers and molecular alterations may help in establishing diagnosis in ambiguous cases of pediatric brain tumors. In addition to routine immunohistochemical markers like GFAP, synaptophysin, NFP, NSE, etc. many immunohistochemical tests (IHC), fluorescence *in situ* hybridization (FISH) and polymerase chain reaction (PCR) based assays are available, which help in making a correct diagnosis. For example MIB-1 labeling index is used as an adjunct to histological grading. These should be used for correct tumor characterization.

Cerebrospinal Fluid Studies

Cerebrospinal fluid (CSF) should be sampled only when CT scan and/or neurosurgical opinion determines the study is safe to perform, because of the risk of coning in patients with untreated raised intracranial pressure.

The following studies are recommended:

- Cell count with cytocentrifuge for cytology of tumor cells
- Glucose and protein
- α -fetoprotein (AFP)
- Human chorionic gonadotropin (hCG).

Cerebrospinal fluid (CSF) is of value in the evaluation of tumors that are in proximity to the circulating CSF (medulloblastoma, ependymoma, brainstem glioma).

Alpha-fetoprotein (AFP) and beta-human chorionic gonadotropin (β -hCG) in the CSF may be elevated in non-germinomatous CNS germ cell tumors.

Bone Marrow and Other Diagnostic Studies

Bone marrow and bone scan studies are indicated in patients with medulloblastoma/embryonal tumors and supratentorial PNET, because of the risk of extra-neural dissemination.

Baseline Investigations Prior to Commencing Treatment

- Ophthalmologic and endocrine assessment as indicated.
- Audiogram and glomerular filtration rate (GFR) prechemotherapy.
- Routine hematological and biochemical assessment prechemotherapy.
- Sperm cryopreservation should be considered for adolescent males undergoing intensive chemotherapy.

MANAGEMENT

Treatment/care should be planned in a co-ordinated fashion. A single pediatric oncologist and his team should ideally supervise care.

Neurosurgery

Surgery is usually the first step in treatment in most of the tumors. Wherever possible, surgeons should aim for gross total or near total resection especially when the tumor is in a non-eloquent area and the risks of resection are considered acceptable. Resection of a tumor usually gives rapid relief from distressing symptoms (e.g. raised ICP). When debulking is carried out, a complete macroscopic resection is preferable to partial removal. Where biopsy is considered in preference to more extensive resection, image

directed biopsy should be used rather than freehand needle. Histological reporting should use one of the accepted grading systems (WHO). Early postoperative imaging (48-72 hours) should determine the extent of tumor resection and must be performed.

In case an urgent procedure is needed for raised ICP and hydrocephalus, ventriculostomy should be done and definitive procedure carried out after 1 to 2 days once the edema and raised ICP has subsided. Recently ventriculostomy is being done minimal invasively by endoscopic techniques.

Perioperative Seizure Medications

Considering the lack of evidence supporting the use of prophylactic anticonvulsants, these should not be administered routinely to patients who have newly diagnosed brain tumors and should be tapered and discontinued in the first postoperative week in patients who have not experienced a seizure. Long-term treatment with anticonvulsants is indicated in patients with brain tumor who suffer a seizure.

Radiotherapy Treatment

Most of the patients (especially those who are more than 3 years of age) require radiotherapy. The acceptable and effective total tumor dose for patients is variable for various tumors ranging from 21-60 Gy. Localized irradiation is preferable to whole brain irradiation except in primitive embryonal tumors where craniospinal irradiation is given. Appropriate customized immobilization should be made for each child. A detailed study of all preoperative and postoperative imaging, preferably with the help of a radiologist and operating neurosurgeon should be undertaken for determining accurate extent of disease for volume generation. Volumes should encompass the presenting enhancing radiological abnormality with appropriate margins as per the histologic subtype of the tumor. All efforts should be made to consider high precision conformal techniques in order to minimize doses of radiation to normal healthy tissues as much as possible. In very young children, radiation may have to be given under short anesthesia and necessitates some adjustments in the techniques. The time from surgery to start of radiotherapy should be kept to a minimum ideally, four weeks. Children may experience mild nausea about 30 minutes to one hour after treatment, especially in the first few fractions. Hair loss (localized/ global depending upon the volume and technique) starts about two to three weeks into treatment. Children may feel tired and sleepy at the end of a course of radiation.

More recently newer radiotherapy techniques like Intensity—modulated radiation therapy (IMRT), 3-D conformal planning techniques, use of Proton beams, etc. have been in an effort to deliver therapy in more efficient manner with less long-term side effects.

Chemotherapy

The role of chemotherapy in managing brain tumors is increasing every day. Routine adjuvant chemotherapy at primary diagnosis is recommended for primitive embryonal tumors, high grade glioma, intracranial germ cell tumors, low grade gliomas of optic pathway affecting vision or other low grade gliomas presenting at a very young age and/or progressing despite radiotherapy. If the pediatric oncologist determines that chemotherapy should be administered the appropriate treatment is varied for various brain tumors.

Long-term Follow-up Care

Survivors of CNS tumors may experience many difficulties. Determinants of late effects in the survivors of brain tumors are: Host factors—Age, genetics and premorbid conditions; tumor factors—Site, histology, biology and outcome; treatment factors—Surgery, radiotherapy and chemotherapy. The functional complexity of the CNS, and the susceptibility of the developing brain to injury, results in special requirements for surveillance following treatment.

COMMON PEDIATRIC CNS TUMORS

For most tumors, the same modalities of treatment are used (i.e. surgery, radiation, and in an increasing number of patients chemotherapy), depending on the type of tumor present, its location and the age of the child.

GLIOMAS (ASTROCYTOMAS)

Astrocytomas are the most common pediatric CNS malignancy accounting for about 50 percent of all CNS tumors. They are usually divided into low-grade gliomas (WHO grade I and II) and high-grade gliomas (WHO grade III and IV).

The different histological variants are:

- *Pilocytic astrocytoma*: Characterized by a fibrillary background and Rosenthal fibers. These tumors behave as benign and grow slowly (WHO grade I)
- *Diffuse or fibrillary astrocytoma*: It is more cellular and infiltrative (WHO grade II)
- *Anaplastic astrocytoma*: It is highly cellular with significant cellular atypia. It is locally invasive and aggressive (WHO grade III)
- *Glioblastoma multiforme*: Demonstrates increased nuclear anaplasia, pseudopalisading and multinucleate giant cells (WHO grade IV).

The other less common forms are Pleomorphic xanthoastrocytomas (classified as WHO grade II subtype, but often behave more aggressively) and Pilomyxoid astrocytomas have variable predictability and may present with diffuse disease.

Gliomas can arise in both infratentorial as well as supratentorial compartment. Very rarely do they have neuraxis dissemination.

Management

Low-Grade Gliomas

On CT, diffuse astrocytomas appear as ill-defined, homogeneous masses of low density without contrast enhancement. MRI usually shows a mass that is hypodense on T1-weighted and hyperintense on T2-weighted images with little enhancement.

Surgical

Complete surgical resection is curative for most, and even with incomplete excision, long-term progression-free survival is common. If subsequent progression occurs, then re-resection generally is undertaken.

Radiotherapy

For patients who have significant residual or progressive disease not amenable to resection, irradiation with focal conformal techniques to a dose of 5000 cGy to 5500 cGy is warranted.

Chemotherapy

Is reserved for very young children and infants and most commonly include Carboplatin and vincristine.

Overall 5-year survival is 95 percent, while progression-free survival is 88 percent.

HIGH-GRADE GLIOMAS

Frequently between 5 and 10 years of age, anaplastic astrocytoma and Glioblastoma are high-grade gliomas (HGGs). On CT and MRI, HGG typically appear as irregularly shaped lesions with partial contrast enhancement and peritumoral edema with or without mass effect.

Management

Surgical

Radical (greater than 90%) surgical resection is the most powerful predictor of favorable outcome in HGG when followed by irradiation.

Radiotherapy

Local or wide-field irradiation to 5000 cGy to 6000 cGy is the mainstay of therapy. The addition of radiation therapy has improved 5-year survival rates (10 to 30%) compared with surgery alone (0%).

Chemotherapy

Most recently, temozolomide and concurrent radiation followed by maintenance temozolomide therapy is being increasingly utilized following significant survival advantage demonstrated in adult glioblastomas. High-dose

chemotherapy for HGG has shown effective responses, and despite significant associated toxicity, may warrant further investigation.

CHIASMATIC GLIOMAS

Gliomas of the optic chiasm are usually low-grade. Commonly associated with Neurofibromatosis type 1 (NF-1). In children who have NF-1, tumor biopsy for histologic confirmation is not necessary because of the highly characteristic appearance on MRI.

Management

Radiation therapy with 5000 cGy to 5500 cGy generally is reserved for older children who have progressive or symptomatic tumors. Therapy with Carboplatin and vincristine has demonstrated tumor shrinkage and/or stabilization in over 90 percent of children younger than 5 years of age.

BRAINSTEM GLIOMAS

Brainstem gliomas (BSGs) comprise 10 to 15 percent of all pediatric CNS tumors. BSGs most commonly arise in the pons (diffuse intrinsic pontine glioma). They have an almost uniformly dismal prognosis. In contrast, those arising from midbrain or medulla are likely to be low-grade lesions that have a more indolent course and better outcome.

Diffuse pontine gliomas show CT and MRI characteristics similar to HGG within an enlarged pons. Low-grade BSGs are relatively discrete, often exophytic, and contrast enhancing with cyst formation.

Management

Surgical resection is not usually possible because of the proximity to vital structures. There is no apparent benefit from a surgical biopsy when the imaging and clinical picture are indicative of a diffuse infiltrating pontine glioma. For focal tumors (nontectal), complete resection may be safe and may not require any further therapy. Treatment is local irradiation with 5400 cGy. Over 90 percent of patients who have diffuse intrinsic lesions transiently respond, but ultimately succumb to disease progression within 18 months of diagnosis. Neither hyper fractionated radiotherapy nor chemotherapy has been shown to add benefit. Following the success of temozolomide in adult high-grade gliomas, similar schedule has been attempted in these patients but without any significant gain in outcome. Low-grade lesions are treated with similar irradiation doses but overall respond less favorably than their counterparts in other locations.

MEDULLOBLASTOMA

Medulloblastoma, arises in the posterior fossa, and is the most common malignant brain tumor of childhood representing approximately 20 percent of all childhood brain tumors. It arises from the posterior fossa but can have

leptomeningeal dissemination in about 30 to 40 percent of the cases. Less commonly (approximately 4%) it can spread to extra CNS sites like bones, bone marrow, liver, etc.

Staging studies should include MRI of the spine (with contrast, preferably preoperatively), lumbar CSF cytology, bone scan, liver function tests, and bone marrow examination.

Histology and cytogenetics of the original tumor are essential to evaluate for large cell anaplastic subtype and for monosomy 22, which is characteristic of *atypical teratoid/ rhabdoid tumor (AT/ RT)*.

Specific molecular genetic abnormalities like MYC-C, ERBB2 (markers of poor prognosis) and TRK-C (associated with good prognosis) should be tested if available.

Management

The initial step in treatment is surgical resection in most of the patients. Total or near-total resection of the primary tumor site is associated with better survival, predominantly in non-disseminated patients. Significant postoperative complications may occur, and 25 percent of patients may develop cerebellar mutism syndrome following resection of midline cerebellar tumors.

Following surgery, patients usually are stratified into one of two risk groups, based on extent of surgical resection and disease extent at the time of diagnosis (Table 3).

Medulloblastoma: Radiotherapy and Chemotherapy

- *Patients greater than 3 years of age with average-risk disease* are to be treated with craniospinal (2340 cGy) and local boost radiotherapy (5580 cGy), supplemented with adjuvant chemotherapy. Local tumor bed boost (with 1.5-2.0 cm margin, as opposed to whole posterior fossa boost) should be done with conformal RT techniques if available.

Different chemotherapeutic regimens have shown benefit in medulloblastoma. Probably the best tested is the use of vincristine during radiotherapy and the combination of CCNU, cisplatin and vincristine, or cyclophosphamide, cisplatin, and vincristine following radiotherapy. The use of preradiotherapy chemotherapy has resulted in inferior survival.

With such combination approaches used event free survival is about 80 percent in this group.

- *Children older than 3 years who have high-risk medulloblastoma* are treated with higher doses of craniospinal radiation therapy (3600 cGy) and similar doses of local radiotherapy, as used for children with average-risk disease, and chemotherapy during and after radiation therapy. This group has approximately a 50 percent to 60 percent 5-year disease-free survival with this treatment modality.

Recent trials have included the use of carboplatin as a radiosensitizer during radiation therapy and the delivery of higher-dose chemotherapy, essentially an intensified cisplatin, cyclophosphamide, vincristine, and etoposide regimen, supported by peripheral stem cell rescue, following radiotherapy, with possibly better results.

- Treatment of *patients younger than 3 years* is problematic, because of the immaturity of the brain and the resultant deleterious effects of whole brain irradiation, increased likelihood of dissemination at the time of diagnosis in younger patients. Infants who have desmoplastic/ nodular tumors are quite responsive to chemotherapy, and 75 percent or greater of patients harboring this histologic variant may be cured by chemotherapy alone. Outcome is less favorable in infants who have classical, undifferentiated medulloblastoma, especially in those who have disseminated disease at the time of diagnosis. More intensive chemotherapeutic regimens using peripheral stem cell support or regimens that have been supplemented with high-dose, intravenous, and intrathecal methotrexate have shown possible increased efficacy.

SUPRATENTORIAL PRIMITIVE NEUROECTODERMAL TUMORS

They are relatively uncommon, comprising 2.5 percent of all childhood brain tumors. These are morphologically similar to “medulloblastoma” but located supratentorially. Biologically they have been seen to behave differently than medulloblastomas.

Table 3: Risk stratification of medulloblastoma

Risk category	Average	High
Extent of disease	Negative CSF Normal MRI of spine No leptomeningeal disease away from the primary site of tumor	Positive CSF cytology Positive MRI of spine with Gd-DTPA Leptomeningeal disease present away from the primary site of tumor
Volume of residual tumor	≤1.5 cm ²	>1.5 cm ²
Histology	Undifferentiated	Large-cell anaplastic
Age at diagnosis	>3 years	<3 years

Management

Surgical: Forms the mainstay of the treatment, but the degree of surgical resection has been related variably to outcome.

Radiotherapy and Chemotherapy: Postsurgical management has been similar to that employed for high-risk medulloblastoma patients.

Prognosis is worse than medulloblastoma.

PINEOBLASTOMAS

They are a subvariant of embryonal tumors and are managed similarly to high-risk medulloblastomas.

Atypical Teratoid/Rhabdoid Tumors

These tumors usually occur in children younger than 3 years. Immunohistochemical studies demonstrated that AT/ RTs were different from medulloblastomas, they are positive for epithelial membrane antigen, vimentin, cytokeratin, glial fibrillary acidic protein, and, at times, smooth muscle actin and neurofilament protein. Dissemination has been reported in approximately 25 percent of patients at diagnosis.

Management of AT/ RTs has been extremely problematic. Outcome after treatment of infants on protocols used for children younger than 3 years with medulloblastoma, including high-dose chemotherapy protocols, has been disappointing, with prolonged survival occurring in less than 20 percent of patients who had nondisseminated tumors, primarily in those who had undergone a total or near-total resection. Survival seems more favorable in patients older than 3 years at diagnosis treated with extensive resections, craniospinal and local boost radiotherapy, and chemotherapy.

EPENDYMOMA

Five to ten percent of all childhood brain tumors are ependymomas. Most arise in the posterior fossa (most commonly from fourth ventricle) but can also arise in the supratentorial compartment. Approximately 5 percent of ependymomas are disseminated at the time of diagnosis.

Management

Surgery

Mainstay of the treatment is surgery. The degree of surgical resection is a critical determinant of outcome. Those who have total or near-total resections have the highest likelihood of long-term disease control. Second-look surgery after chemotherapy but before radiation may be considered if possible in view of crucial role of extensive surgery in patients with ependymomas.

Radiotherapy

The need for radiotherapy in totally resected nonanaplastic ependymomas is somewhat controversial. Small series have suggested that totally resected supratentorial lesions can be treated with surgery alone. Most patients with completely resected infratentorial tumors have received radiotherapy, with resultant 5-year progression-free survival rates of 75 to 80 percent. Local radiotherapy, using conformal treatment planning and doses ranging between 5500 cGy and 5960 cGy, is as effective as craniospinal and local boost radiotherapy. Patients who have an aplastic tumors may fare less well. Patients, who have subtotally resected ependymoma, after local radiotherapy, have 5-year progression-free survival rates of probably no higher than 50 percent.

Chemotherapy

Combination therapy with radiation and chemotherapy has been reserved predominantly for children older than 3 years and those patients who have subtotally resected and/or anaplastic tumors. Ependymomas comprise 20 percent of infratentorial tumors in infants. In children younger than 3 years chemotherapy usually is used in attempts to delay the need for radiotherapy, although there has been renewed interest in using local radiotherapy in children as young as 1 year who have infratentorial tumors, especially for patients who have tumors not amenable to total surgical resection.

GERM CELL TUMORS

Approximately 2 to 5 percent of all childhood brain tumors are germ cell tumors. Origin is in the pineal and suprasellar region, but may occur throughout the brain. Majority are germinomas (~55%), teratomas, and mixed germ cell tumors (~33%), and the remaining 10 percent are malignant endodermal sinus tumors, embryonal cell carcinomas, choriocarcinomas, and teratocarcinomas.

Histological confirmation is usually, but not always, required for the diagnosis of germinomas and distinction from other pineal region tumors such as pineoblastomas, pineocytomas, and teratomas. Elevated CSF and, in selected cases, blood levels of AFP and β -hCG can be used to confirm a mixed germ cell tumor. Highly elevated levels of β -hCG alone are diagnostic of a choriocarcinomas.

Surgery

Usually is preserved for those patients for whom CSF markers cannot make a diagnosis or when the tumor is very large and requires debulking.

Radiotherapy

Ninety-five percent or more of patients with pure germinomas can be cured, including those with disseminated disease at the time of diagnosis by craniospinal plus local boost radiotherapy.

Chemotherapy

Germinomas are also chemosensitive, and treatment with preradiation chemotherapy followed by more localized radiotherapy, usually whole ventricular therapy, may be as effective and result in somewhat less sequelae because of the avoidance of whole-brain radiation. Mixed germ cell tumors on the other hand have only a 40 to 60 percent likelihood of long-term disease control after treatment with radiotherapy. In these patients, multidrug chemotherapeutic regimens, either given before or after radiotherapy, have resulted in better survival rates.

CRANIOPHARYNGIOMAS

Five to ten percent of all childhood brain tumors are craniopharyngiomas. These tumors commonly present with failure of growth, delayed sexual maturation, weight gain, and, in some cases, diabetes insipidus.

Management

Optimal management is still controversial. Complete tumor removal results in an 80 to 95 percent 10-year progression-free survival rate and cure, but this often are associated with significant behavioral and neurocognitive difficulties and permanent endocrine insufficiency. Most patients will need growth, thyroid, cortisol supplementation and chronic DDAVP replacement after total resection. Partial tumor resection and/ or cyst aspiration followed by radiotherapy is alternative approach. It is as effective in controlling disease and result in less morbidity. Conservative surgery and modern high precision radiotherapy employing conservative margins associated with excellent outcome in terms of survival and preservation of function is being increasingly adopted. Intracavitary brachytherapy using p32 or y90, repeated cyst aspiration, or the use of intracyst bleomycin may be useful in selected situations. At present there is no established role for chemotherapy in craniopharyngioma.

CHOROID PLEXUS TUMORS

The treatment of choice for choroid plexus papilloma is surgical removal. Risk of surgical mortality is high due to marked vascularity of tumor, the massive hydrocephalus and very young age. Choroid plexus carcinomas are locally invasive. For long-term disease control gross total resection is recommended. Optimal treatment for subtotally resected choroid plexus carcinomas is unclear. Adjuvant chemotherapy and radiotherapy have been used and may result in tumor response.

SPINAL CORD TUMORS

Spinal cord tumors may be extremely difficult to diagnose in young children. They may present with delays in walking and gait disturbances. Tumors in the conus region result in bowel and bladder difficulties. In total, spinal cord tumors account for less than 10 percent of all CNS neoplasms. The most common primary CNS lesions are gliomas and ependymomas.

Management

Treatment of low-grade spinal astrocytomas is by extensive surgical resection or by partial resection followed by radiotherapy, or possibly, in very young children, chemotherapy. The outcome for children with ependymomas is variable. Long-term control after resection is possible and adjuvant radiotherapy is a useful adjunct. High-grade lesions are difficult to resect. Most patients relapse within 3 to 5 years of diagnosis despite adjuvant radiotherapy.

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*Nehal S Parikh, Stephen S Roberts***EPIDEMIOLOGY**

In children, neuroblastoma is the most common extracranial solid tumor ranging from 8 to 10 percent of all childhood cancers; while in infancy it remains the most commonly diagnosed cancer. The prevalence of neuroblastoma in most industrialized countries is 1 case per 7,000 live births, with an incidence approximating 8-10 children with neuroblastoma (NB) per million per year.^{1,2} NB is slightly more prevalent in boys compared to girls 1.1 to 1. Although the incidence appears to be uniform throughout the world, the rates in low-middle income countries are less clear; several reports have suggested that rates are lower, particularly in sub-Saharan Africa.³ It is not clear if this is due to under-reporting and under-diagnosing or truly reflective of lower incidence pattern and genetic diversity of tumor predisposition in certain areas. Numerous researchers have monitored the incidence of neuroblastoma through large screening studies in infants and children. Despite an increased detection of low stage neuroblastoma in infants, the prevalence or the mortality rates of those children over one year of age with higher stage disease were not reduced.⁴⁻⁹ The uncertain benefits of routine screening programs have led to halting global screening projects.

PATHOGENESIS

Neuroblastoma is a model disease where genetic understanding of the tumor has facilitated biology-based risk stratification and treatment. Numerous genetic changes identified in NB have been strongly correlated with disease outcome and are an integral part of our understanding of the development, treatment and outcome of this disease. Recent discoveries in the germline mutations in the anaplastic lymphoma kinase (ALK) and PHOX2B genes in a small subset of NB patients (less than 2%) has

been linked to familial predisposition for development of NB.^{10,11} In contrast, acquired somatic changes in neural crest stem cells appear to have a higher likelihood of developing neuroblastoma.¹²

Many aggressive neuroblastomas contain genomic level instability, resulting in chromosomal rearrangement, and unbalanced translocation, in contrast the less aggressive neuroblastic tumors tend to have mitotic defects leading to chromosomal gains and losses, including amplifications, translocations and whole chromosome losses and gains.¹³ There have been reports of prognostic significance in non-random changes identified in many of the patients with neuroblastoma. The NB's that are characterized by loss and gain of whole chromosomes and few or no segmental chromosome abnormalities are generally hyperdiploid, lack genetic changes associated with biologically unfavorable disease, and are most commonly seen in younger children less 18 months of age. These neuroblastoma tumors generally have excellent prognosis, with many undergoing spontaneous differentiation and/or apoptosis.² It has been suggested that neuroblastomas that are biologically unfavorable do not evolve from favorable tumors but are distinct subtypes from the beginning. Therefore, NBs that are characterized by recurrent segmental chromosome abnormalities have non-random alterations of numerous chromosomes, including deletions of 1p36 and 11q and unbalanced gain of chromosome 17q.¹⁴ However, the most critical genomic alteration is amplification of the MYCN oncogene, occurring in approximately 20 percent of neuroblastoma, which is typically associated with advanced disease, older age (>18 months), and a poorer outcome.^{15,16} MYCN testing and characterization of the tumor is currently considered the standard part of the diagnosis, as it clearly has biological and treatment importance.

PATHOLOGY

Neuroblastoma is the most common extracranial small, round, blue-cell tumor of childhood. Other malignancies that appear similar on the H&E staining include non-Hodgkin lymphomas, Ewing sarcoma family tumors, peripheral primitive neuroectodermal tumors, and soft tissue sarcomas such as rhabdomyosarcoma. Neuroblastic tumors typically arise from the neural crest derived cells of the sympathetic chain. The spectrum of neuroblastic cell differentiation and maturation is represented by three histopathological subtypes: neuroblastoma, ganglioneuroblastoma, and ganglioneuroma.^{2,17} These cells are small and uniform in size, with dark nuclei and little cytoplasm. Nearly all but the most primitive neuroblastoma form neuropil, collections of primitive neurites; In contrast, a minority of tumor tissue will have a classic finding in neuroblastoma, the Homer-Wright pseudorosette, which is a ring of neuroblasts surrounding a core of eosinophilic neuropil. Ganglioneuromas represent a fully differentiated, benign collection of mature ganglion cells, Schwann cells and neuropil. The characterization of tumor subtype as ganglioneuroblastoma represents the spectrum of differentiation between malignant neuroblastoma and mature, benign ganglioneuromas.^{2,18}

Prognostic significance of the histopathologic differentiation has been documented by Shimada, et al. They have identified patient age, Schwannian cell stroma, mitosis-karyorrhexis index, and differentiation state to designate tumors as favorable or unfavorable. A recent modification of the system was adapted for wider global utility and is now known as the international neuroblastoma pathology classification (INPC) system.¹⁸

CLINICAL MANIFESTATIONS

The clinical manifestations are primarily dependent on the location of the primary and metastatic tumors. Approximately 65 percent of primary tumors arise in the abdomen; remaining are seen in the thoracic, cervical or pelvic region. A small cohort of patients (1%) have no identifiable primary neuroblastomas.² The incidence of neuroblastoma peaks between the ages 0-4, with less than 5 percent of the patients presenting after 10 years of age.¹⁹ Neuroblastoma is often disseminated at diagnosis, with spread most commonly involving locoregional lymph nodes, bone, bone marrow, and liver. Lung and central nervous system metastases are rare.²⁰

Localized abdominal neuroblastomas may present with distended abdomen or pain, but is often asymptomatic and discovered incidentally by a caregiver. Thoracic neuroblastomas are also frequently discovered incidentally on chest radiographs obtained for unassociated medical reasons. High-level thoracic lesions have been shown to cause Horner syndrome (unilateral ptosis, myosis, and anhydrosis). Although rarely seen, large thoracic tumors can result

in mechanical obstruction leading to superior vena cava and superior mediastinal syndromes. In approximately 5 to 15 percent of patients with neuroblastoma, extension via the neural foramina of the vertebral bodies is seen and can cause nerve root or spinal cord compression resulting in symptomatic weakness, paralysis, bowel and/or bladder dysfunction and radicular pain.²¹⁻²³ Bone marrow involvement may lead to marrow space replacement and resultant anemia and bleeding; widespread cortical bone metastases are frequently seen and can cause fever, pain, limp, and significant irritability in younger children.²⁴

Neuroblastoma is notably associated with several classic presentations. Tumor infiltration of the periorbital bones in metastatic disease may present with proptosis and periorbital ecchymoses.²⁵ A subset of infants classified as stage 4s will frequently present with multiple bluish, painless, subcutaneous nodular lesions.²⁶ Rarely, these infants may have massive involvement of the liver leading to respiratory, circulatory and renal compromise.^{27,28}

Two distinct paraneoplastic syndromes have been associated with neuroblastoma. Opsoclonus-myoclonus syndrome (OMS), found in 2-3 percent of patients with neuroblastoma is characterized by rapid and shifting eye movements (dancing eyes), myoclonus, and ataxia.²⁹ OMS considered to be an immune-mediated targeting of antibodies against the tumor and the elements of the normal nervous system; typically seen in children with low stage disease and an excellent prognosis.^{30,31} Despite remission from the neuroblastoma, 90 percent will have long-term neurologic sequelae, including significant cognitive deficits due to the presumed secondary impact on the normal nervous system.²⁹ VIP syndrome is an intractable secretory diarrhea, with hypokalemia and dehydration caused by tumor secretion of vasoactive intestinal peptide. Usually seen in patients with ganglioneuroblastomas or ganglioneuromas and removal of the primary tumor typically leads to resolution of the diarrhea with an excellent long-term survival.³²

DIAGNOSIS

A complete physical examination should evaluate for any masses, adenopathy, bony defects, organomegaly and a careful assessment for neurological weakness or paralysis. A diagnosis of neuroblastoma requires clear pathologic review with demonstration of either the neuroblasts from tumor biopsy or unequivocal presence of neuroblastoma in a bone marrow aspirate/biopsy along with the elevated urine catecholamine levels. Genetic analysis of neuroblastoma, such as DNA ploidy, MYCN amplification, and chromosomal aberrations, has been shown to guide treatment and has prognostic implications for neuroblastoma.¹⁶

The imaging modality of choice for delineation of the primary tumor is CT scan of the chest, abdomen, and

pelvis, with further evaluation of the spine for paraspinous tumors. A bilateral bone marrow evaluation should be done in all patients for staging evaluations. ^{123}I or ^{131}I -MIBG has guided evaluation of metastatic foci, including bone. Current studies report that ^{123}I -MIBG is more sensitive and specific than a Tc-99 bone scan or ^{131}I -MIBG. Approximately 10 percent of tumors are not MIBG avid and may require other radiologic modalities for assessment. Recent studies suggest that ^{18}F FDG positron emission tomography (PET) has been useful for lower stage patients, but ^{131}I -MIBG remains the gold standard for high stage disease.³³

DIFFERENTIAL DIAGNOSIS

Although intrathoracic neurofibromatosis tumors appear similar to neuroblastomas radiologically, they tend to be more nodular in outline, and grow along the course of the intercostal nerves, resulting in characteristic indentations along the inferior costal margin of the tumor. Other retroperitoneum tumor includes Wilms tumor; these tend to feel smooth to palpation in contrast to the nodular feel of a neuroblastoma and generally lack the characteristic intratumoral calcifications seen in imaging studies of NBs. Cervical adenitis and lymphoma may be challenging to distinguish from cervical neuroblastoma on certain radiologic imaging. Tumor extension through the neural foramina causing spinal cord compression may result in weakness or paralysis of the lower extremities. A complete history, physical exam and imaging studies may help to differentiate NB from other primary neurologic causes of weakness and paralysis. Since NB metastasizes to the bone marrow, it can mimic leukemia with pallor, fatigue, recurrent fevers, and bruising.

TREATMENT

Neuroblastoma is a distinct tumor with biological variability and its approach to therapy, from observation alone in very low risk stages to intensive, multi-modality therapy

for the high risk stages. These divergent treatments are determined based upon risk group stratification. In 2009, the international neuroblastoma risk group (INRG) task force proposed a new stratification schema called the INRG classification system, which is now in widespread use.¹⁶ This schema includes INRG stage (Table 1), age, histologic category, grade of tumor differentiation, MYCN status, presence/absence of 11q aberrations, and tumor cell ploidy (Table 2). Of these, the key criteria for risk assignment are disease stage, patient age (less than 18 months versus greater than 18 months) at diagnosis, and MYCN amplification status. Based on this stratification, patients are classified into four different risk groups: very low, low, intermediate, and high risk, with treatment based upon this classification.³⁴

VERY LOW RISK DISEASE

Patients with INRG-defined very low risk disease have small tumors (or asymptomatic MS disease) will usually regress spontaneously or undergo differentiation into benign ganglioneuromas. These tumors have been successfully managed with close observation without therapeutic intervention. Preliminary unpublished reports from a recently completed children's oncology group study of observation of perinatal neuroblastoma showed event-free and overall survival rates of 97.7 and 100 percent, respectively.

Ms disease (formerly called stage 4s disease, where "s" represents "special") is an entity unique to neuroblastoma. This stage has been revised to include age up to 18 months at diagnosis with metastatic disease limited to the liver, skin and bone marrow.³⁵ Despite being metastatic at the time of diagnosis, the overall prognosis for patient with Ms is extremely good. Recent reports have shown overall survival rates of 92 percent.³⁶ In this cohort, the very young infants (usually less than 2 months of age at diagnosis) may initially have a rapid tumor progression leading to massive hepatomegaly and respiratory and cardiovascular compromise, which can be life-threatening

Table 1: International neuroblastoma risk group staging system*

Stage	Description
L1	Localized tumor not involving vital structures as defined by the list of image-defined risk factors** and combined to one body compartment
L2	Locoregional tumor with presence of one or more image-defined risk factors
M	Distant metastatic disease (except stage MS)
MS	Metastatic disease in children younger than 18 months with metastases confined to skin, liver, and/or bone marrow

*Table modified from "The International Neuroblastoma Risk Group (INRG) Staging System: An INRG Task Force Report", J Clin Oncol 27:298-303.

**Image-defined risk factors are surgical risks factors detected by imaging studies that make safe, complete resection of the tumor impractical at the time of diagnosis. See the primary reference for a full listing of these risk factors.

Table 2: International neuroblastoma risk group classification system*

<i>INRG stage</i>	<i>Age (months)</i>	<i>Histologic category</i>	<i>Grade of tumor differentiation</i>	<i>MYCN</i>	<i>11q aberration</i>	<i>Ploidy</i>	<i>Pretreatment risk group</i>
L1/L2		GN maturing; GNB intermixed					Very Low
L1		Any, except GN maturing or GNB intermixed		NA			Very Low
	<18	Any, except GN maturing or GNB intermixed		AMP			High
					No		Low
				NA	Yes		Intermediate
L2			Differentiating	NA	No		Low
	≥18	GNB nodular; neuroblastoma	Poorly differentiated or undifferentiated		Yes		
				NA			Intermediate
				AMP			High
	<18			NA		Hyperdiploid	Low
	<12			NA		Diploid	Intermediate
M	12 to <18			NA		Diploid	Intermediate
	<18			AMP			High
	≥18						High
					No		Very Low
MS	<18			NA	Yes		High
				AMP			High

*Table modified from “The International Neuroblastoma Risk Group (INRG) Staging System: An INRG Task Force Report”, J Clin Oncol 27:298-303.

without expeditious therapy. Chemotherapy as per the intermediate risk group protocols have been used successfully to stabilize the patient and reverse the course of rapid tumor progression.³⁷ Low-dose radiotherapy (3 – 6 Gy divided into several fractions) should be reserved for those patients with life-threatening complications and an inadequate response to initial chemotherapy course.² MYCN amplification in this group has been shown to have poorer prognosis and have required more intensive therapies per the high-risk protocols.³⁸

LOW RISK DISEASE

Low risk patients include those with stage L1 or L2 disease, are generally of younger age at diagnosis (<18 months) and do not have MYCN amplification. Surgical resection of the tumor with >50 percent resected has shown to correlate with > 95 percent overall survival.³⁹ Chemotherapy and radiation therapy are rarely needed and should

be reserved for the patient that experiences disease recurrence.

INTERMEDIATE RISK DISEASE

Treatment of intermediate risk patients is guided by patient's age, biological characteristics of the tumor, and stage of the tumor. The children's oncology group study A3961 significantly de-intensified therapy based on certain biological features of the tumors. The 3 year overall survival of 96 percent was noted for the entire group, with 98 percent in the group with the favorable biological features and 93 percent among the patients with unfavorable biological features.³⁷ Currently, efforts are underway to further reduce chemotherapy in select patients without biologically unfavorable segmental chromosomal abnormalities. Importantly, these studies have shown that aggressive surgery and radiation therapy are not required to achieve excellent results. Therefore, surgical

resection should be focused on removing the bulk of the tumor without increasing risk of morbidity and mortality. Radiation therapy should be reserved for those intermediate risk patients with refractory disease and/or those who encounter local recurrence.⁴⁰

HIGH-RISK DISEASE

Most patients defined as having high-risk disease are over the age of 18 months with metastatic disease at diagnosis, regardless of their other biological risk factors including MYCN amplification.^{16,41} However, it is clear that infants and patients with non-metastatic disease who have MYCN amplification have aggressive disease and a worse prognosis and should also be classified as high-risk patients.^{2,38,42} Other biological features that have been correlated with poorer outcomes are elevated ferritin and LDH levels at diagnosis. At this time, it is unclear, if these markers can serve as surrogate for absence of MYCN testing/availability. High-risk neuroblastoma is treated with aggressive, multi-modal therapy including surgery, radiotherapy, chemotherapy, and biological/immunotherapy. The current treatment regimens followed by the major cooperative groups in North America, Europe, and Japan includes three broad treatment phases: intensive induction chemotherapy, consolidation therapy, and maintenance therapy.

The goal of induction chemotherapy is bulk tumor reduction with dose and time intensive chemotherapy. The current COG induction regimen is built upon the Memorial Sloan-Kettering Cancer Center experience with the addition of cyclophosphamide and topotecan in the first two cycles, followed by two alternating cycles each of cyclophosphamide, doxorubicin and vincristine followed by cisplatin and etoposide. The European-based SIOPEX group utilizes an intensively timed regimen of cisplatin (C), vincristine (O), carboplatin (J), etoposide (E), and cyclophosphamide (C) called “rapid COJEC”. In this regimen, eight cycles of these drugs in various combinations are given every ten days regardless of hematopoietic recovery. Although direct comparison of induction regimens have not been done, the response rates of each of these clinical trials have shown that high-dose platinum and alkylator-based regimens have overall induction response rates (CR+VGPR+PR) of 70-80 percent depending upon the report.⁴³⁻⁴⁷

Consolidation therapy targets potentially resistant neuroblastoma cells using high-dose/myeloablative chemotherapy and radiation therapy. Several studies have been conducted that suggest myeloablative, autologous stem cell supported consolidation regimens have improved survival in high-risk neuroblastoma patients.⁴⁸ However, controversy remains as to the optimal conditioning regimen. The SIOPEX group recently closed their trial after interim results suggested that busulfan and melphalan was superior to cisplatin, etoposide and melphalan.

Neuroblastoma is considered a radiosensitive tumor and radiation therapy of 20–36 Gy to the primary site is routinely given to high-risk patients.²

Maintenance therapy is biological and/or immunotherapy targeting minimal residual disease (MRD). 13-cis retinoic acid has been shown to improve outcomes in high-risk patients when given in the MRD setting.⁴⁸ It is typically given as a monthly 14-day cycles for six months. Additionally, the children's oncology group recently reported that the addition of immunotherapy using the chimeric antibody ch14.18 directed at the neuroblastoma tumor antigen GD2, combined with the cytokines granulocyte-macrophage colony stimulating factor (GM-CSF) and interleukin-2 (IL-2) significantly improved survival in these patients.⁴⁹ Memorial Sloan Kettering Cancer Center has also reported excellent anti-NB response using the anti-GD2 mouse monoclonal antibody 3F8.⁵⁰ Currently, however, anti-GD2 immunotherapy remains available only as part of research studies; efforts are underway to commercialize the ch14.18 antibody, and future therapies will likely incorporate immune-based therapies within the standard approach.

RELAPSED NEUROBLASTOMA

Low and intermediate-risk patients who have local relapse are highly salvageable, often with only a second surgery.⁵¹ Patients with high-risk neuroblastoma who have disease recurrence, however, remain an enormous challenge. Although there are anecdotal reports of cure after relapse, to date there are no widely accepted curative approaches to these patients. The camptothecin analogues topotecan and irinotecan combined with cyclophosphamide or temozolomide have shown some activity in these patients in various studies.⁵²⁻⁵⁵ Oral etoposide is also frequently given, with some patients showing some improvements.⁵⁶ However, none of these regimens are curative. Recurrent high-risk neuroblastoma patients should be considered for enrollment on experimental therapeutic trials when available.

PROGNOSIS

Prognosis varies greatly by risk group. Currently, with observation and/or surgical resection alone, patients with low risk disease have overall survival rates in excess of 95 percent in the developed world.³⁹ Intermediate risk patients also do very well with moderate chemotherapy and have overall survival rates of over 87 percent.³⁷ Prognosis for high-risk disease, however, remains poor. Historically, 5 year event-free survival rates have been less than 20 percent. Using the current intensive, multimodality therapy regimens, long-term survival rates have increased to approximately 40-50 percent.⁵⁷ While this is an improvement over historical rates, there is room for substantial improvement. Additionally, significant long-term side effects of intensive

therapy remain a large issue for those high-risk patients that are cured of their disease.⁵⁸

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Soft Tissue Sarcomas in Children

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Soft tissue sarcomas (STS), the fifth most common solid tumors in children, are relatively rare and account for about 6 to 7 percent of all childhood malignancies. Pediatric STS are a heterogeneous group of malignant tumors originating from primitive mesenchymal tissue that share some biologic characteristics but differ in histology. Rhabdomyosarcomas (RMS) which are tumors of striated muscle, and undifferentiated sarcomas represent more than half of all pediatric STS and nonrhabdomyosarcoma soft tissue sarcomas (NRSTS) account for the remainder.

RHABDOMYOSARCOMA

Childhood rhabdomyosarcoma, a soft tissue malignant tumor of skeletal muscle origin, accounts for approximately 3.5 percent of the cases of cancer among children aged 0 to 14 years and 2 percent of the cases among adolescents and young adults aged 15 to 19 years. The incidence is 4.5 per million children and 50 percent of cases are seen in the first decade of life.

Overall, the male-to-female ratio is 1.3:1. The incidence curve shows two peaks which tend to be associated with different locations. Patients aged 2 to 6 years tend to have head and neck or genitourinary tract primary tumors, whereas adolescents aged 14 to 18 years tend to have primary tumors in the extremities, trunk, or paratesticular location. Several distinct histologic groups have prognostic significance, including embryonal rhabdomyosarcoma (ERMS), which occurs in 55 percent of patients; the botryoid variant of ERMS, which occurs in 5 percent of patients; alveolar rhabdomyosarcoma, which occurs in 20 percent of patients; and undifferentiated sarcoma, which occurs in 20 percent of patients.

Most cases of rhabdomyosarcoma occur sporadically, with no recognized predisposing factor or risk factor. Several genetic syndromes and environmental factors are associated with increased prevalence of

rhabdomyosarcoma. Genetic syndromes include neurofibromatosis, Li-Fraumeni syndrome (germline mutation of the tumor suppressor gene *TP53*), Rubinstein-Taybi syndrome, Gorlin basal cell nevus syndrome, Beckwith-Wiedemann syndrome, Costello syndrome. There may be association with congenital anomalies GU tract, CNS (i.e. Arnold-Chiari malformation) gastrointestinal and cardiac anomalies. Environmental factors that may predispose the development of rhabdomyosarcoma, include parental use of marijuana and cocaine, intrauterine exposure to X-rays and previous exposure to alkylating agents. The alveolar variant (reminiscent of lung alveoli) is usually associated with chromosomal translocations, t(2;13) or t(1;13). The resulting hybrid molecule is a potent transcription activator which is believed to contribute to the cancerous phenotype by abnormally activating or repressing other genes. The embryonal subtype usually has a loss of heterozygosity at band 11p15.5.

CLINICAL PRESENTATION

The most common sites of occurrence of RMS are the head and neck region, extremities, and genitourinary (GU) tract. Other sites include the trunk, orbit, and retroperitoneum. The botryoid variant of ERMS arises in mucosal cavities, such as the bladder, vagina, nasopharynx, and middle ear. Lesions in the extremities are most likely to have an alveolar type of histology. Metastases are found predominantly in the lungs, bone marrow, bones, lymph nodes, breasts, and brain. Typical presentations by the location of nonmetastatic disease include: orbital disease—proptosis or squint, paratesticular—painless scrotal mass, vagina—protruding polypoid mass, extremity—painless mass, parameningeal (ear, mastoid, nasal cavity, paranasal sinuses, infratemporal fossa, pterygopalatine fossa)—upper respiratory symptoms or pain, and retroperitoneal mass.

DIAGNOSTIC EVALUATION

Imaging

Plain radiography of the primary site and of the chest is helpful in determining the presence of calcifications and bone involvement of the primary tumor and to search for metastatic lung lesions. CT scan of the chest is done to evaluate for metastases to the lungs and may be useful to assess local bony erosion, or for assessing liver metastases with abdominal or pelvic primary tumors. MRI of the tumor region gives better definition of the mass and its invasion of adjacent organs, especially in orbital, paraspinous, or parameningeal regions. Radionuclide bone scan helps identify metastases to the bones.

Tissue Diagnosis

Open biopsy enables adequate tissue sampling for diagnosis and molecular studies. Core needle biopsy is an alternative. Depending on the location, definitive surgery can be postponed to allow for neoadjuvant chemotherapy to shrink the tumor. Bone marrow aspiration and biopsy is done for metastatic spread to bone marrow. Rhabdomyosarcoma is one of the small, round blue-cell tumors of childhood. Occasionally, these types of tumors can be difficult to differentiate. Rhabdomyosarcoma cells tend to have variable differentiation along the myogenesis pathway and demonstrate positive immunohistochemical results for muscle-specific markers, such as myoglobin, actin, and desmin.

MANAGEMENT

Treatment in patients with rhabdomyosarcoma (RMS) involves a combination of surgery, chemotherapy, and radiation therapy. Because the treatment plan is complicated and prolonged and because many medical issues are unique to pediatric oncology, patients should be referred to a center with personnel who are skilled in caring for children with cancer.

At present, patients are categorized according to their risk, which takes into account the location of the tumor and the histologic and surgical results. Low-risk patients are those who have the best prognosis, whereas intermediate-risk or high-risk patients have an increased risk of having relapses and incurable disease. All patients with metastatic disease (group IV, stage 4) are considered high-risk, except those younger than 14 years with embryonal rhabdomyosarcoma (ERMS). Although all patients require chemotherapy, regimens vary depending on the stage and group.

- Surgicopathologic (clinical) group (Groups I–III are for localized disease).
 - Group I: Tumor completely removed
 - Group II: Microscopic residual tumor, involved regional nodes, or both

- Group III: Gross residual tumor
- Group IV: Distant metastatic disease
- Tumor, nodes, and metastases (TNM) staging system
 - Tumor: Confined to the site of origin (T1) or extends beyond the site of origin (T2)
 - Node: No regional node involvement (N0), regional node involvement (N1), or nodes unknown (NX)
 - Metastasis: No metastasis (M0), or metastases present at diagnosis (M1)
- RMS staging system
 - Stage 1: Orbit, head, and/or neck (not parameningeal) involvement, and involvement of the GU tract (not bladder or prostate)
 - Stage 2: Other locations, N0 or NX
 - Stage 3: Other locations, N1 if the tumor is less than 5 cm or N0 or NX if the tumor more than 5 cm
 - Stage 4: Any site with distant metastases

Surgical management of rhabdomyosarcoma varies depending on the location of the tumor. If feasible, tumors should be excised promptly and without unacceptable disfigurement or loss of function. Even if metastatic disease is present, surgical excision of the primary site should be performed, if possible. The surgical result helps determine the clinical grouping to be used for treatment stratification. Standardized surgical guidelines for the various sites are followed in the various protocols for RMS. Standard therapy for rhabdomyosarcoma (RMS) includes chemotherapy combined with surgical resection, radiotherapy, or both for local control, if necessary. RMS are very sensitive to chemotherapy and radiotherapy and in many sites such as the orbit, parameningeal and GU, this is the mainstay of local therapy, particularly when the tumor is of the embryonal subtype. Extremities are unfavorable sites for RMS because of high incidence of alveolar histology, and large size of tumors.

The prognosis for a child or adolescent with rhabdomyosarcoma is related to the age of the patient, site of origin, widest diameter of the tumor, resectability, presence of metastases, number of metastatic sites or tissues involved, presence or absence of regional lymph node involvement, histopathologic subtype (alveolar vs embryonal). Children aged 1 to 9 years have the best prognosis, while those younger and older fare less well. Primary sites with more favorable prognoses include the orbit and nonparameningeal head and neck, paratestis, vulva, vagina, uterus (nonbladder, nonprostate genitourinary tract), and biliary tract. Patients with smaller tumors (<5 cm) have improved survival compared with children with larger tumors. Children with metastatic disease at diagnosis have the poorest prognosis. Rhabdomyosarcoma is usually curable in most children with localized disease who receive combined modality therapy, with more than 70 percent surviving 5 years after diagnosis. The outcome of RMS patients has significantly improved with around overall survival of 65 percent for all patients. These modalities have however,

not improved survival rates in patients with metastatic disease. Novel therapies in development include, oral maintenance therapy, oncolytic viruses and immunotherapies, such as monoclonal antibodies and vaccines.

NONRHABDOMYOSARCOMA SOFT TISSUE SARCOMAS

This heterogeneous group of NRSTS tumors include neoplasms of smooth muscle (leiomyosarcomas), connective tissue (fibrosarcoma, liposarcoma, desmoplastic small round cell tumor), vascular tissue (hemangiopericytoma), and the peripheral nervous system. Synovial sarcomas, fibrosarcomas, and malignant peripheral nerve sheath tumors predominate in pediatric patients. NRSTSs are more common in adults than children, therefore, much of the information regarding the treatment and natural history of children with these lesions has been on the basis of adult studies. The prognoses of infants and young children with NRSTS tend to be better than those of adolescents and adults with similar diagnoses. Substantial improvement in understanding the tumor biology and better treatments through cooperative groups has resulted in survival rates rising from 30 to 40 percent in the 1970s to 60 to 70 percent currently.

EPIDEMIOLOGY

NRSTS account for 2 to 4 percent of tumors globally, however may be as high as 15 to 40 percent in some African countries because of the HIV epidemic and high incidence of Kaposi's sarcoma. In most populations boys have a higher incidence rate than girls. The age distribution for NRSTS shows a U-shaped curve with two incidence peaks: in infants under 12 months and adolescents between 15 to 19 years of age.

Risk Factors

Genetic and environmental factors have been associated with the development of NRSTS. Heritable cancer-associated changes of the p53 tumor suppressor gene can occur in families with Li Fraumeni syndrome. Approximately 4 percent of patients with neurofibromatosis type 1 develop malignant peripheral nerve sheath tumors. Patients with familial adenomatous polyposis are at increased risk for developing desmoid tumors. Some NRSTSs (particularly malignant fibrous histiocytoma) can develop within a previously irradiated site; others (e.g. leiomyosarcoma) have been linked to Epstein-Barr virus infection in patients with AIDS. The Childhood Cancer Survivor Study has shown that overall survivors tend to have an increased risk of developing a secondary sarcoma.

Molecular Pathogenesis

The molecular mechanisms responsible for the heterogeneity of NRSTS are not known, however at least a dozen

translocations have been described in STS tumors. These need the influence of other cytogenetic anomalies to create a permissive environment for tumorigenesis.

Clinical Presentation

Although they can develop in any part of the body, NRSTSs arise most commonly in the trunk and extremities. These neoplasms can present initially as an asymptomatic solid mass, or they may be symptomatic because of local invasion of adjacent anatomical structures. Systemic symptoms (e.g. fever, weight loss, and night sweats) are rare. Hypoglycemia and hypophosphatemic rickets have been reported in cases of hemangiopericytoma, whereas hyperglycemia has been noted in patients with fibrosarcoma of the lung. Approximately 15 to 30 percent of patients have metastatic disease at presentation commonly in the lungs. Other common sites for metastases include the skin, bone, liver, and lymph nodes. Spread to the brain, omentum and/or peritoneum is described as well.

Diagnostic Evaluation

When a suspicious lesion is identified it is crucial that a complete workup followed by adequate biopsy be performed. Generally, it is better to image the lesion prior to any interventions. Radiologic imaging should include local and chest X-ray, MRI of affected region and a CT scan of the chest for metastasis. Tc 99 bone scan may be useful for assessing skeletal involvement by tumor. PET-CT scan may help differentiate a benign from a malignant lesion and also to evaluate residual disease. Bilateral iliac crest bone marrow aspiration and biopsy are recommended.

Obtaining adequate tumor tissue is crucial to allow for conventional histology, immunocytochemical analysis, and other studies such as light and electron microscopy, cytogenetics, fluorescence *in situ* hybridization, and molecular pathology. For this reason, limited open biopsy (or multiple core-needle biopsies) is strongly encouraged so that adequate tumor tissue can be obtained for crucial studies. Incisional biopsies are acceptable but should not compromise subsequent wide local excision, and extensive dissection around the lesion must be avoided. Transverse extremity incisions should be avoided to reduce skin loss, as should extensive surgical procedures prior to definitive diagnosis.

Histologic Classification

Pediatric soft tissue sarcomas are classified histologically according to the soft tissue cell they resemble and include the following:

Tumors of fibrous tissue

- Fibromatoses (desmoid tumors).
- Adult and infantile fibrosarcoma.
- Dermatofibrosarcoma.

Fibrohistiocytic tumors

- Malignant fibrous histiocytoma (MFH) (also called undifferentiated pleomorphic sarcoma, or spindle cell sarcoma).

Tumors of adipose tissue

- Liposarcoma.

Tumors of smooth muscle

- Leiomyosarcoma.

Tumors of peripheral nervous system

- Malignant schwannoma (malignant peripheral nerve sheath tumor [MPNST]).

Tumors of bone and cartilage

- Extraosseous osteosarcoma.
- Extraosseous myxoid chondrosarcoma.
- Mesenchymal chondrosarcoma
- Tumors of more than one tissue type
- Malignant mesenchymoma.
- Malignant Triton tumor
- Malignant ectomesenchymoma

Tumors of unknown histogenesis

- Alveolar soft part sarcoma (ASPS).
- Clear cell sarcoma (malignant melanoma of soft parts [MMSP]).
- Desmoplastic small round cell tumor
- Epithelioid sarcoma.
- Synovial sarcoma.
- Undifferentiated soft tissue sarcoma
- Tumors of vascular structures
- Angiosarcoma.
- Hemangioendothelioma.
- Hemangiopericytoma.
- Lymphangiosarcoma.

STAGING OF THE TUMOR

Clinical staging has an important role in predicting the clinical outcome and determining the most effective therapy for pediatric soft tissue sarcomas. Several adult and pediatric series have shown that patients with large or invasive tumors have a significantly worse prognosis than do those with small, noninvasive tumors.

Nonmetastatic Disease

- *Group I:* Tumor completely resected with histologically negative margins.
- *Group II:* Grossly resected tumor with microscopic residual tumor.
 - *IIA:* Grossly resected tumor with microscopic residual disease.
 - *IIB:* Regional disease with involved nodes completely resected with no microscopic disease.

- *IIC:* Regional disease with involved nodes grossly resected but with evidence of residual microscopic disease and/ or histologic involvement of the most distal regional lymph node in the dissection.

- *Group III:* Incomplete resection or biopsy with gross residual tumor.

Metastatic Disease

- *Group IV:* Any localized or regional tumor with distant metastases present at the time of diagnosis.

The other schema typically used to stage pediatric soft tissue tumors is the TNM system of the International Union Against Cancer. In most cases, accurate histopathologic classification of soft tissue sarcomas alone does not yield optimal information about their clinical behavior. Therefore, several histologic parameters, including degree of cellularity, cellular pleomorphism, mitotic activity, degree of necrosis, and invasive growth, are evaluated in the grading process.

Treatment Option Overview

Because of the rarity of pediatric nonrhabdomyosarcomatous soft tissue sarcomas (NRSTSs), all children, adolescents, and young adults with these tumors should have their treatment coordinated by a multidisciplinary team comprised of pediatric oncologists, surgeons, and radiotherapists. To better define the tumors' natural history and response to therapy, children with rare neoplasms should be considered for entry into national or institutional treatment protocols. Because soft tissue sarcomas are most common in adults, many treatment modalities are extrapolated from experiences in adult patients. Some pediatric NRSTSs are associated with a better outcome. This difference is most pronounced for infants and children younger than 4 years with fibrosarcoma, which is a locally aggressive but nonmetastatic tumor. These patients have an excellent prognosis given that the tumor is highly chemosensitive and surgery alone can cure a significant number of these patients. Soft tissue sarcomas in older children and adolescents often behave similarly to those in adult patients.

Every attempt should be made to resect the primary tumor with negative margins before or after chemotherapy. Involvement of a surgeon with special expertise in the resection of soft tissue sarcomas in the decision is highly desirable. Radiation therapy is indicated for patients with inadequate surgical margins and for larger, high-grade tumors. When using both surgery and radiation therapy, local control of the primary tumor can be achieved in more than 80 percent of patients. Brachytherapy and intraoperative radiation may be applicable in select situations. The role of adjuvant (postoperative) chemotherapy remains controversial. Synovial sarcoma appears to be more sensitive to chemotherapy than many other soft tissue sarcomas.

Therapeutic strategies for children and adolescents with soft tissue tumors are similar to those for adult patients, though there are important differences. Improved outcomes with multimodality therapy in adults and children with soft tissue sarcomas over the past 20 years has caused increasing concern about the potential long-term side effects of this therapy in children, especially when considering the expected longer life span of children versus adults. Therefore, to maximize tumor control and minimize long-term morbidity, treatment must be individualized for children and adolescents with NRST.

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Malignant Bone Tumors in Children

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Malignant bone tumors constitute approximately 6 percent of all childhood malignancies.

Osteosarcoma (56%) and Ewing sarcoma (34%) are most frequently encountered malignant bone tumors in children and adolescents.

CONVENTIONAL OSTEOSARCOMA

Definition

Primary intramedullary high-grade malignant sarcoma in which neoplastic cells produce osteoid.

Epidemiology

- Most common primary nonhematopoietic malignancy of bone
- Its incidence in USA is 4 to 5 per million individuals with 1000 to 1500 new cases diagnosed annually which accounts for approximately 20 percent of all primary malignant cell tumors
- It most frequently occurs in second decade of life with 60 percent of tumors occurring in patients younger than 25 years
- Although 30 percent occurring in patients over 40 years of age, the predisposing condition should always be considered in older patients (e.g. Paget's disease of bone, postradiation sarcoma)
- Male to female ratio 3:2
- Osteosarcoma in children 5 years and younger is very uncommon, and they account for less than 2 percent of osteosarcomas in the pediatric population.

Sites of Involvement

- Conventional osteosarcoma shows a profound propensity for involvement of the long bones of the appendicular skeleton; in particular, the distal femur, proximal tibia, and proximal humerus

- Within the long bones the tumor is mostly centered in metaphysis (90%) followed by diaphysis (9%), and rarely in epiphysis
- Although the long bones remain the most frequent site of involvement, the nonlong bone (i.e. jaws, pelvis, spine, and skull) involvement tends to increase with age.

Clinical Features

- Classic presentation of conventional osteosarcoma typically is progressively enlarging, painful mass
- Deep seated and boring in nature, the pain is frequently noted months prior to diagnosis, and usually increases in intensity over time, eventually becoming unbearable
- Average duration of symptoms is 3 months
- Skin overlying the tumor may be warm, erythematous, edematous, with prominent engorged veins. Large tumors may restrict range of motion, decrease musculoskeletal function, produce joint effusion and, in advanced cases, result in weight loss and cachexia
- A sudden fracture through destructive mass may be found.

Imaging

- Osteosarcoma has extremely variable radiographic appearances
- Conventional tumors present as a large, destructive, poorly defined, mixed lytic and blastic masses accompanied by cortical destruction and tumor extension into soft tissue.
- Tumor/periosteal interaction may lead to variety of manifestations secondary to periosteal elevation (e.g. Codman triangle) and periosteal reactive bone formation.

- Occasionally the tumor may demonstrate perpendicular or radiating striations called “sunburst”. CT and MRI may be helpful in delineating the extent of the tumor preoperatively.

Gross

- Osteosarcoma is often a large (over 5 cm), metaphyseally centered, fleshy or hard tumor which may contain cartilage
- It frequently transgresses the cortex and is associated with a soft tissue mass

Histopathology

- Presents as highly anaplastic, pleomorphic tumor in which the tumor cells may be: epithelioid, plasmacytoid, fusiform, ovoid, small round cells, clear cells, mono- or multinucleated giant cells, or spindle cells producing osteoid
- Conventional osteosarcoma can also produce varying amounts of cartilage and/or fibrous tissue
- Many investigators further subdivide conventional osteosarcoma in terms of predominant matrix
- This divides conventional sarcoma into three subtypes: osteoblastic (50%), chondroblastic (25%), and fibroblastic (25%) osteosarcoma. Figures 1A to D showing the classical features on skiagram and the histopathological findings.

Osteoblastic Osteosarcoma

- Bone and/or osteoid are the predominant matrix
- The extremes of matrix production are thin arborising osteoid to dense, compact osteoid and bone (sclerotic).

Chondroblastic Osteosarcoma

- Chondroid matrix is predominant
- It tends to be high-grade hyaline cartilage, which is intimately associated, and randomly mixed, with non-chondroid elements.

Fibroblastic Osteosarcoma

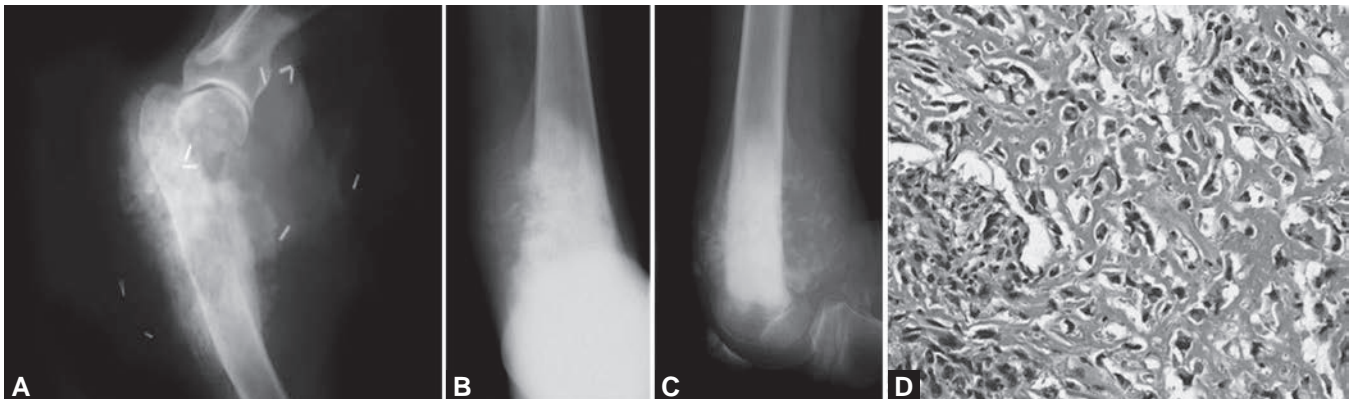
- A high-grade spindle-cell malignancy with sometimes minimal amount of osseous matrix with or without cartilage
- In general, the overall histological appearance is similar to fibrosarcoma or pleomorphic undifferentiated sarcoma (malignant fibrous histiocytoma).

Genetics

- Loss of heterozygosity of chromosome arm 3q, 13q, 17p, and 18q most frequent
- Amplification at 1q21-23 and 17p are frequent findings in conventional osteosarcoma.

Prognosis

- Untreated, conventional osteosarcoma is fatal
- Aggressive local growth and rapid hematogenous systemic dissemination are bad prognostic features
- Although metastases may affect many sites, pulmonary metastases are the most frequent site of clinically significant systemic disease
- In children, the treatment of conventional osteosarcoma is tailored to the location, size and stage of the tumor
- Eradication of the primary tumor and the elimination of any metastases is the goal of therapy
- Limb salvage resection is the convention for appendicular tumors, and surgical excision in combination with radiation is employed for tumors that are not resectable entirely with negative margins
- Adjuvant chemotherapy is usually employed in the preoperative setting and continued after surgical resection
- Survival is directly related to response to preoperative therapy. In those patients whose tumors have >90 percent tumor necrosis, long-term survival is generally 80 to 90 percent
- In patients with <90 percent response to therapy the survival is poor, usually <15 percent.



Figs 1A to D: Skiagram of the osteogenic sarcoma and the histopathological features
(For color version see plate 9)

TELANGIECTATIC OSTEOSARCOMA (FIGS 2A TO D)**Definition**

Malignant bone forming tumor characterized by large spaces filled with blood with or without septa.

Epidemiology

- Rare subtype, accounting for less than 4 percent of all cases of osteosarcoma
- It most frequently occurs in the second decade of life but was described in younger patients
- Male to female ratio 1.5:1.

Sites of Involvement

- Most tumors involve metaphyseal region of long tubular bones
- Distal femoral metaphysis is the single most common anatomic site, followed by the upper tibia and proximal humerus or proximal femur.

Clinical Findings

- Similar to conventional osteosarcoma
- Characteristic clinical finding of this tumor is pathological fracture (1/4 of the cases), because of massive bone destruction.

Imaging

- Purely lytic, large bone destruction without distinct surrounding bony sclerosis
- Tumor commonly shows extension into soft tissue
- Most lesions are located in metaphysis, and usually extend into the epiphysis
- Tumor often expands the cortex of bone and disrupts the cortex
- Periosteal reaction including Codman's triangle and onion skin are frequent
- MRI, a T1-weighted image shows heterogeneous low signal intensity, and T2-weighted image shows high signal intensity with several cystic foci and fluid-fluid level with an extraskeletal extension of the tumor, similar to aneurysmal bone cyst.

Gross

- Tumors show dominant cystic architecture in the medullary space
- Cystic portion of the tumor is filled incompletely with blood clot which is described as "a bag of blood"
- There is no sclerotic tumor bone formation.

Histopathology

- Tumor contains blood-filled or empty spaces separated by thin septa simulating aneurysmal bone cyst
- A few of the tumors are more solid and have smaller cystic spaces
- Higher power view shows the cystic spaces lined by benign-looking giant cells without endothelial cells
- The septa are cellular, containing atypical mononuclear tumor cells
- Tumor cells are hyperchromatic and pleomorphic with high mitotic activity including atypical mitoses
- Amount of osteoid varies, but usually fine, and lace like osteoid is observed in minimal amount
- Cellular septae contain many benign looking multinucleated giant cells, which may lead to a mistaken diagnosis of benign or even malignant giant cell tumor.

Genetics

Mutations in *TP53* and *RAS* genes.

Prognosis

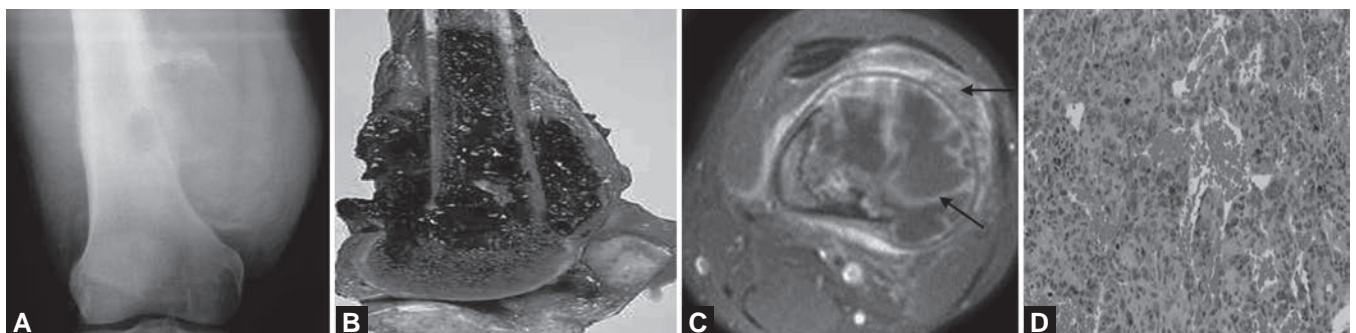
- Similar to conventional osteosarcoma
- Sensitive to chemotherapy.

SMALL CELL OSTEOSARCOMA (FIGS 3A AND B)**Definition**

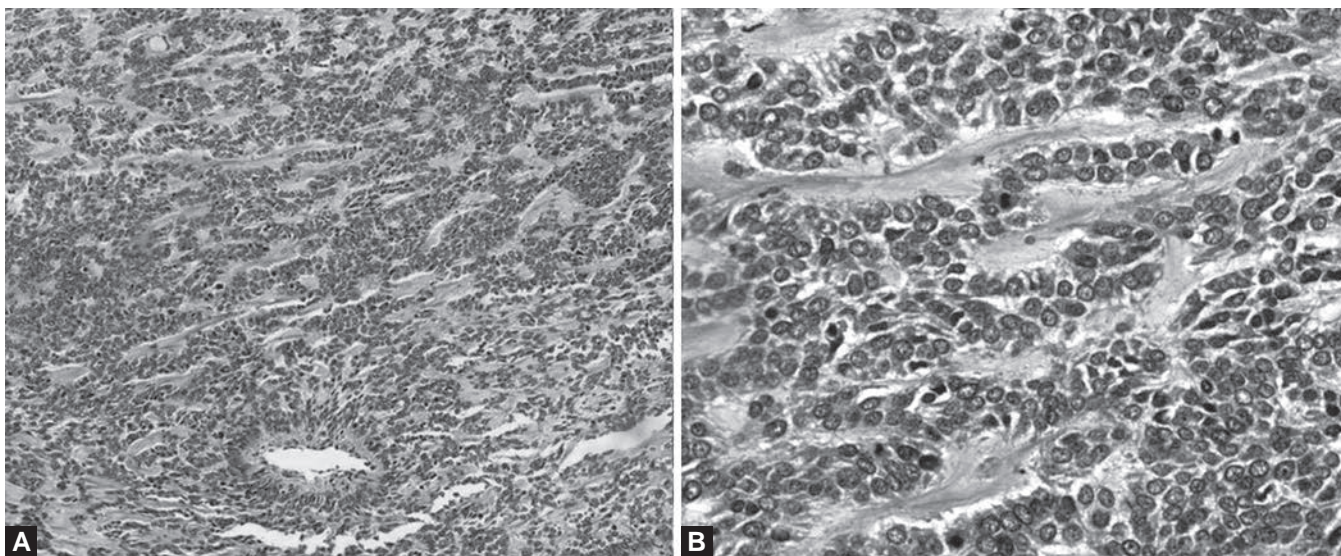
Osteosarcoma composed of small cells with variable degree of osteoid production.

Epidemiology

- Small cell osteosarcoma comprises 1.5 percent of osteosarcomas
- Patients range from 5 to 80 years of age, although most patients are in the second decade
- There is slight predilection for females.



Figs 2A to D: Telangiectatic osteosarcoma (For color version see plate 9)



Figs 3A and B: Small cell osteosarcoma (For color version see plate 9)

Sites of Involvement

Metaphysis of long bones. Rarely, multiple sites are involved.

Clinical Findings

Pain and swelling of involved site.

Imaging

- Aggressive process with destruction of the cortex
- There is always a lytic component, usually admixed with radiodense areas
- Mineralized tissue is seen, either intramedullary and/or in soft tissue tumor extension.

Histopathology

- Small cell osteosarcoma is composed of small cells associated with osteoid production
- Nuclear diameter of round cells can range in size from very small to medium; the smaller one are comparable to those of Ewing sarcoma or lymphoma
- The cells have scanty amounts of cytoplasm. Nuclei are round to oval and the chromatin may be fine to coarse
- Mitoses range from 3 to 5/HPF
- In the less frequent spindle cell type, nuclei are short, oval to spindle, have a granular chromatin, inconspicuous nucleoli and scanty amounts of cytoplasm
- Lace-like osteoid is always present
- Biopsy from small cell osteosarcoma may be problematic, especially from the peripheral surface of the tumor, because may not always show osteoid and may resemble Ewing sarcoma

- In this cases cytogenetic study for t (11,22) is the best diagnostic tool, which is negative in small cell osteosarcoma.

Immunohistochemistry

Positive for CD99, vimentin, osteocalcin, osteonectin.

Genetics

Negative for t(11,22)

Prognosis

Poor

LOW-GRADE CENTRAL OSTEOSARCOMA (FIGS 4A AND B)

Definition

Low-grade osteosarcoma that arises from the medullary cavity of bone.

Epidemiology

- Accounts for less than 1 percent of primary bone tumors and only 1 to 2 percent of all osteosarcomas
- Males and females are equally affected.
- The peak incidence is in 2nd to 3rd decades of life.

Sites of Involvement

- Approximately 80 percent of low-grade central osteosarcomas are located in the long bones with predilection for the distal femur and proximal tibia
- Flat bones are uncommonly affected.

Clinical Features

- Pain and swelling are usual features
- The duration of pain may be many months or even several years.



Figs 4A and B: Low-grade central osteosarcoma (For color version see plate 10)

Imaging

- Large metaphyseal or diaphyseal intramedullary tumors
- It is not uncommon to see extension into the end of the bone when the epiphyseal plate is closed
- Majority of tumors are poorly margined, up to 1/3 may show intermediate or well defined margins suggestive of indolent or benign lesion
- Trabeculation and sclerosis are common findings that reflect indolent nature of this tumor
- Cortical destruction is the most convincing radiographic feature to support malignant nature of the tumor
- The majority of low-grade central osteosarcomas will show some degree of cortical destruction with or without soft tissue extension.

Gross

Cut surface of a low-grade central osteosarcoma shows a gray-white tumor with a firm and gritty texture arising from within the medullary cavity.

Histopathology

- Low-grade osteosarcoma is composed of a hypo- to moderately cellular fibroblastic stroma with variable amounts of osteoid production
- The collagen producing spindle cells are arranged in interlacing bundles that permeate surrounding pre-existing bony trabeculae and bone marrow similar to that of desmoplastic fibroma
- Tumor cells show some degree of cytological atypia
- Nuclear enlargement and hyperchromasia are evident
- Occasional mitotic figures are identified
- Variable patterns of bone production are seen

- Some tumors contain irregular anastomosing, branching, and curved trabeculae simulating the appearance of woven bone in fibrous dysplasia (no atypia seen in spindle cells of fibrous dysplasia)
- Small scattered foci of atypical cartilage are occasionally seen
- In addition, benign multinucleated giant cells have been reported in up to 36 percent of cases.

Genetics

Recurrent gains in minimal common regions at 12q13-14, 12p, and 6p21.

Prognosis

- Low-grade central osteosarcoma behaves in a much more indolent fashion conventional osteosarcoma
- High incidence of local recurrence after inadequate excision
- Recurrence may exhibit higher grade or differentiation with the potential for metastases.

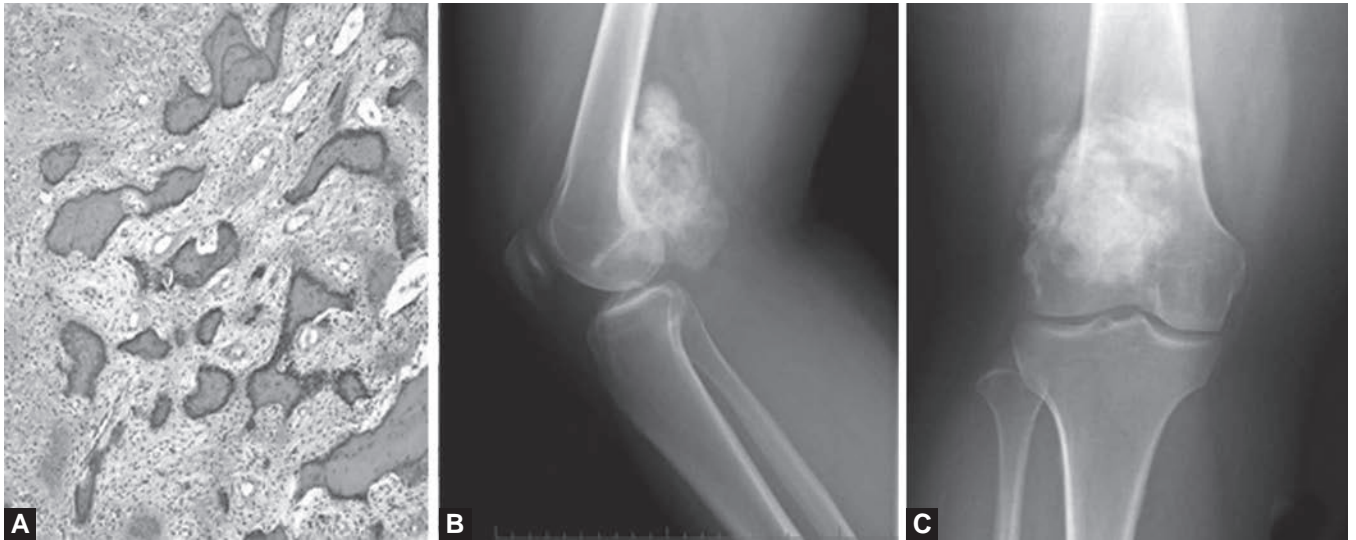
PAROSTEAL OSTEOSARCOMA (FIGS 5A TO C)

Definition

Parosteal osteosarcoma is a low-grade osteosarcoma which arises on the surface of bone.

Epidemiology

- Although rare, parosteal osteosarcoma is the most common type osteosarcoma of the surface of bone
- It accounts for about 4 percent of osteosarcomas
- There is a slight female predominance
- Most of the patients are young adults, about 1/3 occur in 3rd decade of life.



Figs 5A to C: Parosteal osteosarcoma (For color version see plate 10)

Sites of Involvement

- Seventy percent of cases involve the surface of the distal posterior femur
- The proximal tibia and proximal humerus are also common.

Clinical Findings

- Painless swelling; inability to flex the knee may be the initial symptom
- Some patients may complain of a painful swelling.

Imaging

- Heavily mineralized mass attached to the cortex with broad base
- Tumor has tendency to wrap around the involved bone
- CT and MRI are useful in evaluating the extent of medullary involvement.

Gross

- Parosteal osteosarcoma presents as a hard lobulated mass attached to the underlying cortex
- Nodules of cartilage may be present
- Occasionally, the cartilage will be incomplete cap-like covering the surface and thus suggesting a diagnosis of osteochondroma.

Histopathology

- Parosteal osteosarcoma consist of well formed bony trabeculae in spindle cell stroma
- The spindle cells show minimal atypia, mitoses can be found with difficulty, atypical forms are not present.

- The bony trabeculae are arranged in a parallel manner and simulate normal bone
- The trabeculae may or may not show osteoblastic rimming
- About 50 percent of the tumors will show cartilaginous differentiation. This may be in the form of hypercellular nodules of cartilage within the tumor or as a cap on the surface
- When cartilage cap is present may be mildly hypercellular, and the cells may show mild atypia and lack columnar arrangement seen in osteochondroma
- Unlike fatty and hematopoietic marrow, as seen in osteochondromas, there is spindle cell proliferation between bony trabeculae
- About 15 percent will show high-grade spindle cell sarcoma (dedifferentiation).

Prognosis

Excellent with 91 percent overall survival at 5 years.

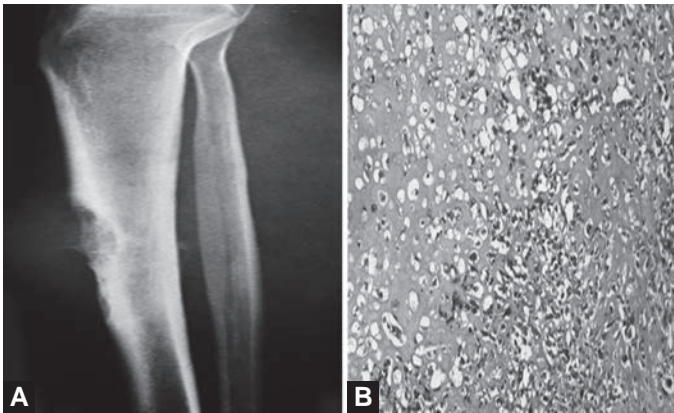
PERIOSTEAL OSTEOSARCOMA (FIGS 6A AND B)

Definition

Periosteal osteosarcoma is intermediate grade chondroblastic osteosarcoma arising on the surface of the bone.

Epidemiology

- Accounts for less than 2 percent of all the osteosarcomas
- Of the surface osteosarcomas, it is more common than surface high-grade osteosarcoma, but about 1/3 as common as parosteal osteosarcoma
- The peak incidence is the 2nd and 3rd decades of life.
- There is a slight male predominance.



Figs 6A and B: Periosteal osteosarcoma
(For color version see plate 10)

Sites of Involvement

Diaphysis or diaphyseal-metaphyseal area of long bones, with the tibia and femur most commonly affected.

Clinical Features

Painless mass or limb swelling is the most common initial finding with pain and tenderness later developing in the affected area.

Imaging

- Arising on the surface of a bone, displays nonhomogenous, calcified spiculations that are disposed perpendicular to the cortex and give overall sunburst appearance
- The lesion decreases in density from the cortical base to the surface, where the tumor has a relatively well demarcated margin
- Commonly, the cortex appears thickened as a result of the production of ossified matrix
- A Codman's triangle is commonly present
- CT and MRI important in the evaluation of tumor size, integrity of the cortex, and soft tissue extension.

Gross

Tumor arises from the bone surface and may involve part of the bone or the entire circumference.

Histopathology

- Periosteal osteosarcoma has the appearance of a moderately differentiated chondroblastic osteosarcoma
- Ossified mass is generally found arising from the cortex, and is made up of relatively mature bone
- Cartilagenous component predominates, but elements of intermediate grade osteosarcoma are invariably present
- Cartilagenous component may show varying degrees of cytological atypia and matrix may be myxoid

- Periphery is most of the time not calcified and made of fascicles of spindle cells.

Prognosis

- Better prognosis than conventional osteosarcoma, but still have tendency to recur and metastasize
- Medullary involvement of the bone may have poorer prognosis
- About 70 percent recurrence rate after excision
- Rate of metastasis has been reported to be about 15 percent.

HIGH-GRADE SURFACE OSTEOSARCOMA (FIGS 7A TO C)

Definition

High-grade bone forming malignancy which arises from the surface of the bone.

Epidemiology

- Less than 1 percent of all osteosarcomas
- Peak incidence is in 2nd decade of life
- There is slight male predilection.

Sites of Involvement

Femur is most commonly affected followed by the humerus and tibia.

Clinical Features

Patients commonly present with the mass or pain in the area of the tumor.

Imaging

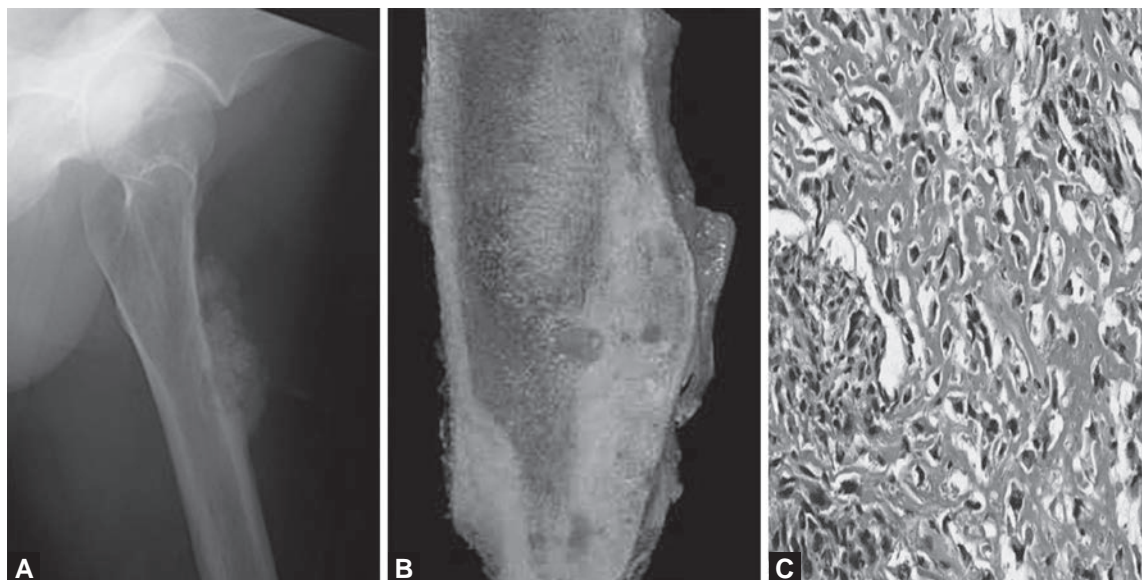
- Surface mass, partially mineralized, extending to soft tissue
- The underlying cortex is commonly partially destroyed, and periosteal new bone is commonly present at the periphery of the tumor
- Cross sectional imaging may show minimal medullary involvement, but the tumor is most commonly relatively well circumscribed at its soft tissue margin.

Gross

Tumor is situated on the surface of the bone and commonly erodes the underlying cortical bone.

Histopathology

- Show similar morphology to conventional osteosarcoma
- Regions of predominantly osteoblastic, chondroblastic or fibroblastic differentiation may predominate
- However, all tumors will show high-grade cytological atypia and lace-like osteoid as seen in conventional osteosarcoma.



Figs 7A to C: High-grade surface osteosarcoma (For color version see plate 11)

Prognosis

As in conventional osteosarcoma, prognostic feature is response to chemotherapy.

SECONDARY OSTEOSARCOMA

Definition

Bone forming sarcomas occurring in bones affected by pre-existing abnormalities the most common being post-radiation therapy changes, Paget disease, and rarely various other disorders.

POSTRADIATION OSTEOSARCOMA

Epidemiology

- Constitute 3.4 to 5.5 percent of all osteosarcomas and 50 to 60 percent of radiation-induced sarcomas
- It is estimated that the risk of developing osteosarcoma in irradiated bone is 0.03 to 0.8 percent
- Children treated with high-dose radiotherapy and chemotherapy are at greatest risk
- The prevalence of postradiation osteosarcomas is increasing as children survive treatment of their malignant disease.

Sites of Involvement

Any irradiated bone, but the most common locations are the pelvis and the shoulder region.

Clinical Findings

- History of previous radiation therapy and tumor developing in the path of radiation beam

- A symptom free latent period may be long (median of 11 years), and inversely related to the radiation dosage
- Radiation doses are usually greater than 20 Gy.

Imaging

- Tumors are densely sclerotic or lytic lesions with a soft tissue mass
- Radiation osteitis is present in about 50 percent of cases (trabecular coarsening and lytic areas in cortex).

Histopathology

High-grade osteosarcoma predominate (see conventional osteosarcoma).

Prognosis

Five-year survival rate is of 68.2 percent for patients with extremity lesions, 27.3 percent for patients with axial lesions.

Treatment of Patients with Recurrent Disease

In majority (85%), recurrences occur in lungs. Some predictors of relapse are:

1. Completeness of surgical resection.
2. Early vs late (more than 1 year after treatment) relapse.
3. Malignant pleural effusion, unresectable lung hilar involvement, more than 16 nodules on CT or extrathoracic disease.
4. Prior treatment (those relapsing after multiagent chemotherapy have worse prognosis). Adjuvant chemotherapy with drugs not used before is recommended.

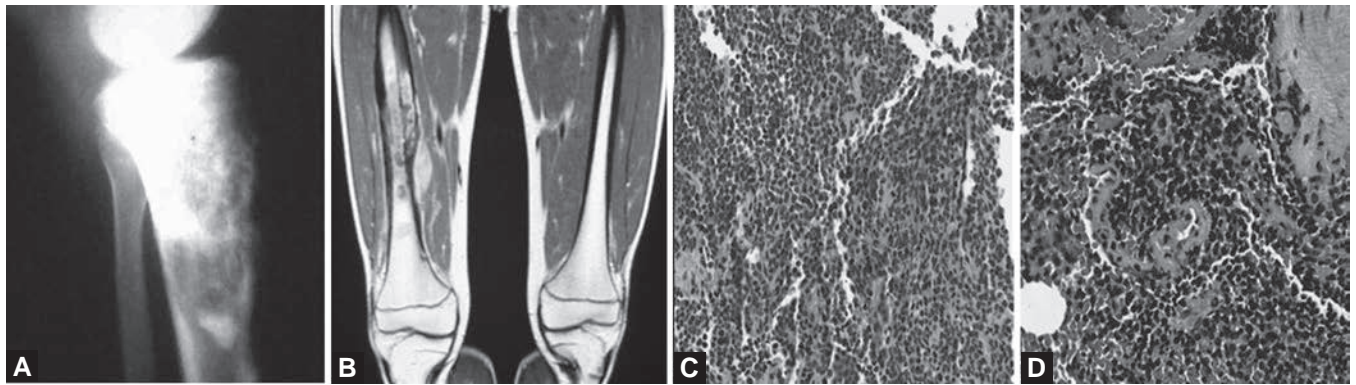


Fig. 8A to D: Ewings sarcoma (For color version see plate 11)

(Ifosfamide, etoposide, cyclophosphamide, topotecan, etc.)

EWING SARCOMA/PRIMITIVE NEUROECTODERMAL TUMOR (FIGS 8A TO D)

Definition

- Ewing sarcoma/primitive neuroectodermal tumor (PNET) are defined as small round cell sarcoma (belong to group of pediatric small blue cell tumors) that show varying degrees of neuroectodermal differentiation
- Ewing sarcoma is term used for those tumors which lack neuroectodermal differentiation, and PNET has been described for tumors with neuroectodermal differentiation.

Epidemiology

- Ewing sarcoma accounts for 6 to 8 percent of primary bone tumors
- It is the second most common sarcoma of bone in children
- Male: Female ratio 1.4:1
- Nearly 80 percent are younger than 20 years of age and the peak incidence is during the second decade of life.

Sites of Involvement

- Arises in the diaphysis or metaphyseal-diaphyseal portion of long bones
- The pelvis and ribs are also common locations.

Clinical Features

- Pain and a mass in the involved area are the most common clinical symptoms
- Fever, anemia, leukocytosis and increased sedimentation rate are often seen.

Imaging

- Ill defined osteolytic lesion involving diaphysis of long bone or flat bone is the most common feature
- Permeative or moth eaten bone destruction often associated with “onion-skin” like multilayered periosteal reaction is characteristic
- The cortex overlying the tumor is irregularly thinned and thickened
- A large ill-defined soft tissue mass is frequently seen
- Expansile bone destruction with soap-bubble appearance might be seen.

Gross

The tumor in bone and soft tissue is tan-gray and often necrotic and hemorrhagic.

Histopathology

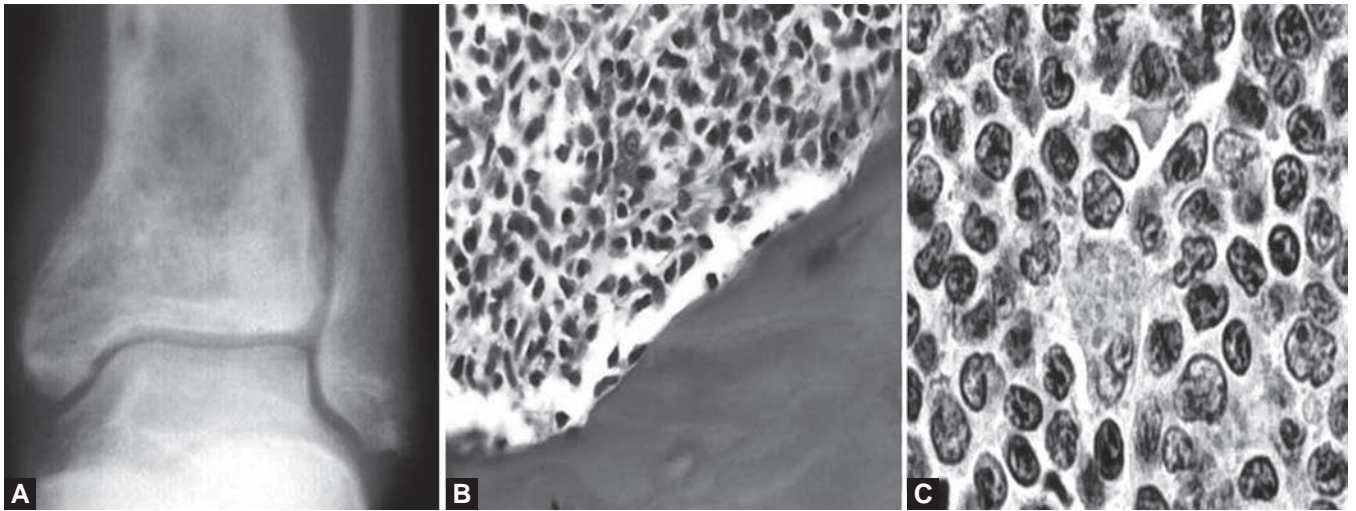
- Most cases are composed of uniform small round cells with round nuclei containing fine chromatin, scanty clear or eosinophilic cytoplasm, and indistinct cytoplasmic membranes, whereas in others, the tumor cells are larger, have prominent nucleoli, and irregular contours
- The cytoplasm of the tumors frequently contains PAS positive glycogen (diastase sensitive)
- In some cases Homer-Wright rosettes are present
- Necrosis is common with viable cells frequently perivascular in distribution.

Immunophenotype

- Positive: Fli-1, CD99, vimentin, neuron specific enolase (NSE), PAS+ diastase sensitive
- Negative: S100, CD45, muscular and vascular markers

Genetics

- t(11,22) (q24;q12): 85 percent.



Figs 9A to C: Lymphoma of bone (For color version see plate 12)

- $t(21;22) (q22;q12)$: 10 to 15 percent
- $t(7;22)$, $t(17;22)$, $t(2;22)$: 1 percent.

Prognosis

- Has improved with adjuvant therapy
- Important prognostic features include the stage, anatomic location and the size of the tumor
- Tumors that are metastatic at the time of the diagnosis, arise in the pelvis, and when they are large tend to do poorly.

LYMPHOMA OF BONE (FIGS 9A TO C)

Definition

Malignant lymphoma is a neoplasm composed of malignant lymphoid cells, producing an intramedullary tumor mass.

Epidemiology

- Malignant lymphoma involving bone is not common, accounting for approximately 7 percent of all bone malignancies
- Lymphomas involving bone account for about 5 percent of extranodal lymphoma
- Patients may be of any age group but there is tendency to involve adults, especially older patients, although there were cases of young children causing difficult diagnostic differentiation from Ewing sarcoma.

Sites of Involvement

- Affects portion of bone with persistent bone marrow
- Femur is the most commonly involved single site
- It is extremely unusual to see malignant lymphoma involving the small bones of the hand and feet.

Clinical Features

- Majority of patients present with bone pain
- Some patients may present with palpable mass
- Patients with primary lymphoma of bone rarely present with systemic symptoms like fever or night sweats
- Lymphoma involving bone may be separated into four groups:
 - A single skeletal site, with or without regional lymph node involvement;
 - Multiple bones are involved, but there is no visceral or lymph node involvement;
 - Patients present with a bone tumor but work-up shows involvement of other visceral sites or multiple lymph node sites;
 - Patient has a known lymphoma and the bone biopsy is done to r/o involvement of bone; groups 1 and 2 are considered primary lymphoma of bone.

Imaging

- In the long bones, diaphysis tends to be more involved
- Tumor tends to involve a large portion of bone; it is not unusual to see destruction of more than half of the bone
- The process is poorly demarcated with a wide area of transition from normal bone
- There may be variable sclerosis; rarely, the tumor is very sclerotic or entirely lytic
- Most of the time there is mixture of sclerotic and lytic areas
- Cortex is frequently destroyed and there is large soft tissue mass
- A purely sclerotic lesion may be mistaken for Paget's disease

- If the cortex is not involved, the marrow destruction may not be obvious on plain roentgenograms
- Radionuclide bone scan is almost always positive.

Gross

- Large portion of bone is involved, with cortical destruction
- The lesion has the soft fish-flesh appearance of lymphoma.

Histopathology

- Majority of lymphomas involving bones show diffuse growth pattern
- Follicular small cell cleaved cell lymphoma is common in bone marrow, although in most of the cases does not present as destructive bone tumor
- Consequently, most of the bone lymphomas are diffuse large cell type
- It has characteristic permeative growth pattern
- Bony trabeculae may appear normal or may appear thickened or irregular. Ninety-two percent of primary non-Hodgkin's, lymphoma of bone was found to be of the large B cell type and only 3 percent diffuse follicle centre cell and 2 percent immunocytoma
- One problem with the diagnosis of lymphoma in bone is that the cells tend to get crushed

- If a bone biopsy shows such a crush artifact, a diagnosis of malignant lymphoma should be suspected
- Hodgkin's lymphoma may involve the skeleton as a manifestation of a widespread disease and produce a tumor mass but primary manifestations are rare.

Prognosis

- Prognosis of lymphoma is associated with cell type and stage of disease
- Patients older than 60 y/o have a worse overall survival and a worse progression-free period
- Patients with immunoblastic subtype has a worse survival than the centroblastic mono/polymorphic subtype or the centroblastic multilobulated subtype.

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Pediatric Non-Hodgkin's Lymphoma

Revathi Raj

INTRODUCTION

Lymphomas are malignant neoplasms of lymphoid lineage. Broadly classified as either Hodgkin disease (Hodgkin's disease) or as non-Hodgkin's lymphoma (NHL), lymphomas are clinically, pathologically, and biologically distinct. Major advances have been made in the treatment of childhood non-Hodgkin's lymphoma (NHL). Different NHL subtypes require different treatment strategies. The therapy groups as per the National Cancer Institute (NCI) formulation are lymphoblastic lymphoma (LBL) of precursor B- or T-cell type, mature B-cell neoplasms (B-NHL), and anaplastic large cell lymphoma (ALCL). Accurate diagnostic classification is crucial for allocating patients to appropriate treatment groups. Therapy protocols designed to treat children with acute lymphoblastic leukemia (ALL) have proven highly efficacious for treating children with LBL and are associated with event-free survival (EFS) rates up to 80 percent. For children with B-NHL, a strategy of rapidly repeated short, dose-intense courses proved more efficacious, with EFS rates up to 90 percent. Patients with ALCL have the highest relapse rates and hence additional maintenance regimen with vinblastine seems to add benefit. All these treatments have considerable toxicity. However, the chance to survive after relapse is dismal due to the almost complete lack of established salvage regimen. Since the late 1960s, treatment outcomes for children with non-Hodgkin lymphoma have steadily improved. Even for patients with advanced disease, event-free survival rates are 65 to 90 percent. We need to strike a balance between treatment burden and individual patient risk for failure to achieve optimal outcome.

PATHOPHYSIOLOGY

Most malignancies arise as disease localized in the organ or tissue of origin. They may then secondarily spread by means of local extension or distant metastases. In contrast,

non-Hodgkin lymphoma is best regarded as a systemic disease because of the unique anatomy of the lymphoid system and because of the physiology of lymphoid cells, which tend to migrate whether they are normal or malignant. Childhood non-Hodgkin's lymphoma generally manifests as bulky extramedullary (usually extranodal) disease with or without demonstrable dissemination. The distinction between non-Hodgkin's lymphoma and acute leukemia is arbitrary. Therefore, these entities are best considered in terms of a spectrum ranging from clinically localized disease to overt leukemia. In most treatment protocols, acute leukemia is now defined on the basis of marrow involvement above some threshold (typically a blast count of >25%) irrespective of the presence of bulky extramedullary disease. In contrast, a tumor accompanied by marrow involvement below this threshold constitutes stage 4 lymphoma.

ETIOLOGY

Immunosuppression and Viral Infection

Immunosuppressed individuals, such as those with HIV infection or those who have undergone bone marrow transplantation, are at increased risk for developing non-Hodgkin lymphoma. Epstein-Barr virus, which causes B-cell proliferation and *in vitro* immortalization, has been implicated in most of these lymphomas. Patients successfully treated for Hodgkin disease are at increased risk for developing non-Hodgkin lymphoma.

Geographic Location

In sub-Saharan Africa, the development of endemic Burkitt lymphoma is strongly associated with previous exposures to both malaria (with resultant T-cell suppression) and the Epstein-Barr virus. Recent speculation suggests that mosquito-borne arboviruses may also play a role in the development of Burkitt lymphoma in this

part of the world. In addition, exposure to 4-deoxyphorbol ester from the plant *Euphorbia tirucalli* (by means of goat's milk) is tentatively implicated in the pathogenesis of endemic Burkitt lymphoma.

Genetic Causes

The genetic basis of pediatric non-Hodgkin lymphoma has been studied extensively. Each subtype of non-Hodgkin lymphoma is characterized by one or more molecular alterations that contribute to the malignant phenotype. Many of these alterations are chromosomal translocations involving genes for immunoglobulin or T-cell receptor (TCR) molecules. During normal lymphocyte development, these loci undergo recombination that enhances immunologic diversification. However, mistargeted recombination leads to translocations with other genes, typically those that regulate cell growth. The resulting dysregulation of these other genes contributes to the transformed phenotype. The t(8;14) translocation for Burkitt lymphoma, translocations involving 1 of the TCR loci for example t(11;14) (*p13;q11*) translocation for T-lymphoblastic lymphomas and t(2;5) (*p23;q35*) translocation for anaplastic LCLs in children are some hallmark cytogenetic changes.

CLINICAL PRESENTATION

NHL can affect any part of the body and extranodal presentation is the hallmark of pediatric NHL. In general, patients often appear ill. They occasionally have a low-grade fever. Patients may present with pallor, respiratory distress, pain, and discomfort. T-NHL presents characteristically as mediastinal masses, B-NHL as an abdominal mass and ALCL as skin, lung or bone involvement. Common clinical manifestations include.

- A jaw or orbital mass is present in as many as 10 percent of patients in developed countries. It is particularly common in African patients with endemic Burkitt lymphoma.
- Cervical or supraclavicular masses or adenopathy is firm, fixed, and nontender.
- Dyspnea or stridor may occur in patients with a mediastinal mass. In those with superior vena cava syndrome, distended neck veins and plethora may be observed.
- Decreased breath sounds are secondary to bronchial obstruction or pleural effusion.
- Thoracic dullness to percussion may be present with pleural effusion.
- Abdominal distention or a mass may be present with or without tenderness, rebound tenderness, and/or shifting dullness.
- Painful skin lesions suggest an anaplastic LCL.
- Obtundation, agitation, and meningismus may be observed in individuals with CNS involvement.

- Focal pain or swelling in the extremity may be present in patients with primary bone lymphoma.
- Relatively uncommon physical findings include the following:
 - Nasopharyngeal mass
 - Parotid enlargement
 - Nephromegaly
 - Testicular enlargement.

DIAGNOSTIC WORKUP

- Complete blood count with differential and a platelet count in patients with non-Hodgkin lymphoma (NHL) to assess for possible involvement of the bone marrow and to determine the patient's transfusion requirements.
- Blood and urine cultures if patient has a fever, especially if it is associated with neutropenia.
- Assess the patient's renal and hepatic function and to monitor for possible tumor lysis syndrome. Lactate dehydrogenase at diagnosis had prognostic significance in many analyses of treatment outcomes.
- HIV and EBV screening.

IMAGING STUDIES

- Chest radiography
- Ultrasonography
- Computed tomography
- *Bone scanning and skeletal surveys*: When additional symptoms are present, these tests help in identifying additional sites of disease.
- *Positron emission tomography*: Positron emission tomography (PET) has recently been used for determining sites of active disease
- Echocardiography baseline before patient is given chemotherapy with anthracyclines which can cause cardiomyopathy.

PROCEDURES

- Bilateral (superior to unilateral) bone marrow aspiration and biopsy
 - Biopsy is necessary to assess for evidence of bone marrow involvement in patients with lymphomas.
 - A finding of more than 25 percent marrow blasts is generally regarded as diagnostic of acute leukemia. Levels of involvement lower than this with lymphoma indicate stage 4 disease.
- Biopsy
 - A histologic diagnosis must be obtained. Immunohistochemistry to identify correct subtype helps plan therapy.
 - For patients with an abdominal tumor, tissue is generally available from resection or intraoperative biopsy.

- Patients with mediastinal disease frequently have enlarged supraclavicular or cervical nodes, which can enable diagnosis without thoracotomy.
- As an alternative, a diagnosis may be made by using pleural fluid or by using involved bone marrow (especially if CBC counts are abnormal and/or if imaging studies demonstrate abnormal signal intensity of the marrow). In rare cases, cerebrospinal fluid (CSF) can be used.
- *Lumbar puncture with determination of the CSF cell count and differential:* This test is done to assess CNS involvement, the presence of which alters therapy.

HISTOPATHOLOGY (FLOW CHART 1)

Lymphoblastic Lymphomas (Fig. 1)

Lymphoblastic lymphoma cells are indistinguishable from the lymphoblasts of acute lymphoblastic leukemia (ALL). The cells are monotonous and associated with a high nuclear-to-cytoplasmic ratio. Their nuclei are often convoluted and contain finely stippled chromatin. Nucleoli are usually visible but are not prominent. Immunohistochemical analysis usually reveals T-cell markers, including CD5 and CD7. Common ALL antigen (CALLA) is occasionally observed.

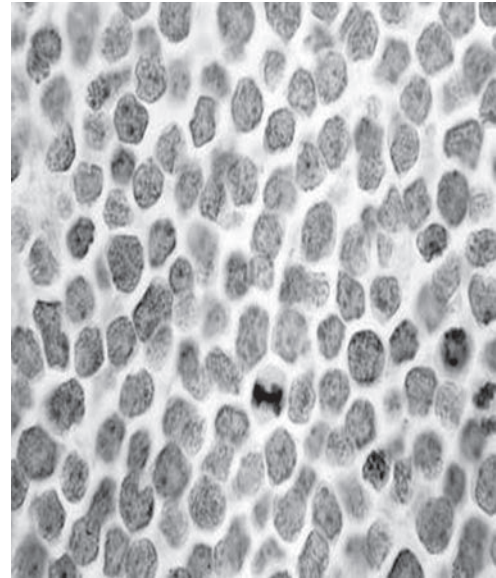
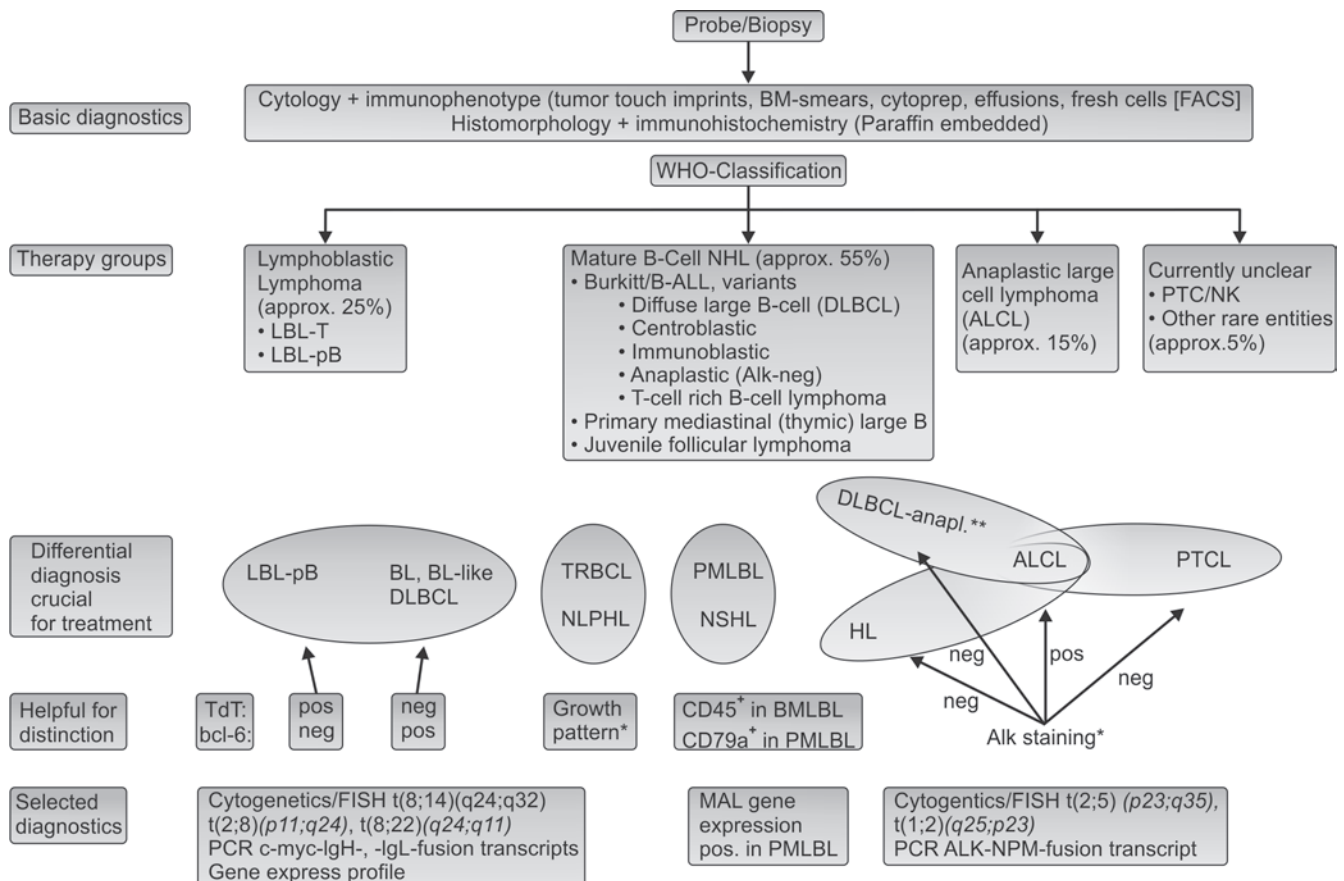


Fig. 1: Lymphoblastic lymphoma demonstrating the fine, blastic chromatin pattern without significant nucleoli and scanty cytoplasm. There is a high mitotic rate and diffuse effacement of nodal structures. Occasional tangible body macrophages are noted admixed with the neoplastic cells (For color version see plate 12)

Flow chart 1: Classification of NHL based on histopathology into 3 different treatment groups



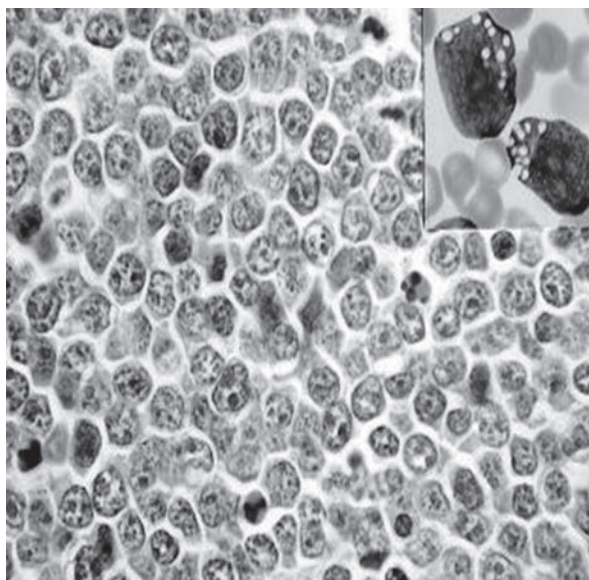


Fig. 2: Burkitt's lymphoma demonstrating the uniform neoplastic cells of intermediate size with coarser chromatin and several indistinct nucleoli and scanty cytoplasm. The inset shows a touch imprint of the tumor demonstrating the characteristic lipid vacuoles in the cytoplasm and the rounded nuclear contours (For color version see plate 12)

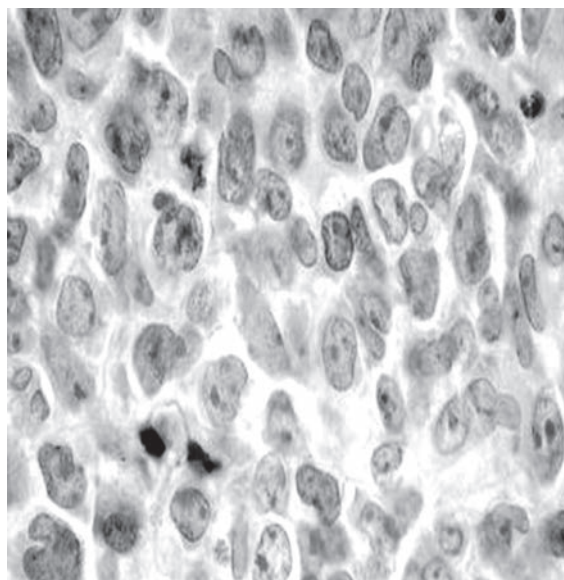


Fig. 3: Diffuse large B-cell lymphoma demonstrating the large neoplastic cells with moderate amounts of cytoplasm and somewhat irregular nuclear contours

Mature B Cell Lymphomas (Figs 2 and 3)

Burkitt lymphoma cells are notably uniform in size and shape, and they usually contain multiple prominent nucleoli. The tumor cells are mature B cells, as evidenced by the surface expression of immunoglobulin (usually immunoglobulin M), CD19, CD20, and HLA-DR. CALLA is usually present.

Anaplastic Large Cell Lymphomas (Fig. 4)

Anaplastic LCLs express CD30, or Ki-1+ antigens on immunohistochemistry.

Staging

Several systems for classifying non-Hodgkin lymphomas have been proposed. The St Jude system (the Murphy system) is used clinically.

- *Stage I:* Single extranodal tumor or single anatomic area (nodal), excluding the mediastinum or abdomen
- *Stage II:* Single extranodal tumor with regional node involvement; primary GI tumor with or without associated involvement of mesenteric nodes, with gross total resection; or, on same side of diaphragm, 2 or more nodal areas, or 2 single (extranodal) tumors with or without regional node involvement
- *Stage III:* Any primary mediastinal, pleural, or thymic intrathoracic tumor; any extensive and unresectable abdominal tumor; any primary paraspinal or epidural tumor regardless of other sites; or, on both sides

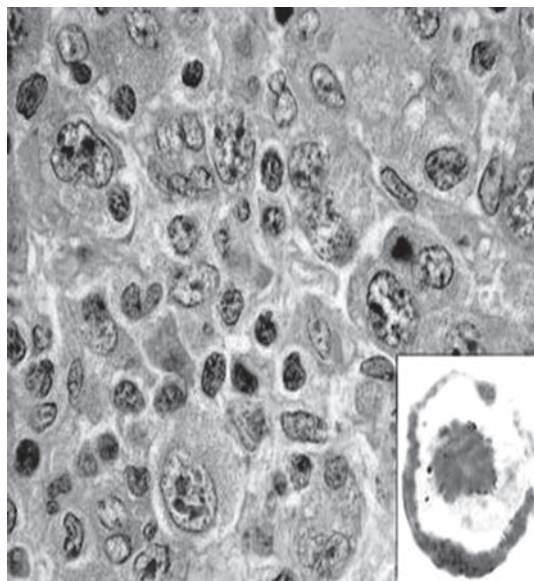


Fig. 4: Anaplastic large-cell lymphoma demonstrating the large neoplastic cells with marked variation in size and occasional multinucleated cells. The cells characteristically stain with CD30 (Ki-1), as seen in the inset

of the diaphragm, 2 or more nodal areas, or 2 single (extranodal) tumors with or without regional node involvement

- *Stage IV:* Any of the above with initial CNS or marrow (<25%) involvement.

THERAPY

All patients need administration of intravenous fluids at twice the maintenance rates, usually without potassium. We need to add sodium bicarbonate to the intravenous fluid to achieve moderate alkalization of the urine (pH of approximately)⁷. This measure enhances the excretion of tumor metabolites. Allopurinol is used to prevent or correct hyperuricemia. In high-risk situations (extreme elevations of lactate dehydrogenase [LDH] and/or uric acid or evidence of impaired renal function at presentation), consider administration of recombinant urate oxidase (rasburicase). The patient's laboratory values need to be monitored for tumor lysis syndrome throughout initial therapy. Testing may be needed as often as 2 to 4 times per day. This follow-up is especially important during the first 48 to 72 hours of therapy in a patient with bulky disease. If present, fever simply may reflect the underlying malignancy. However, consider beginning empiric broad-spectrum antibiotic coverage until sepsis or focal infection (e.g. due to bowel perforation) is excluded.

LYMPHOBLASTIC LYMPHOMA

The chemotherapy protocol is similar to that of acute lymphoblastic leukemia. The treatment is divided into phases of induction, consolidation, reintensification and maintenance, and includes drugs like corticosteroids, vincristine (VCR), anthracyclines, L-asparaginase (L-Asp), cyclophosphamide (CP), methotrexate (MTX), cytarabine, 6-mercaptopurine (6-MP), and 6-thioguanine. High-dose (HD) MTX (5 g/m² intravenous over 24 hours) gives good CNS prophylaxis. Treatment duration is for 24 months. Most relapses occur early, and late relapses are rare. In patients with T-LBL most relapses occur during the first 12 months after diagnosis, suggesting that the duration of maintenance can be reduced.

B-NHL

The extremely high proliferative activity of BL necessitates the use of short high dose chemotherapy. The basic principle is to maintain cytotoxicity active drug concentrations over a period that is sufficient to affect as many lymphoma cells as possible during the vulnerable active cell cycle, using either fractionated administration or continuous infusion. Other principles are combining drugs with different mechanisms of action and few overlapping toxicities; high-dose intensity over time by keeping between-treatment intervals short; and efficient CNS-directed therapy to address the strong tendency for invasion of the CNS, especially that of BL. Therapeutic strategies that adhere to this principle of rapidly repeated 4- to 7-day courses composed of corticosteroids, VCR, CP or ifosfamide, HD MTX, cytarabine, doxorubicin, etoposide, and triple drug (MTX/cytarabine/corticosteroid)

intrathecal therapy resulted in EFS rates up to 90 percent in large, multicenter studies.

COMPONENTS OF ALCL

Alkylating agents, HD MTX, and etoposide are main components of ALCL therapy. Doxorubicin, VCR, and steroids are also key component drugs. Adding vinblastine as a single agent during maintenance seems to have a survival advantage.

SUMMARY

Childhood NHL is on the increase and effective treatment protocols are available for the different subtypes. Initial accurate histopathological classification, staging and risk stratification to plan therapy is the most important aspect of improving cure rates. Early stages have about 90 percent cure rates and late stages about 50 to 60 percent. Therapy carries significant toxicity and adequate supportive care is required to deliver high doses of chemotherapy safely to children. NHL in childhood comprises a small percentage of childhood cancer and in our country should be treated in large cancer centers using standard pediatric protocols for optimal outcomes.

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Hodgkin's Lymphoma

Rachna Seth

INTRODUCTION

Hodgkin's lymphoma (HL) is a neoplasm primarily of B cell lineage involving lymph nodes and the lymphatic system with unique molecular, histologic, immune phenotypic and clinical features. HL, which represents about half of all childhood lymphomas which are the third most common malignancies in children, can be cured in >80 percent of patients and in >90 percent with limited stage disease.

Hodgkin's lymphoma (HL) is uncommon below the age of 5 years and exhibits three distinct forms in developing countries: the childhood form (younger than 14 years), a young adult form (15-44 years) and an older adult form (55-74 years). There is a significant male preponderance (10:1) in children with HL below 7 years of age with almost equal sex distribution (1:1.1) beyond 12 years of age.¹

The vast majority of patients achieve disease remission with multiagent chemotherapy with/without radiotherapy. The therapeutic success of HL demonstrated the benefits of multidisciplinary expertise and coordination from pathologic diagnosis to radiologic evaluation to irradiation and medical oncology treatments. The improved cure rates for HL have increased so extensively that there is emerging concern relating to long-term toxicity of chemotherapy and radiotherapy.

EPIDEMIOLOGY AND ETIOLOGY

The etiology of Hodgkin's lymphoma is believed to be multifactorial with a role for infectious agents, genetic susceptibility, socioeconomic factors and environment and immune dysregulation.¹⁻⁴

Evidence for Genetic Contribution in the Etiology of HL

Genetic susceptibility and familial aggregation seem to play an important role in Hodgkin's lymphoma. Siblings

have a seven-fold increase in the risk and multiple studies have confirmed a gender concordance of sibling pairs. A strong evidence of genetic susceptibility further comes from a 100-fold increased risk in monozygotic twins compared with dizygotic twins. Some studies have shown a 100-fold increased risk in monozygotic twins compared with dizygotic twins.

Several groups have described human leukocyte antigen (HLA)-related susceptibility and resistance to HL. Recent data has also shown that HLA in EBV-related HL thereby strengthening the fact that HL is related to a genetically related immune response to an environmental pathogen.

Epstein-Barr Virus Infection and Hodgkin's Lymphoma

Epidemiologic studies have suggested links between Hodgkin's lymphoma and viral illnesses like Epstein-Barr virus (EBV) and EBV viral DNA can be found in Hodgkin's- Reed-Sternberg cells (HRS). EBV-positive classic Hodgkin's lymphoma tumors differ geographically and are more common in developing countries. EBV is also common in mixed-cellularity Hodgkin's lymphoma and young children.

PATHOLOGY

Hodgkin's lymphoma is characterized by a minority of malignant cells that account for 0.1 to 10 percent of total cell population of the tumor. The majority of tumor is composed of an infiltrate of inflammatory cells (histiocytes, plasma cells, lymphocytes, eosinophils, neutrophils) and fibrosis (Table 1).

The current WHO histological classification of Hodgkin's lymphoma recognizes two major subtypes of HL.⁵

- i. *Nodular lymphocytic-predominant Hodgkin's lymphoma (NLPHL)*: This subtype of HL is characterized by large cells with multilobed nuclei referred to as popcorn

Table 1: Hodgkin's lymphoma—histopathological classification

<i>Histology</i>	<i>Pathology RS</i>	<i>Other</i>	<i>Prognosis</i>
Lymphocyte predominance (10-15%)	Rare	Predominance of normal appearing lymphocytes, few RS cells, no fibrosis	Excellent
Nodular sclerosis (20-50%)	Frequent 'lacunae'	Lymphoid nodules collagen bands that divides lymphoid tissue into nodules	Very good
Mixed cellularity* (20-40)	Numerous	Pleomorphic infiltrates paucity of lymphocytes	Good
Lymphocyte depletion (5-15%)	Often	Paucity of lymphocytes fibrosis and necrosis common but diffuse	Poor

RS—Reed-Sternberg cell; *most common in developing countries and in children

Table 2: Ann-Arbor staging system for Hodgkin's lymphoma

<i>Stage</i>	<i>Involvement</i>
I	Single lymph node region (I) or one extralymphatic site (I _E)
II	Two or more lymph node regions on same side of diaphragm (II) or one or more lymph node regions on same side of diaphragm plus local extralymphatic extension (II _E)
III	Lymph node regions on both sides of the diaphragm (III) which may be accompanied by local extralymphatic extension (III _E)
IV	Diffuse involvement of one/more extralymphatic organ/sites
A	No B symptoms
B	Presence of at least one of the following: <ol style="list-style-type: none"> 1. Unexplained weight loss >10% baseline during 6 months before staging 2. Recurrent unexplained fever > 38 degree centigrade 3. Recurrent night sweats
X	Bulky tumor

cells. Nodular lymphocytic-predominant Hodgkin's lymphoma patients generally asymptomatic and present with localized nonbulky disease.

- ii. *Classical Hodgkin's lymphoma:* The hallmark of classic HL is the R-S cell. This is a binucleated or multinucleated giant cell that is often characterized by a bilobed nucleus with two large nucleoli, giving an owl eye appearance to the cells. There are four varieties of this subgroup each characterized by the number of R-S cells, characteristics of inflammatory milieu and the presence or absence of fibrosis.

On immunophenotyping, the classic subtypes of Hodgkin's lymphoma are positive for CD15 and CD30 and may be positive for CD20, whereas NLP Hodgkin's lymphoma is negative for CD15 and CD30 but positive for CD20 and CD45.⁶

STAGING AND PROGNOSIS

The Ann-Arbor staging system has stood the test of time in HL patients were described into four stages based on the extent of lymph node involvement and disseminated disease (Table 2).

Stage I: Involvement of single nodal area.

Stage II: Involvement of two/more nodal areas on one side of the diaphragm.

Stage III: Involvement of nodal areas on both sides of the diaphragm.

Stage IV: Disseminated disease involving one/ more extranodal sites.

In addition to recording the extent of disease, the staging system also reflect the absence (A) or presence (B) of systemic symptoms. The extranodal lesions are denoted with (E).

Modifications in the Ann-Arbor staging were done in 1989 in Cotswolds (UK). The major proposed alteration was to designate bulky tumors with diameters 10 cm or greater. This was based on the appreciation that large mediastinal disease, then defined as a tumor with a maximum diameter greater than one-third of the maximum intrathoracic diameter on standing chest radiograph conferred a poor prognosis. It then became a convention to designate mediastinal disease as bulky (either by original definition and/or 10 cm or greater disease by CT scan) or not bulky by the cotswolds modification.

Bulky tumor is defined as either a single mass of tumor tissue exceeding 10 cm in largest diameter or a mediastinal

mass extending one-third of the maximum transverse intrathoracic diameter measured to the inside of the ribs on a standard posteroanterior chest radiograph.

E lesion localized extranodal extension of HL from a contiguous/nearby nodal site is noted with the designation E.

Other abbreviations used in classification include CS (Clinical stage when classification of disease is based on physical examination and imaging technique) and PS (Pathological stage when classification is based on biopsy reports).

DIAGNOSIS AND EVALUATION

Hematological and blood chemistry evaluation is nonspecific but useful to define extent of disease. Poor prognostic markers include ESR of more than 50 mm/h, hemoglobin concentration less than 10.5 g/dl, white blood cell count of 15,000/ μ l or less, absolute lymphocyte count less than 600/ μ l and albumin level less than 4 g/dl.

Chest radiography, CT, MRI, or ultrasonography of the neck, chest or abdomen may be indicated as per disease involvement. Positron emission tomography (PET) CT is used to identify the extent of disease (highly recommended).

The role of FNAC in establishing the diagnosis of HL is controversial. Core needle biopsy may be used but the optimum sample is an excisional biopsy of the lymph node. Histopathologic studies include hematoxylin and eosin staining and special immunohistochemical staining for surface markers such as CD3, CD15, CD20, CD30 and CD45. CHL cells usually express CD15 and CD 30 but lack CD20 and CD45. LPHL cells are usually CD45 and CD20 positive and do not express CD15 and rarely express CD30. Epithelial membrane antigen is expressed by LPHL and not CHL.⁶

Bone marrow biopsy is needed with suspected bone marrow involvement and in stage IIB, III or IV or abnormal blood counts.

Computerized tomography (CT) scan is currently the recommended modality in the staging and assessment of response at the end of therapy in patients with Hodgkin's lymphoma. The drawbacks of CT scan include its failure to differentiate areas of necrosis and fibrosis in residual masses from viable tumor thus creating a therapeutic dilemma whether the patient requires further treatment or not. It also fails to identify tumor deposits in unenlarged nodes thus underestimating the stage of the disease before starting therapy.

Fluorine-18-fluorodeoxyglucose (18F-FDG) positron emission tomography (PET) has been widely established in the treatment protocol of non-Hodgkin's lymphoma. In recent times it is being used with increasing frequency in Hodgkin's lymphoma, for staging at the time of diagnosis, to differentiate persistent, active disease from residual, but inactive masses at the completion of therapy as well as

for monitoring for relapse. The uptake of the radioactive glucose analog 2-[18F] fluoro-2-deoxy-D-glucose (FDG) correlates with proliferative activity in tumors undergoing anaerobic glycolysis. However, PET alone has lower specificity because of poor localization details. Introduction of combined PET and CT (18F-FDG-PET/CT) technology has revolutionized imaging by fusing functional and anatomical data. It is now being used for staging, response monitoring and prognostication of tumors. The limitations are the high cost and unavailability of the diagnostic test at many centers. PET CT should be performed about 3 weeks after chemotherapy and about 8 to 12 weeks after radiotherapy.

FDG-PET has also been studied as a predictor of outcome in Hodgkin's lymphoma. A negative interim PET after 2 cycles of chemotherapy was associated with an increased 2 year progression free survival rate compared to the PET positive group.

The role of PET in guiding involved-field radiation therapy in pediatrics is being explored. Gallium scanning has been replaced by PET scanning. Bone scanning is used when bony metastases are suspected but the same information may be obtained with PET scanning.⁷

CLINICAL FEATURES

- Hodgkin's lymphoma typically presents insidiously with supradiaphragmatic lymphadenopathy. The low neck and supraclavicular nodes are particularly common sites. HL presenting as mediastinal masses and features of superior mediastinal syndrome (chest pressure, cough, dyspnea,) is not uncommon; however mediastinal involvement is often asymptomatic. 10 percent patients may have an initial subdiaphragmatic presentation. The peripheral lymph nodes have a characteristic rubbery consistency and are painless.
- A subset of 30 percent patients presents with fever and night sweats without peripheral adenopathy. The constellation of fever, night sweats and unexplained weight loss constitutes the classic 'B' symptoms of HL and serve as hallmarks of the disease and serve as prognostic factors.
- Another constitutional complaint is unexplained pruritus which should create suspicion and lead to complete physical examination and chest radiography.
- Presentations of classical HL correlate with histologic subtype, gender and age. Nodular sclerosis presents as limited or extensive disease with mediastinal involvement in 75 percent cases. Older and immunodeficient patients are more likely to have B symptoms, advanced disease and mixed cellularity histology. NLPHL has a marked male preponderance and usually occurs in peripheral nodes above or below the diaphragm sparing the mediastinum. NLPHL patients are usually asymptomatic with single node involvement.

- Bone involvement by classical HL may cause pain.
- Bone marrow involvement rarely results in cytopenias and has been associated with a variety of paraneoplastic syndromes that may be the presenting feature of the disease, e.g. HL, Neurologic disorders and jaundice. Other uncommon sites of involvement include the GIT and skin.
- Splenic involvement occurs in 30 to 40 percent of HL. Studies have shown that enlarged spleen, involvement of 3/more lymph node areas and bulky disease are predictable risk factors for HL splenic deposits. It has also been seen that CT scan/ultrasonography is significantly associated with relapse and contributes to a poor outcome in children treated with chemotherapy alone.

PROGNOSIS

The prognosis for patients of HL has steadily improved over the past 50 years as a result of advance sin diagnosis and therapy. Currently cure is expected for the great majority of patients; however management of advanced stage is a challenge.

The International Prognostic Score (IPS) is based on seven factors: Three clinical (age >45 years, male sex, stage 4) and four laboratory values (albumin <4g/dl, hemoglobin <10.5 g/dl), white blood count >15,000/micro liter, lymphocyte count <8 percent or <600 cells/micro liter). Patients are given a score from 0 to 7 and disease is characterized a low (0-1) intermediate (2-3) or high risk (4-7).^{8,9}

Several studies have found that early FDG-PET is superior to the IPS in predicting progression free survival in advanced HL. PET scans are interpreted as negative or positive based on FDG uptake. This is the basis for response based treatment approach and serves to individualize treatment and balance the risks and benefits of the therapeutic approach.

MANAGEMENT

Treatment modalities have varied from total nodal radiation therapy to chemotherapy to combination-chemoradiotherapy with significant improvement in survival rate throughout the last three decades.¹⁰⁻¹⁵

Risk adapted therapy: Various clinical and laboratory features have been identified as poor prognostic factors as have been discussed earlier in children with HL and lead to more aggressive therapy in a particular subset of patients. They are related to tumor burden, tumor spread, B symptoms, response to therapy, biology and host factors.

With advances in diagnostics and improvement in therapeutics and supportive care the overall survival of children with HL has improved significantly. Focus is now on the late/long effects of cancer therapy which include retardation of musculoskeletal growth, increased risk of

cardiovascular disease, second malignancy, gonadal injury, pulmonary fibrosis, etc.

Current approaches use chemotherapy alone with/without low dose involved field radiation therapy (IFRT). The volume of radiation and intensity/duration of chemotherapy are determined by prognostic factors at presentation including presence of constitutional symptoms, disease stage and bulk.

All children generally receive combination chemotherapy as initial treatment. Common regimes currently utilized for treatment include nonalkylating containing regimes such as ABVD (doxorubicin {Adriamycin} bleomycin, vinblastine and dacarbazine), hybrid regimes with lower dose of alkylators, doxorubicin and bleomycin such as COPP/ABV (cyclophosphamide, vincristine, procarbazine, prednisone/doxorubicin, bleomycin and vinblastine), DBVE (doxorubicin, bleomycin, vincristine, etoposide), BEACOPP (bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, prednisone, procarbazine) and VAMP (vincristine, doxorubicin, methotrexate, prednisone).

Several studies have demonstrated that chemotherapy alone is effective therapy for pediatric HL. The advantage of this approach is elimination of radiation associated adverse effects like myocardial dysfunction, musculoskeletal growth deficits and second malignancy. Chemotherapy alone protocols on the other hand rely on higher doses of chemotherapy contributing to chemotherapy related toxicity. Controlled randomized trials suggest that addition of radiation therapy to chemotherapy improves outcomes in children particularly with unfavorable and advanced stage HL.

With the emerging concept of risk directed therapy most children are treated with combination chemotherapy alone or in combination with radiotherapy. The dose of radiation therapy used ranges between 15-25 Gy with modifications based on patients age, response to chemotherapy and presence of bulky/residual tumor.

Superior treatment results and absence of leukemogenesis and permanent gonadal toxicity have made ABVD the preferred front line regimen for HL; however the concerns of this protocol include cardiomyopathy and pulmonary fibrosis. Currently, ABVD/other hybrid combinations are incorporated into risk adapted treatment regimes prescribing fewer cycles of chemotherapy with localized favorable disease. In advanced and unfavorable disease, ABVD is often supplemented with other agents with differing toxicities to improve disease outcome and reduce drug-related toxicity.

With favorable clinical presentation (localized nodal involvement stage (I, II, IIIA), absence of B symptoms and no evidence of bulky disease as defined by size/CxR findings) multiagent regimes mentioned above may be used. Treatment for patients with favorable disease clinical presentation consists of 2 to 4 cycles of chemotherapy

(ABVD/others) and low dose involved field radiation. Several studies have reduced the dose of radiation in patients achieving a favorable response to chemotherapy. There is a possible role of chemotherapy alone without radiotherapy in early stage HL.

Unfavorable clinical presentation is defined as presence of B symptoms, bulky mediastinal/peripheral lymphadenopathy, extranodal extension of disease and advanced disease (stage IIIB-IV). Treatment comprises of more cycles of chemotherapy. Localized disease (stage I, II, IIIA) with unfavorable features may be treated similarly to advanced stage disease in some protocols or given a therapy of intermediate intensity. (4-6 cycles of ABVD with/without radiotherapy). Other possible combinations include COPP/ABVD, MOPP/ABVD, OPPA, Stanford V regimen, BEACOPP. The role of additional radiotherapy in stage III and IV HL remains controversial. It has been shown in studies that adjuvant radiotherapy presents no survival advantage though better local tumor control is obtained.

The use of hemopoietic stem cell transplantation (HSCT) as initial therapy remains controversial because of the overall excellent prognosis of children with advanced and unfavorable Hodgkin's lymphoma. At present HSCT should be reserved for patients after relapse or for those who are refractory to primary conventional therapy.

LATE EFFECTS OF CANCER THERAPY IN HODGKIN'S LYMPHOMA

Survivors of HL experience many long/late effects attributed to chemotherapy alone or in combination to radiotherapy. These include growth retardation (radiation), myocardial dysfunction (anthracycline), pulmonary fibrosis (bleomycin), neuropathy (vincristine), avascular necrosis (steroids) hypothyroidism (radiation) and second malignancy (etoposide) necessitating the need for long-term follow-up after completion of cancer therapy.

CONCLUSION

Hodgkin's lymphoma is a highly curable lymphoma with overall cure rates exceeding 80 percent and over 90 percent with limited stage disease. The improved survival has led to the concern about long-term effects of cancer therapy adversely affecting the quality of life of these children. Considering the prevailing regimes (combined modality therapy) in the management of Hodgkin's lymphoma, priority questions include determination of the minimal number of chemotherapy cycles and identification of patients requiring radiation. The choice between chemotherapy alone protocols and chemoradiotherapy is guided by the desired balance between cure and long-term effects of therapy. Factors contributing to poor outcomes need to

be established for pediatric Hodgkin's lymphoma. With emerging techniques like PET CT, it may be possible to identify the subset of patients whose chemotherapy may be truncated versus those who require intensification of chemotherapy regime to enhance disease control. Discovery of targeted therapy with biologic agents is felt need for the future and may provide an alternative to cytotoxic therapy.

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Stem Cell Transplantation

Satya Prakash Yadav, Anupam Sachdeva, Himani Manchanda

INTRODUCTION

Stem cell transplantation is a generic term covering several different techniques (Flow chart 1). Allogeneic transplants are hemopoietic stem cells from the bone marrow, peripheral blood, or umbilical cord blood of a healthy donor matched for HLA type, who may be a family member or an unrelated volunteer. Autologous transplants are stem cells from the patient's own bone marrow or peripheral blood.

Allogeneic transplantation was first used to treat congenital immune deficiencies, bone marrow failure, and hematological malignancies and is now used routinely for some nonmalignant conditions such as thalassemia. Autologous transplantation was introduced to rescue the bone marrow of patients due to undergo high-dose chemotherapy, and it is now increasingly written into protocols for the primary treatment of solid tumors such as neuroblastoma. Autologous transplantation is also used experimentally to treat difficult autoimmune conditions such as systemic sclerosis and as a vehicle for gene therapy. Knowledge of stem cell transplantation techniques and their clinical application is therefore becoming essential for increasing numbers of medical specialists.

Stem Cell Transplantation Techniques (Flow chart 1)

The first successful bone marrow transplant in humans was performed between identical twins. With a greater understanding of the HLA system, it became possible to perform bone marrow transplants between siblings who were fully HLA identical. Transplantation is widely used for treating congenital bone marrow disorders and malignant hematological diseases. Today, over 350 centers worldwide are performing more than 18000 bone marrow transplants a year. Centers may report their transplants to the European Bone Marrow Transplant Registry and/or International Bone Marrow Transplant Registry (IBMTR), which periodically publishes outcome data.

Probable Future Developments

- Growth of stem cells in the laboratory, enabling wider use of cord blood donations in adults
- Improved techniques to “clean up” autologous stem cell transplants in cancer patients to prevent contamination with tumor cells
- Expansion of indications for transplantation, such as various solid tumors and severe autoimmune conditions.
- Expansion of mini-transplant protocols less intensive chemotherapy or chemoradiotherapy followed by planned infusions of donor lymphocytes as well as stem cells in order to “mop up” remaining tumor cells
- Increased use of donors not matched for HLA type.

DONOR AVAILABILITY

The major factor limiting the number of allogeneic transplants performed is availability of donors.

Sibling Donors

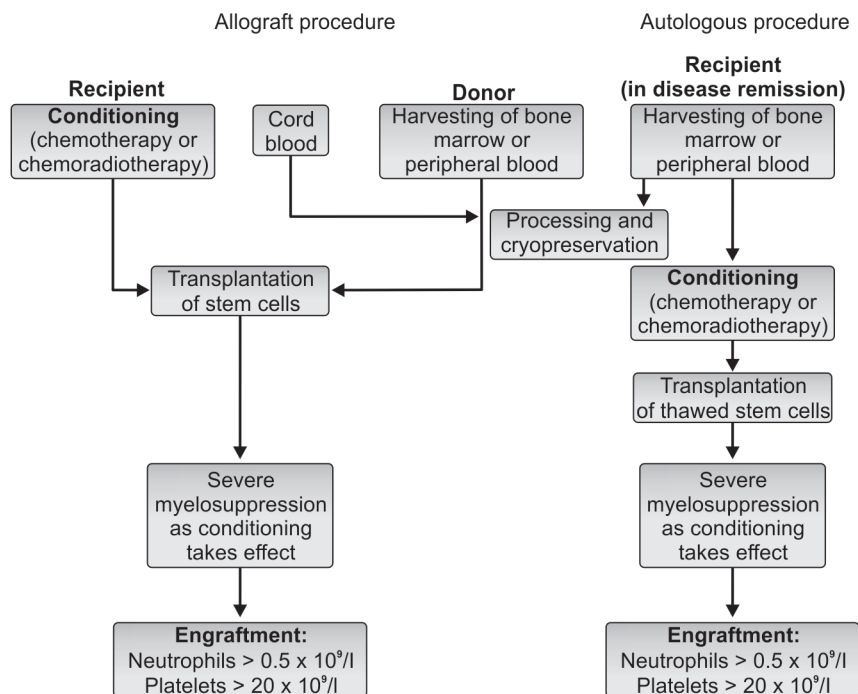
It is known from population based studies that only 20 to 25 percent of patients eligible for allogeneic transplantation will have suitable sibling donors.¹

Matched Unrelated Donors

To make transplants available to a greater number of eligible patients, registries of volunteer bone marrow donors have been developed. These can provide transplant physicians with stem cells from unrelated but matched donors. There are now over 6 million donors registered on national donor panels worldwide.

Transplants from unrelated volunteers are associated with higher morbidity and mortality than transplants from matched siblings, but outcomes are improving,² partly because modern molecular techniques allow closer matching of donors and recipients. Patients with chronic

Flow chart 1: Stem cell transplantation techniques



myeloid leukemia who are considered a good risk for transplantation (aged less than 40 years, seronegative for cytomegalovirus, in chronic phase, and receive a transplant within one year of diagnosis from a closely matched donor) have outcomes approaching those seen in allogeneic transplants between siblings that is, over 70 percent survival at five years.³

Patients with common HLA types have a good chance of getting a match, unlike those with rarer HLA types, such as patients from ethnic minorities or those of mixed parentage. It can take many months to locate, test, get the consent of, and pronounce medically fit a suitable volunteer donor, and delays may be critical in patients with acute leukemia. Their disease may relapse or progress before the search is completed, especially if a search has to be extended outside the country of residence.

Stem Cells from Umbilical Cord Blood

Cord blood from neonates contains substantial numbers of hemopoietic stem cells, which can be harvested at delivery, frozen, and then transplanted to patients who would not otherwise have a donor (Figs 1A and B, Plate 8).⁴ Thousands of such donations are now stored in special banks worldwide, after cell counts and virological screening tests are performed, and inventories of their HLA types are available to transplant centers. Computer records can be scanned quickly, and donations can be matched with potential recipients without the delays inherent in securing an adult donor. In 1988, umbilical cord blood (UCB) hematopoietic stem cells (HSC) from

a related sibling were transplanted successfully into a 5-year-old child with Fanconi anemia by Gluckman and colleagues.⁵ Subsequently, thousands of UCB transplant procedures have been performed worldwide using UCB from related and unrelated donors into pediatric⁶⁻¹² and adult patients.^{9,13-16} UCB offers the advantages of easy procurement, no risk to donors, the reduced risk of transmitting infections, immediate availability of cryopreserved units, and acceptable partial HLA mismatches. Nearly all patients can find at least one potential 4 of 6 HLA-matched UCB units through the Netcord, New York Blood Center, and NMDP Registry or other banks. Such transplants are associated with slightly delayed engraftment but a lower risk of graft-versus-host disease.⁴ Cord blood transplants are usually reserved for children as the calculated stem cell dose in a donation often falls far short of the levels deemed necessary for stem cell engraftment in an adult.

Banked unrelated UCB has emerged as an alternative allogeneic stem cell source, providing available and suitably HLA-matched donors for patients requiring allogeneic transplantation. Early clinical reports of UCB transplantation, in pediatric and adult recipients, show slower rates of hematopoietic engraftment, higher rates of infection, yet importantly, a low incidence of severe (grade III/IV) acute GVHD, even when HLA-disparate grafts are infused. Cellular and molecular mechanisms of reduced incidence of severe GVHD and graft-versus-malignancy effects in UCB grafting need further study. Preliminary observations suggest that UCB from

unrelated donors is a feasible alternative source of stem cells for transplantation in adults, resulting in durable although delayed hematopoietic reconstitution, with low incidence and severity of acute GVHD. Preliminary work examining functionality of UCB-derived CD45⁺ and CD45⁻ stem cells in regenerative medicine applications are intriguing. Strategies to improve kinetics of hematopoietic recovery after UCB grafting in children and adults are warranted.¹⁷

Haploidentical Donor

Haploidentical related donor stem cell transplantation (SCT) has been evaluated over the past two to three decades as an alternative transplant option for the approximately 70 percent of patients who do not have an HLA-identical related donor.¹⁸⁻²⁵ The advantages of haploidentical SCT are that nearly all patients have an immediately available donor and that a stronger graft-versus tumor effect can be realized with partial HLA disparity. The disadvantages of haploidentical SCT are the immunological consequences of crossing the major histocompatibility barrier, namely graft-versus-host disease (GVHD), graft rejection, and delayed or incomplete immune reconstitution. With very intensive conditioning therapy, graft rejection has been largely overcome. Severe acute or chronic GVHD, however, have been formidable obstacles to the success of T cell replete transplants following myeloablative conditioning.¹⁸⁻²⁰

A potentially huge upside of haploidentical SCT exists: namely, an expansion of transplant opportunities for patients without an HLA-matched donor and the potentiation of a graft-versus-tumor effect of the transplant. Haploidentical stem cell transplant strategies may also be important for specific transplantation tolerance induction. Whereas some of the important challenges of haploidentical SCT have been addressed, and at least partially ameliorated (i.e. severe GVHD), other problems, such as delayed immune reconstitution and recurrent malignancy, particularly for patients with advanced disease at the time of transplant, remain significant hurdles limiting long-term success. Given these unresolved issues, the role and timing of haploidentical SCT, especially in relation to other potential alternative donor stem cell sources (cord blood, mismatched unrelated donors), remain to be defined. The most promising approaches to haploidentical SCT involve graft engineering to deplete cells capable of causing GVHD while preserving (or adding back later) cells that are responsible for a graft-versus-tumor effect and for restoring T cell immunity. In this regard, approaches that employ delayed adoptive cellular immunotherapy, including infusion of specific regulatory cells and/or tumor or pathogen-specific cytotoxic T lymphocytes, appear particularly promising.²⁶

Autologous Transplants

Autologous transplantation (using patients as their own donors) is now the most common form of stem cell transplantation. Cryopreservation techniques now allow bone marrow to be stored safely and indefinitely, while the patient undergoes conditioning chemotherapy, without catastrophic loss of stem cells on thawing. Recovery of peripheral blood counts after transplanting cryopreserved marrow previously exposed to chemotherapy was slow, and patients experienced prolonged neutropenia and thrombocytopenia. However, there was no graft versus host disease or prolonged immunosuppression, and the procedure was safer than allogeneic transplantation.

During the early 1980's it was noted that marrow stem cells circulated in the peripheral blood, in small numbers in normal controls but in greater numbers in patients recovering from neutropenia induced by chemotherapy. Stem cell yields increased further if the patient was given bone marrow growth factors such as granulocyte colony stimulating factor during the recovery period. In some patients large numbers of stem cells were found after treatment with the growth factor alone. With this technique, sufficient cells can usually be harvested from the peripheral blood over two to three days to safely perform an autologous transplantation. It was quickly noted that patients receiving this type of transplant recovered their peripheral blood counts more rapidly than the patients given transplants of cryopreserved autologous bone marrow. Peripheral blood is now the preferred source of autologous stem cells for transplantation in adults.^{27,28} In children the choice of peripheral blood or marrow largely depends on the size of the child.

IMPROVING SAFETY AND EFFICACY OF STEM CELL TRANSPLANTATION

Stem cell transplantation is associated with substantial morbidity and (in the allogeneic setting) mortality. Patients may spend considerable periods in hospital and need prolonged convalescence, especially if they are affected by graft-versus-host disease. However, several advances are associated with an improved outlook for patients and have led to increased interest in stem cell transplantation as a treatment.

Reduced Intensity Conditioning (RIC) for Allografts

Conventional conditioning regimens for patients with leukemia are meant to ablate the patient's marrow and all traces of disease before infusion of donor stem cells. The most commonly used preparative regimens for allogeneic HSCT for leukemia include fractionated total body irradiation (TBI) and cyclophosphamide, or busulfan and cyclophosphamide, but non-TBI-based myeloablative regimens

such as melphalan, fludarabine and thiotepa have been reported to facilitate engraftment even in haploidentical transplants.²⁹

However, it is widely recognized that immunocompetent cells in the donation can also help clear the recipient's residual tumor cells—a “graft-versus-tumor” effect^{30,31} and so it may not always be necessary to completely eradicate the disease with conditioning to achieve a cure. This observation led to experimentation with reduced intensity protocols sometimes followed by immunotherapy (see below). Such nonmyeloablative transplants are variously called minitransplants, low intensity transplants, or “transplant-like” conditioning. These techniques are being introduced for older patients or children who are not healthy enough to tolerate conventional, high intensity conditioning and transplantation. It remains to be seen how outcomes will compare with conventional approaches.

RIC allografting has expanded the role of allogeneic transplantation to many patients who until recently were deemed ineligible for this procedure. Although thousands of patients have undergone RIC regimen allografts, only a minority of them have been cured of their disease. As with conventional allografting, GVHD and disease recurrence remain the main barriers to overcome. Current strategies being explored to improve RIC allografting outcomes have focused on combining targeted therapies such as rituximab, imatinib, and gemtuzumab as part of the preparative regimen or as maintenance strategies.³²⁻³⁴ Immunotherapeutic strategies with either vaccines or cellular therapies, particularly NK cell infusions, are also likely to become subject of increasing study.^{35,36}

Reduced intensity conditioning (RIC) regimens are more commonly used for patients who cannot tolerate a conventional myeloablative regimen. Such regimens range from minimal nonmyeloablative, to facilitate engraftment (fludarabine plus low-dose TBI), to more intensive, such as reduced doses of fludarabine plus busulfan.³⁷ The goal is to induce an optimal graft-versus-leukemia (GVL) effect by donor alloreactive effector cells, while minimizing toxicity.³⁸ In patients with nonmalignant diseases, nonmyeloablative regimens with alemtuzumab have been successfully used.³⁹

Donor Lymphocyte Infusions

If a malignant hemopoietic condition relapses after an allogeneic transplant, lymphocyte infusions from the original donor can return the patient to remission by exploiting the graft versus tumor effect.^{32,33} In chronic myeloid leukemia such infusions can result in high rates of remission (60-80%).⁴⁰ Unfortunately, response rates are lower in other diseases,⁴⁰ and treatment may be associated with the development of graft-versus-host disease.

Improved HLA Typing

The most important factor affecting the outcome of allogeneic transplantation is the quality of the HLA match between donor and recipient. New DNA based technologies allow more sophisticated matching and are improving the outcome of this type of transplantation, particularly for unrelated transplants.

Improved Supportive Care

Improvements in the supportive care of transplant patients have followed development of bone marrow growth factors;⁴¹ new antibiotic, antifungal, and antiviral agents; and better immunosuppressive treatments. Additionally, we are able to detect infections earlier, with better tests for cytomegalovirus⁴² and improved imaging techniques for fungal infections.⁴³

Purging of Transplants

An autograft may fail for two reasons. Either the chemotherapy fails to eradicate the tumor, leading to eventual relapse, or the graft may be contaminated with tumor cells, which are reinfused and again cause relapse. To reduce contamination with tumor cells, practitioners may attempt to cleanup (purge) the transplant by using monoclonal antibodies directed against the tumor or by using peripheral blood stem cells instead of marrow. Recent studies, however, have shown that peripheral blood stem cell transplants are not necessarily less contaminated than marrow.⁴⁴

The goal of most *ex vivo* stem cell manipulation is the removal of tumor cells or “unwanted” cells such as T or B lymphocyte populations. A number of techniques for tumor cell purging for autologous transplantation have been described, but no studies have proven that patients receiving purged grafts do better. The removal of T lymphocytes from allogeneic bone marrow grafts for the prevention of GVHD is being used in clinical trials, and a variety of different techniques based on physical separation methods or T cell-specific reagents have been described.⁴⁵ Positive selection of CD34+ stem cells by magnetically activated cell sorting (MACS) as a method for indirect depletion of T lymphocytes, allows the processing of PBSC's. A 100,000-fold reduction of T cells can be obtained, thus allowing the transplantation of large numbers of purified CD34+ stem cells in the matched sibling, matched unrelated or mismatched haploidentical setting without the need for additional pharmacologic GVHD prophylaxis and without clinically significant acute or chronic GVHD occurring.⁴⁶ However, nonengraftment and viral reactivations and infections are significant complications due to this extensive T cell depletion method. This MACS technology also allows the add-back

of a defined number of T lymphocytes to the graft.⁴⁷ More recently, the MACS technology has been used for the negative depletion of T lymphocytes from allogeneic PBSC's, which provides appropriately a 1.5 log greater number of CD3+ cells than CD34+ selection and other non-CD34+ cells that may aid in engraftment.⁴⁸ PBSC grafts depleted of both CD3+ and CD19+ cells to reduce the risk of GVHD and EBV reactivation, respectively, have also been successfully used in haploidentical HSCT.⁴⁹⁻⁵¹

INDICATIONS FOR STEM CELL TRANSPLANTATION

Indications for stem cell transplantation are constantly changing, partly because of the increasing safety of the procedure. Given below are the established and potential indications and is a simplified version of the European bone marrow transplantation guidelines.⁴¹ This is not exhaustive but reflects the current practice of many clinicians performing transplants.

Indications for Stem Cell Transplantation

Established Uses

Allogeneic transplants

- Severe aplastic anemia
- Chronic myeloid leukemia
- Acute myeloid leukemia in first complete remission
- Myelodysplasia
- Acute lymphoblastic leukemia in first complete remission [Ph+ve ALL, Infant ALL t] ^{4,11}
- Severe congenital immunodeficiency (SCID)
- Acute myeloid leukemia and acute lymphoblastic leukemia in second complete remission
- Thalassemia.

Autologous transplants

- Acute lymphoblastic leukemia (certain subtypes)
- Hodgkin's disease in second complete remission
- Non-Hodgkin's lymphoma in second complete remission
- Solid tumors such as neuroblastoma.

Emerging Uses

Allogeneic transplants

- Sickle cell anemia
- Osteopetrosis
- Inherited metabolic disorders
- Hodgkin's disease
- Non-Hodgkin's lymphoma.

Autologous transplants

- Autoimmune disorders, such as systemic sclerosis
- Acute myeloid leukemia
- Solid tumors, such as brain tumors
- Chronic myeloid leukemia
- Hodgkin's disease in first complete remission
- Non-Hodgkin's lymphoma in first complete remission.

Experimental Uses

Allogeneic transplants

- Renal cell carcinoma.

Autologous transplants

- Juvenile chronic arthritis.

Transplant for Solid Tumors and Lymphomas (Autologous and Allogeneic)

Autologous HSCT is a commonly used component of a multiagent treatment program to treat certain high-risk solid tumors and relapsed or refractory Hodgkin or non-Hodgkin lymphoma (NHL). Autologous HSCT is based on the concept that escalating doses of chemotherapy are able to kill greater numbers of tumor cells. Studies in neuroblastoma and lymphoma offer the best clinical evidence for this effect. Published series of certain subsets of patients with relapsed Wilms tumor, metastatic or relapsed Ewing sarcoma, brain tumors (medulloblastoma and PNET but not ependymoma), and metastatic germ cell tumors do suggest a survival benefit, especially in patients transplanted in remission or with chemotherapy-sensitive disease. Ewing sarcoma is the second most common indication for autologous HSCT in the pediatric population; however, no randomized studies have been performed in this group as the study population is small. Allogeneic HSCT is rarely used to treat patients with solid tumors due to increased regimen-related mortality. Recent studies in adults with renal cell carcinoma demonstrated an allogeneic tumor response.⁵¹ Case reports and small series of patients with neuroblastoma, melanoma and Ewing sarcoma are promising for future studies. Allogeneic HSCT is often used to treat patients with Hodgkin or NHL who fail autologous HSCT. Alternatively, reduced intensity conditioning regimens with unrelated or related donor grafts are occasionally used after debulking with autologous HSCT.⁵² However, clinical trials are needed to fully elucidate the role of allogeneic HSCT in treating patients with solid tumors.

Transplant for Immunodeficiencies

Immunodeficiencies are another indication for allogeneic HSCT. Some of the more common immunodeficiencies for which transplantation is performed are severe combined immunodeficiency syndrome (SCIDS), Wiskott-Aldrich syndrome (WAS) and X-linked lymphoproliferative disease (XLP). In patients with SCIDS, HSCT with matched sibling donors is standard therapy, but for patients without such a donor, their lack of recipient T cells to reject donor stem cells make parental grafts acceptable. More recently, matched unrelated donor grafts are increasing in use.⁵³ Regarding the preparative regimen, a consensus has not been reached as many of these patients present with a life-threatening viral infection. For children with WAS,

an X-linked syndrome characterized by micro-thrombocytopenia and eczema, no significant difference in survival exists between receiving a matched sibling and unrelated donor if HSCT occurs before the patient is five years of age. After this age, there is a decrease in survival in the unrelated donor cohort.⁵⁴ Alternative donor transplants with T cell depletion should be performed in clinical trials.

Preparative regimens for immunodeficiencies depend on clinical condition and stem cell source. More recently for those that require conditioning, reduced intensity myeloablative regimens have been prescribed with the addition of a monoclonal antibody directed at ablating lymphocytes.³⁹ For these nonmalignant diseases, engraftment is required though they may survive with a mixed donor chimerism. Future goals for treating these nonmalignant patients should include novel graft engineering to ensure stable donor engraftment with reduction in transplant-related morbidity and mortality and long-term transplantation effects.

Hemoglobinopathies

Sickle cell disease and thalassemia are disorders of hemoglobin, resulting in significant complications and frequent transfusion requirements. HSCT is curative for these patients; however, careful evaluation is necessary to identify appropriate transplant candidates.⁵⁵ Sickle cell patients who experience frequent vaso-occlusive pain crises, frequent hospitalization for acute chest syndrome, or cerebrovascular accidents are candidates for HSCT. Matched sibling transplantation is available for a minority of patients and results in an overall survival rate of 90 percent and disease-free survival rate of 95 percent. Siblings who are carriers are able to serve as donors. Graft failure is a significant complication in patients who have received a large number of transfusions; these patients should be screened for the presence of alloantibodies prior to HSCT. Clinical trials of unrelated donor or mismatched family member donor transplant are underway for sickle cell patients.

Transplant for Metabolic Diseases

Metabolic disorders are a heterogeneous group of rare diseases characterized by a particular enzyme deficiency leading to a lysosomal disorder, with accumulation of substrate within the lysosome. By replacing the hematopoietic system through transplantation, the monocyte-macrophage system is restored to normal enzyme expression, leading to correction of the deficiency, with the caveat that some abnormalities caused by the metabolic disease may not be corrected. For each specific disorder, the appropriate enzyme level should be quantified, when possible, in potential donors. Hurler syndrome, due to a deficiency of α -L-iduronidase, is a commonly transplanted storage disorder.⁵⁶ Other disorders treated

with transplant include Maroteaux-Lamy and Sly syndromes. Hunter, Sanfilippo and Morquio syndromes and X-linked adrenoleukodystrophy typically do not respond to transplantation. Early diagnosis and referral to a transplant center are important because HSCT should be offered in a timely manner, so that HSCT can be performed rapidly as studies have demonstrated that outcomes with transplantation are best if HSCT is performed early and before decline in cognitive function. Enzyme replacement therapy is available for some metabolic diseases and may improve the clinical condition for patients in poor condition prior to HSCT. The role of gene-modified autologous hematopoietic stem cells is theoretical at this point.

Transplant for Osteopetrosis

Malignant infantile osteopetrosis is a rare, autosomal recessive disorder with a high mortality rate if not successfully treated. This disorder, characterized by dysfunctional osteoclasts and lack of bone remodeling, eventually results in bone marrow failure secondary to fibrosis, as well as blindness and deafness. Currently, the only potential for cure is allogeneic HSCT. While a matched sibling donor transplant with a non-TBI based myeloablative regimen is considered standard therapy, few patients have this option. Alternative donor transplants have been performed but engraftment can be difficult due to the fibrosis of the marrow and lack of space, and regimen-related toxicities are common with intense myeloablative regimens.⁵⁷ Clinicians are now pursuing reduced intensity regimens for this patient population in hopes of obtaining engraftment and decreasing regimen-related toxicities. With stable engraftment, bone remodeling, once poor, can begin and bones can achieve a normal appearance by diagnostic imaging and, over time, a normal bone mineral density.⁵⁸

Few randomized controlled trials provide level 3 evidence-based information for or against autologous stem cell transplantation. Such trials are notoriously difficult to perform because of problems in randomizing patients between treatment arms of radically different intensity. Exceptions include the Medical Research Council acute myeloid leukemia 10 trial,⁵⁹ where risk of relapse in the transplantation group was 37 percent compared with 58 percent in the nontransplantation group. More commonly, stem cell transplantation is introduced into patient management because of failure to achieve satisfactory outcomes with standard treatments. Research groups may concentrate on a particular disease to establish the feasibility and outcome of stem cell transplantation. After publication of results some approaches are gradually incorporated into standard clinical practice.

Improvements in HLA matching, treatment of graft-versus-host disease, and supportive therapy have enabled

the wider application of allogeneic transplantation to more diseases, including some nonmalignant but severely debilitating conditions such as thalassemia and inherited metabolic disorders.⁶⁰ A greater understanding of permissible mismatches should allow a better choice of unrelated donors and further improve the outcome of transplantation with unrelated donors.

Autologous stem cell transplants allow escalation of cytotoxic treatments and reduce the period of neutropenia after treatment. They were introduced for disorders where higher doses of conventional chemotherapy might be expected to eradicate the disease such as neuroblastoma,⁶¹ non-Hodgkin's lymphoma, and Hodgkin's disease in second remission. Improved survival in this last, difficult group of patients⁶² led to studies evaluating the merits of autologous transplantation for Hodgkin's disease in first remission and as a means of escalating treatment in solid tumors such as brain tumors and other stage 4 solid tumors.

Autologous stem cell transplantation can also be used to "re-educate" the immune system of patients with some autoimmune diseases, such as systemic sclerosis,⁶³ or to introduce genetically or immunologically modified bone marrow.^{64,65}

Future Developments

Improvements in harvesting techniques and growth of stem cells in the laboratory will lead to increased safety of autografts and an expanding list of indications. Purging of stem cell transplants may become routine to reduce contamination with tumor cells.

Reductions in the intensity of conditioning regimens for allografts will improve safety and increase applicability. Such transplants may be followed by higher relapse rates, but these will be offset by use of graft-versus-tumor effects by infusion of donor lymphocytes. Techniques that potentially offer a higher cure rate than standard approaches will become suitable for many older patients with hematological conditions and cancer. Improved immunosuppression protocols may allow transplantation across different HLA types.

Ongoing research programs with potential clinical applications include development of vehicles for gene therapy, tumor specific vaccines, and radionuclide conditioning agents.

Gene therapy worldwide, there have now been over 300 phase I and II trials of gene therapy for cancer and monogenic disorders.^{65,66} The potential value of such techniques is not in question, but the difficulties of achieving success in clinical settings should not be underestimated; the major barrier is the inability of the inserted gene to reliably reach a sufficient number of target cells.

Tumor specific vaccines to boost patients' immune response to their tumor are now entering clinical trials for non-Hodgkin's lymphoma.⁶⁷ More research is needed into the efficacy and optimal use of this immunotherapy.

Radionuclide labeled conditioning agents have been bound to antibodies directed against stem cell antigens in an attempt to target conditioning radiotherapy to bone marrow cells in order to give a higher dose of radiation to the marrow with fewer systemic side effects.⁶⁸

CONCLUSION

The next five to ten years will be an exciting time for hematology. Currently, we have patients who might benefit from allogeneic transplantation but who do not have a matched donor. The continued expansion of cord blood banks should alleviate this problem, especially if the banks can store donations from ethnic minorities in satisfactory numbers. The expansion of stem cell numbers from these small donations by their culture in the laboratory will, if successful, increase the numbers of allogeneic transplants being performed and potentially increase the numbers of patients being cured.

In addition, we see closer collaboration with other specialists being necessary to assess the place of autologous transplantation in the treatment of more solid tumors and currently intractable autoimmune conditions.

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Transfusion of Blood Components in Children

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When used appropriately, blood transfusion which is an essential part of modern health care can save lives and improve health. Transfusion practice for the neonatal and pediatric population requires an understanding of the physiologic changes that accompany the transition from fetus to neonate, neonate to infant, and throughout childhood. Hematologic values, blood volume, and physiologic responses to stresses such as hypovolemia and hypoxia exhibit wide variations and affect transfusion practice. The most dynamic change occurs during the perinatal period and early infancy (Table 1). Consequently, pediatric transfusion concerns are usually divided into two time periods:

- from birth through 4 months, and
- older infants (> 4 months) and children

With advances in medical care permitting survival in extremely premature babies, specific guidelines and capabilities to provide appropriate blood products for this group of patients is essential (Refer to chapter on Neonatal Blood Component Therapy for details).

This chapter discusses transfusion guidelines for pediatric patients excluding the neonatal age group.

Who should be the Donor?

- Components for transfusion *in utero* or to children under 1 year of age must be prepared from blood donated by donors who have given at least one previous donation within the past 2 years, which was negative for all mandatory microbiological markers.
- Blood donated by family/replacement donors carries a higher risk of transfusion-transmissible infections than blood donated by voluntary non-remunerated donors. Paid blood donors generally have the highest incidence and prevalence of transfusion-transmissible infections.
- Blood should not be transfused unless it has been obtained from appropriately selected donors, has been

screened for transfusion-transmissible infections and tested for compatibility between the donor's red cells and the antibodies in the patient's plasma, in accordance with national requirements.

Concerns with Cytomegalovirus (CMV)

Where many adults are positive for CMV antibodies, the rate of symptomatic CMV infection in newborns is low. CMV may be transfusion-transmitted; however current transfusion practice has made this uncommon.¹ Greatest risk of CMV is in fetuses and infants <1.5 kg, immunodeficient patients and SCT recipients. Studies in this regard have revealed:

- Overall risk of symptomatic posttransfusion CMV infection may be inversely related to the seropositivity in the community.
- Risk of acquiring CMV is directly proportional to the cumulative number of different donor exposures during transfusion.
- CMV in blood is associated with leukocytes.² Risk of transmission can be reduced by using seronegative donors or products which have been processed to eliminate viable CMV containing leukocytes.² Leukocyte

Table 1: Pediatric blood volumes⁸

Age	Total blood volume
Premature infants	100 ml/kg
Term newborns	85–90 ml/kg
>1 month	80 ml/kg
>1 year	70 ml/kg
Top-up transfusion	Desired Hb (g/dl)-actual Hb × weight (kg) × 3 (usually 10-20 ml/kg)
Platelet concentrates	10-20 ml/kg

reduction using highly efficient leukocyte filters appears to be effective.³ Also, deglycerolized RBCs and washed RBCs (controversial) may be useful.

- The “Guidelines of the UK Transfusion Service” state that blood transfused in the first year of life should be CMV negative.⁴ Other authorities recommend components leucodepleted to $<5 \times 10^6$ /unit as they have significant reduction in risk of CMV transmission.⁵ Some clinicians also prefer CMV negative components for hematopoietic stem cell transplant (HSCT) recipients and immunodeficient individuals. However, in an emergency transfusion of leucodepleted components is acceptable.^{4,5}

Leukocyte Depletion

All components other than granulocytes should be leukocyte depleted (not more than 5×10^6 leukocytes per unit) at the time of manufacture.

Irradiation

It is essential for blood components (especially all red cell and platelet components) to be irradiated prior to transfusion in the following cases:

- Intrauterine transfusion (IUT)
- Exchange transfusion of red cells after IUT
- Top-up transfusion after IUT
- When the donation is from a first or second degree relative or HLA selected donor
- When the child has proven or suspected immunodeficiency.

Irradiation is to prevent proliferation of T-lymphocytes, the immediate cause of GVHD. The standard dose of gamma irradiation is 2500 cGy to the central portion of the container with a minimum dose of 1500 cGy delivered to any part of the component.⁵

Side Effects

- Erythrocyte membrane damage and increased supernatant K^+ .
- The expiration date of irradiated red cells is changed to 28 days after irradiation if remaining shelf life exceeds 28 days.⁵

There is no need to irradiate FFP, cryoprecipitate or fractionated plasma products. All granulocytes should be irradiated for patients of any age and transfused as soon as possible after irradiation. The choice of blood group to be transfused is given in Table 2.

WHOLE BLOOD

Description and Storage

A unit of whole blood is collected in CPDA-1, has a volume of approximately 410 ml (350 ml WB plus 63 ml CPDA-1) and a hematocrit of 0.30-0.40, and is stored at 1-6°C and, has a

Table 2: Choice of ABO group for blood products for administration to children¹³

Patient's ABO group	ABO group of blood product to be transfused		
	Red cells	Platelets	FFP*
O			
First choice	O	O	O
Second choice	–	A or B	A or B or AB
A			
First choice	A	A	A
Second choice	O	B ^	AB
Third choice	–	O#	B#
B			
First choice	B	B ^	B
Second choice	O	A#	AB
Third choice	–	O#	A#
AB			
First choice	AB	AB ^	AB
Second choice	A or B	A# or B ^	A#
Third choice	O#	O#	B#

* Group O fresh frozen plasma (FFP) should only be given to patients of group O. Although group AB FFP can be given to people of any ABO blood group, supplies are usually limited.

Components which test negatively for ‘high titer’ anti-A and anti-B should be selected. The use of group O platelets for non-O patients should be avoided as much as possible.

^ - Platelet concentrates of group B or of group AB may not be available.

shelf-life of 35 days. Within 24 hours of collection the platelets as well as the granulocytes in the unit become dysfunctional and the levels of several plasma coagulation factors (in particular factors V and VIII) fall to suboptimal levels.^{6,7}

Indications for Transfusion

Whole blood is used in situations where a rapid, massive blood loss, has occurred. However, in most cases, the resuscitation can be achieved by the use of RBC concentrates and crystalloids or colloid solutions. Should plasma coagulation factor replacement become necessary, the levels of coagulation factors V and VIII in stored WB are rarely sufficient to correct the corresponding deficiency. Given these considerations, most centers preparing blood components provide little or no WB but rather separate WB donations into the more commonly required blood components. WB <5-7 days old may be used for exchange transfusion in newborn infants.

RED BLOOD CELLS

Description and Storage

RBC concentrates are prepared from WB donations. These concentrates can be further modified for use of

specific clinical settings. Characteristics of the various RBC, preparations, including their contents and storage conditions, are summarized in Table 3.

Indications for Transfusion

Oxygen delivery is dependent on:

- *Cardiac output*: In turn dependent on heart rate and stroke volume

- Arterial oxygen content

Thus, tissue hypoxia occurs if there is:

- Decreased Hb
- Cardiac insufficiency.

With a fall in hemoglobin there is an increase in cardiac output with increase of stroke volume in children but an increase of heart rate (primarily) in neonates. The tissue oxygen extraction ratio (ER) also increases from 25 percent basal but in heart and brain the ER is 55-70 percent under basal conditions.

Right-ward shift of Hb oxygen dissociation curve is noted due to increased levels of 2, 3 DPG. In fact children have normally increased levels of 2, 3 DPG and thus lower hemoglobin.⁹

The decision to transfuse should not be based on the hemoglobin level alone, but also on a careful assessment of the child's clinical condition. Both laboratory and clinical assessment are essential. A child with moderate anemia and pneumonia may have more need of increased oxygen carrying capacity than one with a lower hemoglobin level who is clinically stable.

Despite the large numbers of RBC transfusions administered to children, there is a remarkable paucity of scientific data on which to base RBC transfusion decisions. Recommendations for RBC transfusions in children are, therefore, for the most part based on expert opinion and experience and not on scientific studies.

Guidelines for Administration of Red Cells (Table 4)

Indications for RBC transfusion < 4 months of age¹²:

- Asymptomatic with Hb < 7 g/dl with low reticulocyte, or symptomatic anemia with Hb < 10 g/dl
 - On < 35 percent hood O₂/nasal cannula
 - CPAP/IMV with MAP < 6 cm water
 - Apnea/bradycardia, tachypnoea/tachycardia
 - Poor weight gain
- Hb < 12 g/dl
 - On > 35 percent hood
 - CPAP/IMV with MAP > 6 to 8
- Hb < 15 g/dl
 - Cyanotic CHD
 - ECMO

Indications for RBC transfusion > 4 months of age:¹²

- Blood loss
 - > 15 percent total body volume/with hypovolemia
- Hb < 8 g/dl
 - Symptomatic perioperative anemia
 - Chemotherapy/radiotherapy or according to protocol
 - Chronic congenital/acquired anemia
 - Emergency surgery with anticipated blood loss
 - Uncorrectable preoperative anemia
 - Severe infection
- Chronic transfusion dependent states
 - Thalassemia and other hemoglobinopathies
 - Bone marrow failure states
- Patient in overt or impending congestive cardiac failure due to anemia

RBC Transfusions in Specific Situations

Acute Blood Loss

Even with acute hemorrhage, correcting the hypovolemia (with crystalloids and/or colloids) and attempting to

Table 3: Red blood cell components

Component	RBC recovery (%)	Storage	Indication for modified components
RBCs in CPDA-1	> 99	35 days at 1-60°C	
RBC in AS	> 99	35-42 days at 1-60°C	> 80
RBCs, buffy COAT poor	90	35 days	History of repeated febrile and/or allergic reactions
RBCs, washed	80	24 h at 1-6°C	History of repeated febrile and/or allergic reactions unresponsive to buffy-coat poor or leukodepleted RBCs. Prevention of severe allergic reactions or anaphylaxis due to anti-IgA
RBCs, frozen deglycerolized	80	May be stored frozen for up to 10 years (depending on the glycerol concentration). After thawing: storage at 1-60°C for 24 h	Prolonged storage of autologous units or allogeneic units with rare RBC phenotypes
RBCs, leukocyte reduced by filtration	> 90	Pre-storage as for CPDA-1 or AS RBCs Post storage: for immediate infusion	History of repeated febrile and/or allergic reactions prevention of HLA alloimmunization and/or CMV transmission

Table 4: Indications of red cell and platelet transfusion in newborns^{10,11}**Transfusion of red blood cells**

Anemia in the first 24 h	Hb 12 g/dl (HCT 0.36)
Cumulative blood loss in 1 week, neonate requiring intensive care	10% blood volume
Neonate receiving intensive care	Hb 12 g/dl
Acute blood loss	10%
Chronic oxygen dependency	Hb 11 g/dl
Late anemia, stable patient	Hb 7 g/dl
Administration of platelets	
Preterm or term neonate, with bleeding	$50 \times 10^9/l$
Sick preterm or term infant, not bleeding	$30 \times 10^9/l$
Stable preterm or term infant, not bleeding	$20 \times 10^9/l$

stop the bleeding remains the first priority. In patients with hematologic problems, the latter will often include the need to correct thrombocytopenia and/or deficiencies of coagulation factors, treatment to decrease bleeding from damaged mucosal barriers (e.g. with histamine blockers or antifibrinolytics) and/or reversal of the effects of anticoagulant therapy. In patients with normal or near-normal Hb levels prior to the onset of hemorrhage, RBC transfusions may be necessary only if the patient remains unstable following volume resuscitation. However, careful ongoing evaluation of children with acute blood loss for subtle signs of shock is essential. If acute hemorrhage totals >15 percent of blood volume, signs of circulatory failure (tachycardia, decrease of intensity of peripheral pulses, delayed capillary refill and cool extremities) will be observed. However, hypotension will not be present until 25-30 percent or more of the child's blood volume is lost.^{14,15} Another important point is to realize that Hb values may not be accurate indicators of the actual RBC mass in cases of rapid hemorrhage with hypovolemia.

The classification of hemorrhagic shock in children based on systemic signs is shown in Table 5 and guidelines for resuscitation are summarized in Flow chart 1.^{16,17}

Acute Hemolysis

Patients with acute hemolysis are usually normovolemic unlike those suffering an acute hemorrhage which causes both hypovolemia and a decreased RBC mass. The Hb concentration therefore more accurately reflects RBC mass. The decision to administer an RBC transfusion depends upon a combination of factors, including ongoing clinical evaluation, presence or absence of underlying cardiovascular disease, actual Hb concentration, and rate of decrease in Hb.

Chronic Anemia

Factors to be considered should include:

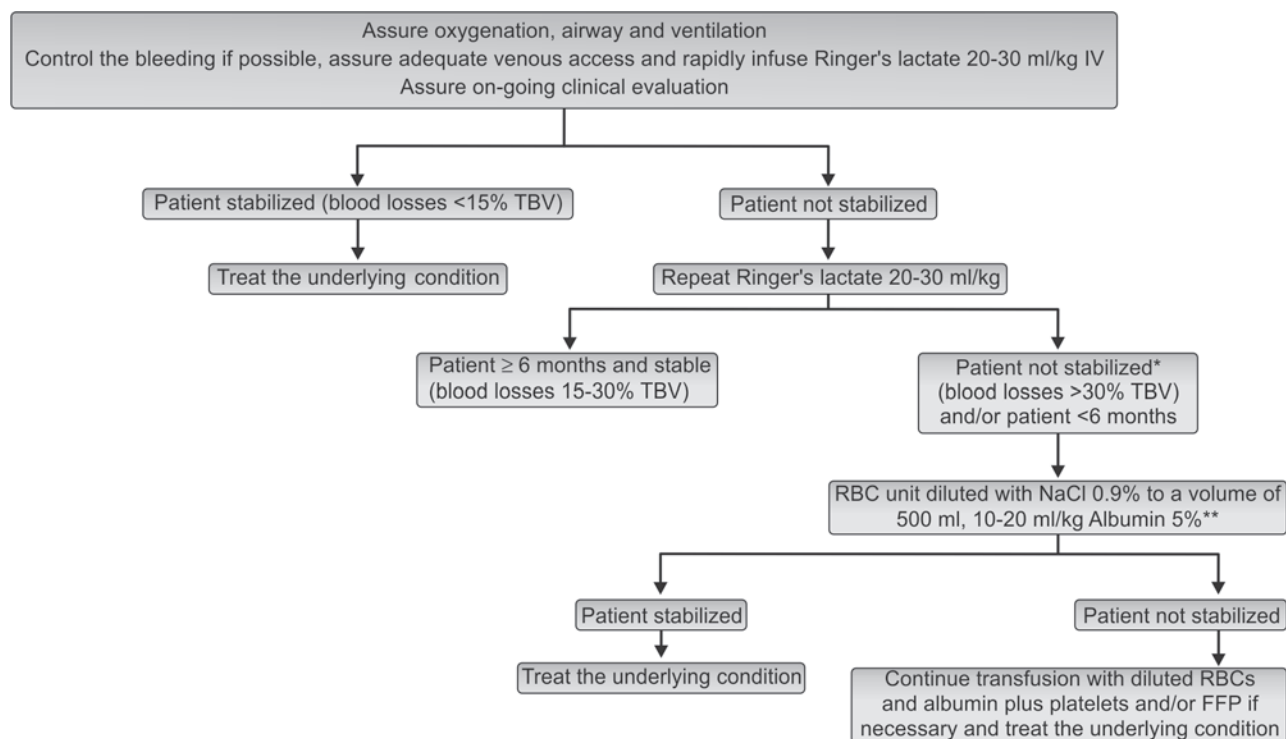
- Presence or absence of symptom and/or abnormal physical signs and the likelihood that these are due to anemia
- Presence or absence of underlying diseases, particularly cardiac diseases which may decrease the patient's capacity for cardiovascular compensation
- Likely evolution of the underlying disease causing the anemia
- Likely evolution of the anemia and its consequences with or without transfusion in both the short- and long term
- Possibility of using alternate, safer therapies for the treatment of the anemia.

Sickle Cell Disease (SCD)

Approximately 6 to 10 percent of children with SCD suffer a stroke; two-third of these children experience recurrent stroke in the absence of transfusion therapy. The goal of transfusion is to reduce the percentage of circulating red cells capable of sickling, without altering blood viscosity. The rate of recurrent stroke has been reduced to <10 percent by maintaining a pre-transfusion hemoglobin level of 8-9 g/dl with HbS level <30 percent, in children who have had a cerebrovascular accident. This can usually be achieved with a simple or partial exchange transfusion every 3 to 4 weeks. There are no definite criteria for when it is safe to discontinue transfusion therapy; therefore, it is often continued indefinitely.¹⁸ Because of concerns about iron overload, some workers follow several uneventful years of transfusions to keep hemoglobin S below 30 percent with a less aggressive protocol that maintains hemoglobin S between 40 and 50 percent.¹⁹ Red cell transfusions are used to treat acute complications associated with the sickle

Table 5: Classification of hemorrhagic shock in pediatric patients based on systemic signs

System	Class I Very mild hemorrhage (<15 TBV loss)	Class II Mild hemorrhage (15-25% TBV loss)	Class III Moderate hemorrhage (26-39% TBV loss)	Class IV Severe hemorrhage ($>40\%$ TBV loss)
Cardiovascular	Heart rate normal or mildly increased Normal pulses Normal blood pressure Normal pH	Tachycardia Peripheral pulses may be diminished Normal blood pressure Normal pH	Significant tachycardia Thready peripheral pulses Hypotension Metabolic acidosis	Severe tachycardia Thready peripheral pulses Significant hypotension Significant acidosis
Respiratory	Rate normal	Tachypnea	Moderate tachypnea	Severe tachypnea
Central nervous system	Slightly anxious	Irritable, confused combative	Irritable or lethargic diminished pain response	Coma
Skin	Warm, pink Capillary refill brisk	Cool extremities, mottling Delayed capillary refill	Cool extremities, mottling or pallor Prolonged capillary refill	Cold extremities, pallor or cyanosis
Kidneys	Normal urine output	Oliguria, increased specific gravity	Oliguria, increased BUN	Anuria

Flow chart 1: Approach to the treatment of hemorrhagic shock in infants and children. TBV = total blood volume; RBC = red blood cells; FFP = fresh frozen plasma

* Patient with significant degrees of anemia prior to acute blood loss will require RBC transfusion support following smaller hemorrhagic losses.

** The use of albumin for fluid resuscitation is controversial.

cell diseases, such as splenic sequestration, aplastic crisis, overwhelming pneumonia or pulmonary infarction. An area that remains unresolved is the necessity of preoperative transfusion and the optimal levels of total hemoglobin and hemoglobin S that should be achieved in preparation for inhalation anesthesia.

- Simple (top-up) transfusion;
 - Splenic or hepatic sequestration
 - Aplastic crisis

The aim is to raise the Hb to the child's normal steady state (never to be raised acutely to >10 g/dl, as this can increase blood viscosity).

- ET in SCD:^{20,21}

- Acute chest syndrome
- Stroke, priapism

In such acute situations in SCD, reducing the HbS percentage in blood to <20 percent requires a total exchange of 1.5 to 2 times the blood volume. ET may also be used to minimize iron overload in patients on regular transfusions.^{19,22}

- Hypertransfusion in SCD:

- Patients on regular transfusion to prevent recurrence of stroke.²³ The rate of recurrent stroke has been reduced to 0-10 percent from ~65 percent by maintaining a pre-transfusion Hb of 8-9 g/dl with an HbS of <30 percent. Due to the risk of iron overload, it may be desirable to follow several years of uneventful transfusion with a less aggressive protocol to maintain HbS between 40 and 50 percent.
- Probably useful to delay or prevent deterioration in end organ failure (e.g. chronic lung disease)
- To prevent the development of stroke in SCD with Doppler and/or MRI evidence of cerebrovascular infarction/hemorrhage in the absence of clinical evidence of stroke.

Normal saline (not FFP or albumin) should be used as volume replacement at the beginning of the exchange prior to starting venesection to avoid dropping the circulating blood volume. ET may also be used to minimize iron overload in patients on regular transfusions.²⁴

Thalassemia

Transfusions are given to children with severe anemia due to thalassemia, notably to improve tissue oxygenation but to suppress erythropoiesis, because the characteristically brisk, ineffective erythropoiesis causes many of the complications associated with thalassemia. The hypertransfusion regimen, in which endogenous erythroid production is suppressed by maintaining a minimum pre-transfusion hemoglobin level of 9-10 g/dl, remains the commonest approach today.²⁵ Super-transfusion programs aim to maintain a pre-transfusion hemoglobin concentration between 11 and 12 g/dl, with the intention of decreasing iron absorption from the gastrointestinal tract. The results of maintaining near normal hemoglobin levels are still controversial. Iron overload is a complication in these patients, requiring institution of regular chelation therapy in early childhood.²⁶ The frequency of red cell alloimmunization in chronically transfused children varies with the disease, the number of transfusions given, and the ethnic background of donors and recipients.^{27,28} Antibodies to the common antigens of the Rh, Kell, Duffy, and Kidd systems are often involved. It may be desirable, therefore, to phenotype the patient's red cell antigens as completely as possible before beginning transfusion therapy, and maintain a permanent record of the results. This can be helpful in selecting compatible blood if alloimmunization occurs.

The practice of transfusing only phenotypically matched units is controversial. In patients who have already become immunized and are at high risk of developing additional antibodies, use of phenotypically matched units maybe a reasonable approach. Leukocyte reduced blood components should be considered for these chronically transfused patients, to diminish development of alloimmunization to HLA antigens and prevent febrile transfusion reactions.²⁹

These children are not just frequently transfused, but are possible future candidates for hemopoietic stem cell transplantation (SCT). Although some clinicians consider blood products that have been depleted to $<5 \times 10^6$ leukocytes/unit to be CMV-safe others consider that more data are needed to demonstrate whether leukodepleted or CMV seronegative components are the best option for minimizing transfusion-transmitted CMV after SCT.

All children on regular transfusions should be vaccinated against hepatitis B as early as possible.

Volume of Blood for Top-up (Standard) Transfusion

A commonly used formula for determining the volume of packed red cells for top-up (standard) transfusion in infants and children is:

$$\text{Volume of blood (ml)} = \frac{\text{Desired Hb (g/dl)} - \text{Actual Hb}}{\text{Weight (kg)}} \times 3$$

The recommended rate of transfusion of red cell products is c. 5 ml/kg/h.

Aim: Current guidelines^{30,31} and the new Thalassemia International Federation guidelines³² recommend:

- Maintaining an average Hb of 12 g/dl
- Maintaining a pretransfusion Hb of 9 to 10 g/dl
- That transfusion should prevent marrow hyperplasia, skeletal changes and organomegaly
- Red cell requirements should be adjusted to accommodate growth and hypersplenism considered if red cell requirements increase unexpectedly
- Iron chelation therapy should be considered after 10 transfusions and started once the ferritin is more than 1000 µg/l (if possible starting after 2 years of age).³²

Red Cell Specification for Transfusion in Thalassemia and SCD

Those on chronic transfusion therapy, particularly those with hemoglobinopathies, but also those with congenital dyserythropoietic anemia, aplastic anemia and other bone marrow failure syndromes, should have an extended red cell phenotype (Rh, K in thalassemia; Rh K, Fy, Jk and MNS in SCD) performed prior to, or as soon as possible after, commencing regular transfusions. This is to facilitate selection of appropriate products should it become necessary, and to minimize alloimmunization. Reviews of

the literature addressing allogeneic red cell and plasma transfusions in children have been published recently^{33, 34}

Red Cell Preparations for Thalassemia and SCD Should

- Be ABO compatible
- Be Rh and K antibody compatible
- Be 35 days old or less (if collected into SAG-M or similar additive system
- Be 28 days old or less (if collected into CPD); there is no overall advantage in using ‘neocytes’ for top-up transfusion^{28,35}
- Be tested for HbS prior to transfusion, as sickle-trait positive red cells should not be transfused;
- Be CMV negative if appropriate.

PLASMA

A typical unit of plasma obtained from a WB donation has a volume of 160-250 ml or 400-600 ml when obtained by plasmapheresis. Immediately following collection from a normal donor, plasma contains approximately 1 unit/ml of each of coagulation factors as well as normal concentrations of other plasma proteins. Coagulation factor V and VIII, known as the labile coagulation factors, are not stable in plasma stored at 1-6°C. Other contents of plasma are given in Table 6. Plasma frozen within 8 hours of donation contains at least 0.70 units/ml of factor VIII and is referred to as fresh frozen plasma (FFP). In plasma frozen 8-72 hours after collection, referred to as frozen plasma the concentration of coagulation factor V and VIII may be reduced by as much as 15 percent.² FFP may be stored for 12 months at -18°C or colder. Storage at minus 30°C or colder is recommended for optimal maintenance of factor VIII levels.

Indications for FFP Transfusions in Children

These are most often generalized from observations in adult patients and/or based on expert opinion. There is

Table 6: Contents of FFP (one unit of FFP = 300 ml)	
Na	165 (48 mmol/unit)
K	3.3 (1.0 mmol/unit)
Glucose	20
Calcium	1.8 (low)
Citrate	20
Lactate	3
pH	7.2–7.4
Phosphate	3.63 (high)

[These values were determined in the Pathology Laboratories of Southampton University Hospitals Trust. The high sodium, glucose, citrate and phosphate levels derive from the anticoagulant preservative mixture, which also lowers the ionized calcium]

broad, general consensus that the appropriate use is limited almost exclusively to the treatment or prevention of clinically significant bleeding due to a deficiency of one or more plasma coagulation factors.³⁶⁻³⁹ Such situations potentially include the presence of:

- A diminution of coagulation factors due to treatment with vitamin K antagonists
- Severe liver disease
- Disseminated intravascular coagulation (DIC)
- Massive transfusion
- Isolated congenital coagulation factor deficiencies for which a safer and/or more appropriate product does not exist.

Situations where FFP Use is not Indicated

- Intravascular volume expansion or repletion (where crystalloids, synthetic colloids or purified human albumin solutions are preferred)
- Correction or prevention of protein malnutrition (where synthetic amino acid solutions are preferred)
- Correction of hypo-gammaglobulinemia (where purified human immunoglobulin concentrates are preferred)
- Treatment of any other isolated congenital pro-coagulant or anticoagulant factor deficiency for which a virus-inactivated plasma-derived or recombinant factor concentrate exists
- As replacement fluid in therapeutic apheresis procedures for disorders other than thrombotic thrombocytopenic purpura/adult HUS unless proven to be beneficial.

Dosage and Administration

Compatibility tests before plasma transfusion are not necessary. Plasma should be ABO compatible with the recipient’s RBC’s (Table 7). Usually, Rh group need not be considered. However, when large volumes of FFP are given to RhD-negative pediatric patients or women of child-bearing age, prevention of RhD immunization by the use of Rh immune globulin should be considered. The dose should be 50 IU anti-D per unit of FFP (200-300 ml) or per 500 ml of platelets transfused, or 250 IU per adult therapeutic dose of platelets.

FFP may be thawed in a water bath at 30-37°C. The dose of FFP depends on the clinical situation and the underlying disease process. When FFP is given for coagulation factor replacement, the dose is 10-20 ml/kg. This dose will usually raise the level of coagulation factors by 20 percent immediately after infusion. Post-transfusion monitoring of the patient’s coagulation status (PT, APTT and/or specific coagulation factor assays) is important for optimal treatment.

All components should be transfused through a standard blood giving set with a screen filter (170-200 µ) or an alternative system incorporating the same filtration.

Table 7: Selection of fresh frozen plasma according to donor and recipient blood group (ABO)

<i>Recipient group</i>	<i>O</i>	<i>A</i>	<i>B</i>	<i>AB</i>
A. High titer (HT) positive or HT untested units				
1st choice	O	A	B	AB
2nd choice	A	AB	AB	A
3rd choice	B	B	A	B
4th choice †	AB			
B. HT negative units‡				
1st choice	O	A	B	AB
2nd choice	A	B	A	A
3rd choice	B	AB	AB	B
4th choice †	AB			

* Group O must only be given to group O recipients.

† Only suitable for emergency use in adults.

‡ Group O must only be given to group O recipients

Table 8: Suggested guidelines for platelet transfusion support of neonates

Prophylactic platelet transfusion

Stable preterm neonates with platelet counts $<30 \times 10^9/L$

Stable term neonates with platelet counts $20 \times 10^9/L$

Sick preterm neonates with platelet counts $<50 \times 10^9/L$

Sick term infants with platelet counts $<30 \times 10^9/L$

Preparation for an invasive procedure, e.g. lumbar puncture or minor surgery in neonates with platelet counts $<50 \times 10^9/L$ and for major surgery in neonates with platelet counts $<100 \times 10^9/L$

Platelet transfusions in neonates with clinically significant bleeding

Neonates with platelet counts $50 \times 10^9/L$

Neonates with conditions that increase bleeding (e.g. DIC) and platelet counts $<100 \times 10^9/L$

Neonates with documented significant platelet functional disorders (e.g. Glanzmann thrombasthenia) irrespective of the circulating platelet count

Where small volumes are drawn into a syringe an appropriate filter must be used. Microaggregate filters (40 μ) are not required for LD components.

PLATELETS

A platelet concentrate (PC) may be prepared from random WB donation or by apheresis procedures. Platelets collected by apheresis procedure, in which a single donor donates the equivalent of 4-8 PCs, are referred to as apheresis PCs. PCs contain a minimum of 5.5×10^{10} platelets/unit, approximately 50 ml of plasma, trace to 0.5 ml of RBC's and, depending upon the preparation techniques, varying number of leukocytes (predominantly monocytes and lymphocytes) up to levels of 10^8 /unit. Apheresis PCs contain a minimum of 3×10^{11} platelets, approximately 250-300 ml plasma, trace to 5 ml of RBCs and, depending on the apheresis technique or instrument,

10^6 - 10^9 leukocytes. Both PCs and apheresis PCs are stored for up to 5 days at 20-24°C with continuous gentle agitation. Indications for transfusion of platelets in newborns are given in Tables 4 and 8.

Indications for Transfusion

- Decreased platelet production
 - Congenital or acquired aplastic anemia.
 - Bone marrow infiltration with leukemic or other malignant cells
 - Myeloablative chemotherapy

Indications of Using Platelets in a >4 month old Child with Thrombocytopenia¹²

- Prophylactic platelets (without bleeding)
 - <5 - $10,000/cu.mm$ in a non-sick child
 - $<20,000/cu.mm$ in a sick child with:

- a. Severe mucositis
- b. DIC
- c. Platelet likely to fall $<10,000/\text{cu.mm}$ before next evaluation
- d. Associated coagulopathy/anticoagulation
- Before surgery
 - a. Bone marrow aspiration/biopsy can be without platelet support
 - b. Lumbar puncture $<30,000/\text{cu.mm}$
 - c. Other surgeries $<50,000/\text{cu.mm}$
 - d. Surgery at critical sites like CNS, eyes $<100,000/\text{cu.mm}$
- $<50,000/\text{cu.mm}$ with acute bleeding, massive hemorrhage, head trauma, multiple trauma
- Chronic stable thrombocytopenia only in presence of significant mucosal bleeding
- Platelet dysfunction only in presence of significant mucosal bleeding
- Chronic stable DIC only in presence of significant mucosal bleeding

A conference addressing platelet transfusion therapy by the National Institutes of Health (1986) concluded that patients with severe thrombocytopenia may benefit from prophylactic transfusions but the threshold value of $20 \times 10^9/\text{L}$ may sometimes be safely lowered.⁴⁰ Another review recommended that only patients with platelet counts $<5 \times 10^9/\text{L}$ should routinely be given prophylactic platelet transfusions, and for those with platelet counts $>5 \times 10^9/\text{L}$ clinical judgment should be used to assess the need for platelet therapy.⁴¹ Prophylactic transfusions at higher platelet counts being reserved for patients in whom additional risk factors exist.⁴²

Two groups of leukemia patients at particularly high risk of fatal hemorrhage during induction chemotherapy, in whom these stringent prophylactic policies may not be applicable, are those with hyperleukocytosis and/or acute promyelocytic leukemia (ANLL, FAB M3). An additional consideration apart from similar risk factors for hemorrhage in patients with solid tumors is the predisposition to hemorrhage associated with local tumor invasion.^{43,44}

In summary, just as the indication for a RBC transfusion should not be determined solely on the basis of an Hb level, the decision to administer a platelet transfusion

should also be individualized, taking into account the clinical situation as well as the platelet level.

Prophylactic platelet transfusions are indicated for thrombocytopenic patients undergoing invasive procedures. At least one study suggests that major surgical procedures can be safely performed at platelet counts of $50 \times 10^9/\text{L}$.⁴⁵ Bone marrow aspiration and biopsy can be safely performed (with respect to local bleeding) at any platelet level. Suggested guidelines for prophylactic platelet transfusions for pediatric patients with thrombocytopenia due to decreased platelet production are summarized in Table 9.⁴⁶

Massive Transfusion

Thrombocytopenia, frequently associated with massive transfusion may be dilutional or consumptive, depending on the underlying etiology of the bleeding. Platelet transfusion therapy should be based on a consideration of several factors including platelet count, an assessment of the role of the thrombocytopenia in the observed bleeding and the estimated hemostatic platelet count necessary for the patient's given clinical situation.

Platelet Dysfunction

Platelet dysfunction may need platelet transfusion in 2 situations: patients taking platelet inhibitory drugs and following surgery with cardiopulmonary bypass pump (CBP). Platelet dysfunction due to platelet inhibitory drugs is unlikely to contribute to bleeding if the platelet count is $>50 \times 10^9/\text{L}$. Treatment with desmopressin acetate has been shown to prevent bleeding complications in patients who have taken aspirin within 7 days of a surgical intervention.^{47,48}

Platelet dysfunction lasting 4-6 hours post-CBP has been well-documented.^{49,50} These patients are usually thrombocytopenic too. Nevertheless, studies have not shown a benefit for the use of prophylactic platelet transfusions for patients undergoing CBP.⁵¹ Platelet transfusions should be reserved for those patients, who following CBP have excessive bleeding thought to be due to platelet function abnormalities and/or thrombocytopenia.^{39,40,52}

Table 9: Suggested guidelines for prophylactic platelet transfusions in pediatric patients with thrombocytopenia due to decreased platelet production

Platelet count $<10 \times 10^9/\text{L}$

Platelet count $<20 \times 10^9/\text{L}$ and bone marrow infiltration, severe mucositis, DIC, anticoagulation therapy, a platelet count likely to fall below $10 \times 10^9/\text{L}$ prior to next possible evaluation, or risk of bleeding due to local tumor invasion

Platelet count $<30-40 \times 10^9/\text{L}$ and DIC (e.g. during induction therapy for promyelocytic leukemia), extreme hyperleukocytosis, or prior to lumbar puncture or central venous line insertion

Platelet count $<50-60 \times 10^9/\text{L}$ and major surgical intervention

DIC = disseminated intravascular coagulation

Dosage and Administration

Platelets should preferably be ABO and RhD identical with the recipient. If these are not available, units with plasma compatible with the recipient's RBC's should be chosen. If even this cannot be ensured, then compatible components lacking high titer anti-A or anti-B should be transfused to group A or B recipients. ABO-incompatible platelets (i.e. platelets with A and/or B antigens given to a donor with a corresponding antibody) are usually clinically effective. However, in some patients particularly those receiving multiple platelet transfusions, there may be a poor post-transfusion response than that obtained with ABO-compatible platelets, and some studies have suggested that the transfusion of ABO-incompatible platelets is associated with the development of platelet refractoriness.^{53,54} Also, there are reports of acute intravascular hemolysis following the transfusion of platelet concentrates containing ABO antibodies incompatible with the recipient's RBCs.^{55,56} Therefore, the preference to use ABO-matched platelets. Testing of PCs for RBC compatibility is not necessary unless red cells are detected by visual inspection.

Platelets do not carry Rh antigens.⁵⁷ However, the quantity of RBC's in platelet concentrates is sufficient to induce Rh sensitization even in immunosuppressed cancer patients.^{58,59} Rh sensitization caused by platelet transfusions in Rh-negative patients can be prevented by the administration of Rh immunoprophylaxis.^{60,61} A dose of 25 mcg (125 IU) of anti-D immunoglobulin will protect against 1 ml of RBC's.⁶²

Infants rarely produce atypical red cell antibodies other than following repeated large volume transfusion and (possibly) the use of blood from donations collected up to 5 days before transfusion.

Administration

All components should be transfused through a standard blood giving set with a screen filter (170-200 μ) or an alternative system incorporating the same filtration. Where small volumes are drawn into a syringe an appropriate filter must be used. Microaggregate filters (40 μ) are not required for LD components.

1 PC/10 kg body weight can be expected to raise the platelet level by $50 \times 10^9/L$ and may be a suitable starting dose. PCs may be pooled before administration or infused individually. An equivalent dose for apheresis platelets is approximately 5 ml/kg. Larger volumes of PCs may be required in patients with increased platelet consumption (e.g. with septicemia or DIC) or splenomegaly.

Volume reduction of the components may be done prior to infusion. However, this extra manipulation leads to platelet loss and if not carefully performed might potentially adversely affect platelet function and/or be a cause of bacterial contamination. Volume reduction should therefore be limited to patients who require severe

volume restriction or situations where ABO-incompatible platelets are the only available PC's for a neonate or child.

Calculation of corrected count increment (CCI), measure of patient response to platelet transfusion that adjusts for the number of platelets infused and the size of the recipient, based upon body surface area (BSA)¹³ is done as follows

$$CCI = (\text{post-count} - \text{pre-count}) \times \text{BSA} / \text{platelets transfused}$$

where post-count and pre-count are platelet counts (μ/L) after and before transfusion, respectively; BSA is the patient body surface area (m^2); and platelets transfused is the number of administered platelets ($\times 10^{11}$). The CCI is usually determined 10 to 60 minutes after transfusion. In the clinically stable patient, the CCI is typically greater than 7500 at 10 minutes to 1 hour after transfusion and remains above 4500 at 24 hours. Both immune and non-immune mechanisms may contribute to reduced platelet recovery and survival. Along with supportive serologic test results, a CCI of less than 5000 at 10 minutes to 1 hour after transfusion may indicate an immune-mediated refractory state to platelet therapy. With non-immune mechanisms, platelet recovery within 1 hour may be adequate, although survival at 24 hours is reduced.

GRANULOCYTE CONCENTRATES

Granulocytes concentrates for transfusion should contain a minimum of 10^{10} polymorphonuclear cells (PMNs)/unit to ensure efficacy. Recently, leukapheresis collections of $>4 \times 10^{10}$ PMNs/unit following donor stimulation with G-CSF have been attempted.^{63,64} However, ethical and viability issues remain. Preparation of granulocytes by pooling buffy coat layers separated from 4 to 8 units of fresh whole blood is another method being tested.

Granulocytes should be transfused as soon as possible following collection and should not be given if stored for >24 hours as function deteriorates rapidly with storage. For the time between collection and infusion, granulocytes concentrates should kept at 20-24°C, with little or no agitation.⁶⁵

Indications for Transfusion

Current indications are for patients with profound neutropenia not expected to recover within a week, or severe forms of congenital neutrophil dysfunction, in whom a severe bacterial infection has been documented and who are clinically deteriorating despite optimal antimicrobial therapy.^{66,67}

Dosage and Administration

Granulocyte transfusions are administered daily until there is evidence of recovery of peripheral neutrophils counts or clinical evidence of recovery from the infection. A daily infusion of 1×10^9 PMNs/kg should be given for neonates and small children, and for larger patients,

$2-3 \times 10^{10}$ PMNs. As there is significant RBC contamination, units must be ABO compatible and if possible RhD negative for RhD-negative recipients. Usual compatibility testing must be done. Allo-immunization frequently occurs in patients receiving granulocyte transfusions and may render the transfusions ineffective and/or be associated with adverse reactions including respiratory distress.⁶⁸ For patients, with HLA- and/or granulocyte-specific alloantibodies, only granulocytes from HLA- and/or neutrophil antigen-compatible donors should be used.

The granulocyte transfusion should be separated from Amphotericin B infusion by 10-12 hours and administered over 2-3 hours without using leukocyte reduction filters. Because most patients receiving these products are severely immunosuppressed, apheresis granulocytes are usually irradiated to prevent TA-GVHD.

CRYOPRECIPITATE

Cryoprecipitate is formed when FFP is thawed at 4°C. The precipitate thus obtained is then refrozen within 1 hour in 10-15 ml of the donor plasma and stored at -18°C or less for up to 1 year. It contains 80-100 units of factor VIII, 100-250 mg of fibrinogen, 40-60 mg of fibronectin and 40-70 percent of the Von Willebrand factor and 30 percent of the factor XIII present in the original unit of plasma.

Indications for Transfusion

- Hemophilia A
- Von Willebrand disease
- Congenital deficiencies of fibrinogen
- Factor XIII deficiency.

Dosage and Administration

Cryoprecipitate contains anti-A and -B so the use of ABO-compatible units is preferable. Rh group need not be considered and compatibility testing is unnecessary. The number of units of cryoprecipitate required is usually based on the amount necessary to obtain a hemostatic level of fibrinogen, i.e. a fibrinogen level $>0.8-1.0$ g/l. If the units are carefully pooled this can usually be accomplished by the transfusion of 1 unit/5-10 kg recipient weight.

Cryoprecipitate is prepared for transfusion by thawing at 30-37°C and mixing the thawed precipitate with 10-15 ml of sodium chloride 0.9 percent if necessary, according to the amount of plasma in the cryoprecipitate unit. The required number of units is then pooled.

Thawed cryoprecipitate should be stored at room temperature and transfused immediately after thawing or within 6 hours after thawing if used as a source of factor VIII. All pooled cryoprecipitate units must be used within 4 hours of pooling.

ALBUMIN

Albumin is derived from pools of donor plasma obtained either from whole blood or from plasmapheresis. It is prepared by the cold alcohol fractionation process (Cohn fractionation) followed by heat treatment at 60°C for 10 hours. Its composition is 96 percent albumin and 4 percent other plasma proteins. Albumin is available as a 25 percent solution in distilled water or as a 5 percent solution in saline. Plasma protein fraction (PPF) is a similar product except that it is subject to fewer purification steps in the fractionation process. PPF is a 5 percent protein solution composed of approximately 85 percent albumin and 15 percent other plasma proteins. All 3 preparations have a physiologic pH and a sodium content of about 145 mmol/L (145 mEq/L). The 5 percent solutions are osmotically and oncologically equivalent to plasma, while the 25 percent solution is osmotically and oncologically 5-fold greater than plasma. These products can be stored for up to 5 years at 2-10°C.

Indications for Transfusion

The indications for the use of albumin (or PPF) are controversial and many transfusion medicine specialists believe this product is overused.^{69,70} In particular, controversy remains concerning these of albumin versus crystalloids or non-blood colloids for intravascular volume expansion.⁶⁹ The 25 percent solution should not be used in dehydrated patients unless it is supplemented by the infusion of crystalloid solutions.

Dosage and Administration

Albumin and PPF do not need to be administered through a filter. Dosage and rate of infusion depend upon the patient's clinical condition. In shock the usual dosage of 5 percent albumin is 500 ml in adults and 10-20 ml/kg in children.

Transfusion Guidelines for Hematopoietic stem cell transplantation (HSCT), malignancies and aplastic anemia

Children receiving chemotherapy and/or radiotherapy or those with aplastic anemia are potential candidates for SCT. While some clinicians consider components that have been depleted to $<5 \times 10^6$ leukocytes per unit to be CMV-safe not all SCT centers agree.

Uniform guidelines are not available or agreed upon for deciding the threshold for transfusion among this group of children. However, there is little doubt about the necessity of blood component therapy and support for them.

Irradiation of blood products is not routinely necessary in children receiving chemotherapy for leukemia or solid tumors.

Indications for Transfusion

Red Cells

There are no controlled trials upon which to base decisions about red cell transfusions in this group of children. The

decision therefore depends on clinical judgment, taking into account the child's general condition, the presence or absence of bleeding and whether or not there are signs of hematological recovery. For children with aplasia, red cell transfusions are usually reserved for symptomatic patients with Hb values <7 g/dl, as sensitization to large numbers of transfusions reduces the chance of a successful outcome.

Platelets

Children with aplastic anemia during and following treatment with ATG/ALG, in particular, may require intensive platelet support. In contrast, some pediatricians are prepared to conduct follow-up lumbar punctures on children with counts as low as $20 \times 10^9/L$, having not experienced unduly high adverse effects. [Note: this recommendation differs from that in the recent Guidelines for the transfusion of platelets¹¹ (*British Committee for Standards in Haematology*, 2003b), where the recommended threshold value is $50 \times 10^9/L$].

Granulocytes

There is no evidence to support the use of prophylactic granulocyte transfusions. Empirical data from some but not all studies support their use in the setting of severe bacterial or fungal infection in neutropenic and, after SCT, to reduce the incidence of infection. However, they increase the risk of platelet refractoriness, and few SCT centers use them.

Therapeutic granulocyte transfusions may have a role in patients with congenital neutrophil dysfunction or severe neutropenia who are suffering from severe bacterial infection, are clinically deteriorating and unlikely to recover in a week despite maximal supportive care, including cytokines. The efficacy of granulocytes collected from G-CSF-stimulated donors may be superior and is currently being evaluated.

Blood Handling and Administration

The serious hazards of transfusion reporting scheme has shown that children as well as adults may be affected by transfusion errors, may suffer from immunological transfusion reactions and may develop transfusion-transmitted infections. There are a number of circumstances that may place infants and children at particular risk. Confusion of maternal and baby (or placental) samples at time of birth, perhaps because of pre-labeling of sample tubes or failure to label a sample from the mother before drawing the placental sample.

Newborn multiple births: Mistakes may occur due to transposition of samples, for example, due to placental sampling with allocation of the wrong placenta to a particular baby or due to confusion arising between laboratory and neonatal unit when the infants are finally named.

Failure to communicate special transfusion needs during shared care can sometimes lead to unfortunate consequences. Failure to apply wristbands, particularly in children who are too young to state their identity and date of birth is another source of errors.

Patients requiring transfusion with only irradiated blood products is another special group where additional verification of transfusion units and provision for a special card identifying their specific transfusion needs may be useful.

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Hemolytic Anemia

Sunil Gomber

Hemolytic anemias result when rate of destruction exceeds the capacity of the marrow to produce red blood cells. There is a reduction of normal red cell survival of 120 days. Premature destruction of red cells may result from corpuscular or extracorporeal abnormalities; immune or nonimmune mechanisms.

CLASSIFICATION OF HEMOLYTIC ANEMIA

- Corpuscular defects
 - Membrane defects
 - a. Hereditary spherocytosis
 - b. Hereditary elliptocytosis
 - c. Hereditary stomatocytosis
 - Enzyme defects
 - a. G6PD deficiency
 - b. Pyruvate kinase deficiency
 - Hemoglobin defects
 - a. Heme: Congenital erythropoietic porphyria
 - b. Globin:
 - i. Qualitative: Sickle cell disease
 - ii. Quantitative: Thalassemia.
- Extracorporeal defects
 - Immune
 - a. Isoimmune: Hemolytic disease of newborn, incompatible blood transfusion.
 - b. Idiopathic: Warm antibody, Cold antibody, cold-warm (Donath Landsteiner antibody)
 - c. Secondary:
 - i. Infections: EBV, CMV, HSV, mycoplasma pneumonia.
 - ii. Drugs: Quinine, quinidine, phenacetin.
 - iii. Hematological disorders: Leukemia, lymphoma.
 - iv. Tumors: Ovarian teratomas.
 - Nonimmune
 - a. Idiopathic
 - b. Secondary.

- c. Drugs: Vitamin K, benzene, lead.
- d. Infections: Infectious mononucleosis, malaria.
- e. Hematological disorders: Leukemia, aplastic anemia.
- f. Microangiopathic hemolytic anemia: Thrombotic thrombocytopenic purpura.
- g. Hemolytic uremic syndrome.

GENERAL CLINICAL FEATURES OF HEMOLYTIC ANEMIA

In general, the manifestations of hemolytic anemias depend upon the duration of the process as well as its severity. Thus, chronic congenital hemolytic anemia can usually be distinguished from acute acquired hemolytic anemia on clinical grounds.

MAJOR CLINICAL FEATURES OF CHRONIC CONGENITAL HEMOLYTIC ANEMIA

Anemia

Severe disease is detected shortly after birth and presents with severe pallor and cardiovascular manifestations. More commonly anemia is mild to moderate because shortened erythrocyte survival is partially offset by increased activity of the marrow.

Jaundice

Jaundice is acholuric. The bilirubin being unconjugated is not excreted in urine. In some instances jaundice is first noticed in the neonatal period. History of episodes of jaundice may be associated with trivial infections and unusual exertion.

Splenomegaly

The spleen typically is enlarged in patients with congenital hemolytic anemia except for patients with sickle cell anemia.

MAJOR CLINICAL FEATURES OF ACQUIRED HEMOLYTIC ANEMIA

If hemolytic anemia develops acutely such as after transfusions of incompatible blood or ingestion of an oxidant drug by patients with G6PD deficiency, the symptoms may suggest an acute febrile illness.

Aching pains in the back, abdomen or limbs are common as are headache, malaise, vomiting, shaking chills and fever. Profound prostration and shock may develop followed by oliguria and anoxia.

In other instances, the clinical settings may be dominated by the manifestations of an underlying disease of which the hemolytic anemia is one manifestation. For example, signs and symptoms of lymphoma, lupus erythematosus or mycoplasma pneumonia may overshadow those of the associated hemolytic process.

SALIENT FEATURES SUGGESTIVE OF HEMOLYSIS

- Anemia and jaundice in an Rh positive infant born to a mother who is Rh negative or group A/B infant born to a group O mother.
- History of progressive pallor, failure to thrive and hepatosplenomegaly in later 6 months of infancy.
- Anemia which does not respond to hematinics or blood transfusions.
- Development of anemia, jaundice or passage of high colored (cola colored) urine after exposure to certain drugs.
- Family history of anemia, jaundice and gallstones.
- Intermittent bouts of jaundice.
- Occurrence of chronic leg ulcers.
- History of colicky pain in right upper abdomen—gallstones.
- Anemia which worsens despite blood transfusions.

CLINICAL FEATURES SPECIFIC TO INDIVIDUAL DISEASES

Corpuscular Hemolytic Anemia

Hereditary Spherocytosis

Anemia, jaundice and splenomegaly are the clinical features most commonly encountered.

Presents in newborns (50% of cases) with hyperbilirubinemia which may require exchange transfusion. Cholelithiasis is common in hereditary spherocytosis. The history of family members with cholelithiasis in 2nd or 3rd decade is a clue to the possibility of HS. Hemolytic crises may be precipitated by infection. Erythroblastic crises is caused by maturation arrest and megaloblastic change in recovery phase usually associated with parvovirus B19 infection.

HEREDITARY ACANTHOCYTOSIS

Steatorrhea

Neurological symptoms—weakness, ataxia, nystagmus, atypical retinitis pigmentosa, macular atrophy and blindness.

G6PD DEFICIENCY

Deficiency of G6PD is the most common metabolic disorder of red cells. It is encountered with greatest frequency in the tropical and subtropical zones of eastern hemisphere. The clinical expression of G6PD deficiency encompasses a continuous spectrum of hemolytic syndromes.

Drug induced hemolysis—seen typically in American blacks. This is an acute self limiting anemia in which hemoglobin is normal between episodes, e.g. primaquin, nalidixic acid, sulphamethoxazole. Infection induced hemolysis—infection is probably the most common factor inciting hemolysis, e.g. Salmonella, *E.coli*, streptococci and viral hepatitis.

Congenital nonspherocytic hemolytic anemia—presents as neonatal jaundice.

Favism occurs most commonly in children between the ages of 1 to 5 years, predominantly in males. Headache, nausea, back pain, chills and fever are followed by hemoglobinuria, anemia and jaundice. Blood transfusion is life saving.

SICKLE CELL DISEASE

Anemia is moderate to severe normochromic, normocytic.

- Vaso-occlusive crises—dactylitis often referred to as hand-foot syndrome is frequently the 1st manifestation of pain in children. Bone crises—manifests as bone pains. Abdominal crises; sickle cell girdle syndrome—due to occlusion of mesenteric blood supply and infarction of liver, spleen and lymph nodes that results in capsular stretching.
- Central nervous system crises—convulsions, vertigo, meningeal signs and cerebral infarction.
- Pulmonary crises; Acute chest syndrome.
- Priapism
- Hematuria
- Hepatic sequestration crises
- Splenic sequestration crises—occurs between 5 to 24 months of age. It presents with sudden onset abdominal pain and splenomegaly. Shock may sometimes be present.
- *Erythroblastic (Aplastic) crises*: It is almost invariably associated with infection. The most common cause is parvovirus B19. It terminates spontaneously usually after 10 days. Hyperhemolytic crises very unusual. May ensue in association with certain drugs or acute infections.

ORGAN DYSFUNCTION IN SICKLE CELL

CNS: Permanent motor disabilities, cortical atrophy and dilatation of ventricles on CT head.

Heart: Cardiomegaly, myocardial dysfunction, cor pulmonale.

Lungs: Pulmonary fibrosis.

Kidney: Nephrotic syndrome, papillary necrosis, renal infarction, pyelonephritis, renal medullary carcinoma.

Liver: Cholelithiasis.

Bones: Dactylitis, osteonecrosis of femoral and humeral head, fish mouth vertebra and hair on end appearance.

Eyes: Retinopathy.

Ears: Sensorineural hearing loss.

Skin: Leg ulcers over external or internal malleoli.

DELAYED GROWTH AND DEVELOPMENT

Functional Hyposplenism

Most children have functional asplenia by 5 years of age.

THALASSEMIA

Children with thalassemia usually become symptomatic as a result of progressive hemolysis with profound weakness and failure thrive during the 2nd 6 months of life.

Classical findings in children with thalassemia include typical facies (maxillary hyperplasia, frontal bossing, depressed nasal bridge), marked hepatosplenomegaly, pathological bone fractures and cachexia.

Pallor, hemosiderosis and jaundice may produce a brownish complexion. Endocrine dysfunction may include hypothyroidism, gonadal failure, hypoparathyroidism and diabetes mellitus.

Congestive heart failure and cardiac arrhythmias are potentially lethal complications.

EXTRACORPUSCULAR HEMOLYTIC ANEMIA

Immune hemolytic anemia can be either isoimmune or autoimmune. Isoimmune may result from mismatched blood transfusion or hemolytic disease of newborn.

HEMOLYTIC DISEASE OF NEWBORN

Severity of hemolytic disease is governed by the amount of maternal IgG anti-D (titre), its binding capacity (avidity for Rh antigen) and the ability of the affected fetus to respond to hemolysis by erythropoiesis without developing hepatocellular damage, portal obstruction and hydrops fetalis.

MILD DISEASE

One half of the affected babies do not need treatment and are mildly anemic at birth. Indirect bilirubin does not exceed 16 to 20 mg/dl.

MODERATE DISEASE

Presents in 25 to 30 percent of affected infants in whom icterus gravis and kernicterus may occur without treatment. The fetus is born in good condition at or near term. Moderate anemia may be present.

Babies who develop kernicterus become deeply jaundiced. On 3rd to 5th day signs of cerebral dysfunction such as lethargy and hyper tonicity develop. They lie in a position of opisthotonus with neck extended and knees, wrists and elbows flexed. Suck is poor with disappearance of grasp and moro's reflex.

Ten percent may survive but develop neurological damage, e.g.: deafness and cerebral palsy.

SEVERE DISEASE

Twenty to Twenty-five percent of affected fetuses become progressively become more anemic and without treatment hydrops fetalis, ascites and anasarca appears. One half of these fetuses become hydropic between 18 to 34 weeks of gestation and the other half between 34 to 40 weeks. With severe hemolysis portal and umbilical venous obstruction with portal hypertension develop. Placenta becomes edematous and cytotrophoblasts persist.

MINOR BLOOD GROUP INCOMPATIBILITIES

Hemolytic disease of newborn can also be caused by non-D alloimmunization. Antibodies reported to cause moderate to severe hemolytic disease include anti-K, -JKa, -JSa, -Ku, -LW, -Dib, -E.

Anti-E and anti-K antibodies are the most common but few of these infants require exchange transfusion or phototherapy. Anti-C when present was more likely to cause hemolytic disease, and in those affected it was more likely to cause disease requiring treatment than anti-E.

Anti-C, -Ce, -Cw, -Kpa, -K, -Fya and -S rarely caused hemolysis severe enough to require treatment after birth.

AUTOIMMUNE HEMOLYTIC ANEMIA

Warm Antibody Type

This is a severe life threatening condition. It lasts 3 to 6 months and occurs predominantly in children 2 to 12 years. It is frequently associated with infection. Onset is with pallor, jaundice, pyrexia and hemoglobinuria or more gradual with fatigue and pallor.

A consistent response to glucocorticoid therapy, and full recovery is characteristic of the acute form.

COLD ANTIBODY TYPE

Cold agglutinin disease is less common in children than in adults, and it more frequently results in an acute, self limited episode of hemolysis. The antibody causes less hemolysis in adults than in children. Spontaneous RBC agglutination is observed in the cold, and RBC aggregates are seen on the blood film. Response to glucocorticoids is infrequent and variable. Splenectomy is not useful in cold agglutinin disease.

Inherited Bone Marrow Failure Syndromes

Nivedita Dhingra, SP Yadav, Anupam Sachdeva

INTRODUCTION

Bone marrow failure can either be acquired (e.g. idiopathic aplastic anemia) or can occur as part of several inherited syndromes. Inherited bone marrow failure syndromes (IBMFSs) are rare genetic diseases characterized by varying degrees of defective production of mature erythrocytes, granulocytes, and platelets in the bone marrow usually in association with one or more somatic abnormalities. These IBMFS include *Fanconi anemia*, *Dyskeratosis congenita*, *Shwachman-Diamond syndrome*, *congenital amegakaryocytic thrombocytopenia*, and, rarely, *Diamond-Blackfan anemia* (Table 1). More than 25 percent of pediatric patients and approximately 10 percent of young adults who present with aplastic anemia have an inherited etiology. The bone marrow failure (which can involve all or a single cell lineage) often presents in childhood but may not do so until adulthood in some cases. Furthermore, some patients initially labeled as having “idiopathic aplastic anemia” actually have underlying IBMFS. Individuals with IBMFS are also predisposed to develop a variety of malignancies and myelodysplastic syndromes.

A wide range of physical anomalies have been described in many IBMFSs, with significant overlap among

the various disorders. These include craniofacial, skeletal, cardiovascular, pulmonary, gastrointestinal, immunologic, renal, and neurologic anomalies as well as those of the skin, eyes, and ears.

All patterns of inheritance are associated with marrow failure disorders. Many IMFS cases are sporadic and could be either recessive or dominant traits with variable expression. Genes for many of the IBMFSs have been identified and cloned, and can be used for diagnostic purposes. A significant portion of the patients with IMFSs do not have known gene defects and cannot be accurately diagnosed by clinical and standard laboratory tests.¹

There have been considerable advances in understanding of the genetic basis of these disorders over the past two decades. These advances have provided a better understanding of normal hematopoiesis and how this is disrupted in patients with bone marrow failure. They have also provided important insights into fundamental biological pathways: DNA repair-FA/BRCA pathway; telomere maintenance- dyskeratosis congenita-related genes; ribosome biogenesis-Shwachman-Diamond syndrome (SDS) and Diamond-Blackfan anemia (DBA) genes. Additionally, as these disorders are usually associated with developmental abnormalities and an increased risk of cancer they

Table 1: Characteristics of the inherited bone marrow failure syndromes

	<i>FA</i>	<i>DC</i>	<i>SDS</i>	<i>DBA</i>	<i>CAMT</i>	<i>SCN</i>
Inheritance pattern	AR, XLR, AD	AR, XLR	AR	AD, AR	AR	AD
Somatic abnormalities	Yes	Yes	Yes	Yes	Rare	Rare
Bone marrow failure	AA (>90%)	AA (~80%)	AA (~20%)	RCA	Meg	Neut
Cancer	Yes	Yes	Yes	Yes	Yes	Yes
Chromosome instability	Yes	Yes	Yes	?	?	?
Genes identified	13	6	1	9	1	3

are providing insights into human development and the genesis of cancer.

FANCONI'S ANEMIA

Fanconi's anemia (FA) was first described in 1927 by Swiss pediatrician, Guido Fanconi in a single family with 3 affected males between 5 to 7 years of age. The condition is clinically heterogeneous, but characteristic features include the progressive development of bone marrow failure and an increased predisposition to malignancy.² Affected individuals may also have one or more developmental abnormality including skin, skeletal, genitourinary, gastrointestinal and neurological anomalies. At presentation patients may have either a classic phenotype comprising physical anomalies and abnormal hematology, or typical physical anomalies but normal hematology, or normal physical features but abnormal hematology. Approximately 30 percent of patients with Fanconi anemia have no overt somatic abnormalities.

It is usually inherited as an autosomal recessive trait but in a small subset of patients it can be an X-linked recessive disorder. FA is found in all races and ethnic groups and occurs with equal frequency in males and females with an estimated carrier frequency of 1 in 300. The majority of patients present towards the end of the first decade of life, usually with bone marrow failure. However, increasingly some patients are being diagnosed in adulthood and many patients diagnosed in childhood now survive into adulthood.

Clinical Features

Hematological Manifestations

A cardinal feature is the gradual onset of bone marrow failure involving one or more hematopoietic cell lineages. Median age of marrow failure is 7 years (range: birth to 31 years).³ Thrombocytopenia associated with elevated levels of HbF and macrocytosis (MCV often >100 fl) usually precede onset of anemia or neutropenia. However FA may present with MDS or AML without prior diagnosis of AA. The development of aplastic anemia can be accelerated by intercurrent infections or by drugs such as chloramphenicol.

Marrow cellularity is best evaluated by bone marrow biopsy as it may be patchy and subject to sampling variation. In the early stages of the disease, the bone marrow can show erythroid hyperplasia, sometimes with dyserythropoiesis and even megaloblastic appearing cells. As the disease progresses, the marrow becomes hypocellular and fatty, and shows a relative increase in lymphocytes, plasma cells, reticulum cells and mast cells. With full-blown marrow failure, the morphology on biopsy is identical to that seen in severe acquired aplastic anemia.

Nonhematological Manifestations

The somatic abnormalities seen in FA can virtually involve any organ system. The major congenital abnormalities include:

- *Skin*: Café-au-lait spots, hyper- and hypopigmentation
- *Growth*: Intrauterine growth retardation, short stature
- *Eyes*: Micro-ophthalmia, short and almond-shaped palpebral fissures, epicanthal folds, hypotelorism, strabismus and cataracts
- *Thumb and radius*: Thenar hypoplasia, absence or hypoplasia of thumbs and/or radius, bifid thumb, abnormal placement of thumb, digitalization of thumb
- *Other skeletal*: Congenital dislocation of hip, clubfoot, scoliosis, Kippel-Feil anomaly, dysplastic or absent ulna, vertebral anomalies
- *Kidney and urinary tract*: Ectopic, horse-shoe, dysplastic, hypoplastic, rotated and absent kidneys, hydronephrosis, urethral stenosis, hydroureter, reflux
- *Ears*: Deafness (usually conductive), abnormal or absent pinna, prominent ears, low set or posteriorly rotated ears, fused ossicles, absent tympanic membrane
- *Genitals*: Males—micropenis, undescended or atrophic testis, hypospadias, phimosis Females—bicornuate uterus, aplasia or hypoplasia of vagina and uterus
- *Cardiopulmonary*: Patent ductus arteriosus, ventricular septal defect, pulmonic or aortic stenosis, coarctation of aorta, tetralogy of Fallot
- *Gastrointestinal*: Esophageal atresia, duodenal atresia, anal atresia, tracheoesophageal fistula, annular pancreas
- *Central nervous system*: Microcephaly, hydrocephalus, Arnold Chiari malformation, Bell's palsy, CNS arterial malformations
- *Endocrine abnormalities*: Hypothyroidism, impaired secretion of growth hormone, hyperinsulinemia and impaired glucose tolerance test.

Cancer Predisposition

The underlying chromosomal instability and defective DNA repair results in an increased predisposition to malignancy and the risk increases with age. Data from the International FA Registry study⁴ demonstrated a crude rate of cancer of 23 percent; 179 patients developed 199 neoplasms. Of these neoplasms, 60 percent were hematologic and 40 percent were non-hematologic. The hematologic malignancies included AML (36%), MDS (31%), and acute lymphoblastic leukemia (3%). The authors suggested that the risk of hematologic and non-hematologic neoplasms increased with advancing age with a 33 and 28 percent cumulative incidence, respectively, by 40 years of age.

Most of the solid tumors described in FA were squamous cell carcinomas involving the gastrointestinal tract at any site from the oropharynx to the anorectal-colonic area.^{4,5}

Less frequently, patients can develop carcinomas of the vulva, cervix, and breast or unusual combinations such as Wilms tumor with medulloblastoma, cancer of the vulva and tongue, hepatic carcinoma and cancer of the tongue, and hepatic carcinoma and esophageal carcinoma.^{4,5}

Pathogenesis and Genetic Aspects

The most striking cellular hallmark of FA is hypersensitivity to a class of DNA damaging agents that create DNA interstrand crosslinks (ICLs), such as mitomycin C (MMC) or diepoxybutane (DEB). Hence, the cells in these patients accumulate DNA damage at an increased rate. ICLs are very toxic lesions. These covalent links prevent DNA unwinding, thereby blocking both DNA replication and transcription. Administration of ICL-inducing chemotherapy has serious side effects on FA patients, as their cells cannot repair crosslinks. Given that it is activated not only by crosslink-inducing chemicals, but also by other DNA damaging agents, such as ultraviolet radiation (UV), ionizing radiation (IR), hydroxyurea, and even spontaneously during replication the FA pathway is likely to be involved in the replication-dependent repair of many types of lesions. The FA pathway is considered to be a guardian of the genome. Studies on the genetic basis of the disease have identified 13 FA genes also known as *complementation groups* which account for >95 percent of cases of FA. The proteins encoded by the Fanconi anemia genes participate in a complicated network important in DNA.

Unrepaired DNA damage can activate pro-apoptotic pathways, leading, for example, to depletion of hematopoietic stem cells, causing pancytopenia. Alternatively, defective DNA repair in FA cells can lead to mutations and translocations that cause inactivation of cell cycle barriers and result in acute myeloid leukemia and other blood and solid tumors.

Laboratory Evaluation

Any child presenting with cytopenias in conjunction with somatic abnormalities characteristic of FA must be investigated for FA. The diagnosis of FA is usually suspected after obtaining a medical, developmental, and family history, as well as conducting a physical examination. Low blood cell counts, red blood cell macrocytosis, high hemoglobin F, increased expression of the i antigen, and varying degrees of marrow hypoplasia are common findings, but are not specific for FA and can be seen in other IBMFs. In patients without physical anomalies, chromosomal breakage analysis using diepoxybutane or mitomycin C will specifically identify FA and lead to the correct diagnosis.

Since it was introduced in 1981⁶ the chromosomal fragility test has become the gold standard for the diagnosis of FA. It is based on the demonstration of increased chromosomal breakage following exposure to clastogens such as MMC or DEB. This response to MMC or DEB distinguishes Fanconi anemia from most of the other

chromosomal breakage syndromes such as ataxia telangiectasia and Bloom's syndrome. The exception is Nijmegen breakage syndrome, where increased chromosomal breakage may be difficult to distinguish from Fanconi anemia.⁸

Chromosomal breakage testing is typically performed on phytohemagglutinin (PHA)-stimulated peripheral blood lymphocytes. Reversion of the Fanconi anemia gene mutation in a somatic cell, typically a lymphocyte, may result in a falsely negative chromosomal breakage test^{9,10} particularly given the relative growth advantage of the reverted clone. For patients with a high clinical suspicion for Fanconi anemia but a negative blood test, the diagnosis of Fanconi anemia may be made by testing skin fibroblasts for chromosomal breakage.

Newer tests that are available in specialized laboratories include flow cytometry and Western blot. Flow cytometry examines cell cycle kinetics and can detect the proportion of cells that are arrested at G2/M after culture with a clastogen such as nitrogen mustard. It has the advantage that it is less labor intensive and thousands of cells can be examined simultaneously.

Prenatal Diagnosis

Diagnostic testing can be performed on fetal amniotic fluid cells obtained at 16 weeks' gestation or on chorionic villus biopsy specimens at 9–12 weeks. A very high degree of prenatal diagnostic accuracy has been documented by looking at both spontaneous and diepoxybutane-induced breaks,⁷ and genetic testing.

Therapy and Prognosis

Because of their clinical complexity, patients with FA should be supervised at a tertiary care center using a comprehensive and multidisciplinary approach. Due to early diagnosis and newer approaches to HSCT, the prognosis of patients with FA has been improved, and the median survival is currently 24 years of age.⁴ If the patient is stable and has only minimal to moderate hematologic changes and no transfusion requirements, a period of observation is indicated. Blood counts may be monitored every 1 to 3 months and bone marrow aspirates and biopsies performed annually for morphology and cytogenetics to identify transformation into MDS/AML. Depending on the types of congenital anomalies, subspecialty consultations, for example, with cardiologists and orthopedic surgeons, can be arranged during this interval.

Hematopoietic Stem Cell Transplant

Hematopoietic stem cell transplant (HSCT) is the only curative option. FA patients have increased sensitivity to chemotherapy and radiotherapy and thus modified conditioning regimens are used.¹¹ It is the treatment of choice for patients with HLA-matched donors. Evidence of MDS

or evolution to leukemia are clear indications for transplant.

Androgens

The overall response rate in the literature is about 50 percent,¹² heralded by reticulocytosis and a rise in hemoglobin within 1 to 2 months. If the other lineages respond, white cells increase next and finally platelets, but it may take many months to achieve the maximum response. When the response is deemed maximal, the androgens should be slowly tapered but not stopped entirely. Oxymetholone is most frequently used at 2 to 5 mg/kg daily with preference for the lowest dose initially. Danazol is another agent being evaluated. The liver function tests must be monitored 3 to 6 monthly while the patient is on steroids due to potential hepatotoxicity.

Cytokines

Studies have demonstrated that G-CSF or GM-CSF can improve the neutrophil counts in FA patients. Therapy instituted if ANC is persistently <500/cumm or fails to rise with serious bacterial infection. G-CSF is typically started at a dose of 5 µg/kg/day while the recommended starting dose of GM-CSF is 250 µg/m²/day. Treatment should generally be discontinued if the neutrophil count fails to improve after eight weeks of G-CSF or GM-CSF therapy.

Adjunctive Therapy

Packed cell transfusions should be considered if the Hb is less than 8 g/dl or if the patient is symptomatic. Platelets are transfused if there is any evidence of cutaneous or mucosal bleeding. Aminocaproic acid in a dose of 50-100 mg/kg every six hours, with a maximum dose of around 12 grams/day is a useful adjunct to platelets in controlling bleeding. High transfusion burden may adversely affect transplant outcomes, so timely consideration of transplant is recommended. The use of family members as directed donors may cause alloimmunization to an antigen that would increase the risk of graft rejection after sibling donor hematopoietic stem cell transplant.

DYSKERATOSIS CONGENITA

Dyskeratosis congenita (DC) is a rare inherited syndrome exhibiting marked clinical and genetic heterogeneity. It is characterized by mucocutaneous abnormalities, bone marrow failure and a predisposition to cancer.¹² Bone marrow failure is the principal cause of premature mortality. It is inherited as an autosomal recessive, dominant or X-linked recessive disorder.

Studies over the last 10 years have demonstrated that DC is principally a disease of defective telomere maintenance. All DC patients have very short telomeres and the genetically characterized cases of DC have mutations in

six genes which either encode components of the telomerase complex. Telomeres are the specialized DNA: protein structures at the ends of chromosomes that prevent the genomic rearrangement of free DNA ends and allow replication of the distal chromosomal ends. Telomerase is the enzyme required for DNA replication at the telomeres. Telomere length shortens as a function of age. Although short telomeres are commonly seen in patients with marrow failure, telomere length is markedly shorter (<1st percentile) in patients with dyskeratosis congenita, even in comparison to other patients with marrow failure.

Clinical Features

Hematological Manifestations

The initial hematologic change is usually thrombocytopenia, anemia, or both, followed by pancytopenia. The red cells are often macrocytic and the hemoglobin F can be elevated. Oddly, early bone marrow aspirations and biopsies may be hypercellular; however, with time all cellular elements decline.

Immunologic abnormalities, including reduced immunoglobulin levels, reduced T- and B-lymphocyte numbers, and reduced proliferation in response to mitogens, may occur in patients with DC.

Nonhematological Manifestations

The classical triad of abnormalities associated with DC is one of abnormal skin pigmentation, nail dystrophy and oral leukoplakia. Lacy reticulated skin pigmentation affecting the face, neck, chest, and arms is the most common finding (89%), and increases with age. There may also be a telangiectatic erythematous component. Nail dystrophy of the hands and feet is the next commonest finding (88%). It usually starts with longitudinal ridging, splitting, or pterygium formation and may progress to complete nail loss. Leukoplakia is most commonly observed over the tongue but other mucosal structures may also be affected. Ophthalmologic, skeletal and dental abnormalities, osteoporosis and pulmonary fibrosis are other frequent findings.

Cancer Predisposition

Cancer develops in at least 10 to 15 percent of patients, usually in the third or fourth decades of life. The types of malignancies are similar to FA, although in DC solid tumors are more common than hematologic malignancies.¹³

Genetics

Six dyskeratosis congenita genes (*DKC1*, *TERC*, *TERT*, *NOP10*, *NHP2*, *TINF2*) have been identified to date. The gene mutated in X-linked DC (*DKC1*) encodes a highly conserved nucleolar protein called dyskerin.¹⁴ Dyskerin associates with the RNA component of telomerase (*TERC*)

where it is important in stabilizing the telomerase complex, which is critical in the maintenance of telomeres.¹⁵ Heterozygous mutations in *TERC* and *TERT* (telomerase reverse transcriptase) have been found in patients with autosomal dominant dyskeratosis congenita and in some patients with aplastic anemia, myelodysplastic syndrome and pulmonary fibrosis.^{16,17} It has also been established that autosomal recessive dyskeratosis congenita is genetically heterogeneous with three subtypes due to biallelic mutations in *NHP2*, *NOP10* and *TERT*.

Laboratory Evaluation and Diagnosis

The median age of diagnosis of the X-linked DC is 15 years (range 0.3–68 years), of the autosomal recessive form is 13 years (range 1.2–42 years), and of the autosomal dominant group is 25 years (range 7–58 years). Thrombocytopenia and anemia usually appear first, followed by pancytopenia. Severe cytopenia eventually develops in about 50 percent of the patients.

A detailed medical, developmental, and family history, along with a physical examination usually yield important diagnostic clues. Low blood cell counts, red blood cell macrocytosis, and high hemoglobin F are usual findings. Bone marrow cellularity can be normal or increased at the onset of cytopenia, but invariably decreases once the cytopenia deteriorates. Mutation analysis of the *DKC1* and genes can provide a molecular diagnosis for patients with the X-linked and autosomal dominant diseases.

Telomere length is emerging as a useful screen for dyskeratosis congenita, although experience with this test is still limited and interpretation must be made within the clinical context. Granulocytes in particular commonly exhibit shortened telomeres. A study measuring telomere lengths in a panel of five lymphocyte subsets plus granulocytes reported that telomere lengths below the 1st percentile for age in at least three different lymphocyte subsets strongly correlated with the diagnosis of dyskeratosis congenita.¹⁸ The interpretation of telomere length in relatives lacking any clinical findings of dyskeratosis congenita warrants further study.¹⁹

Therapy and Prognosis

The mean age of death is approximately 30 years.¹³ The main causes of death relate to either bone marrow failure or malignancy.

Androgens

Androgens, usually combined with low-dose prednisone, can be expected to induce improved marrow function in about 40 percent of patients. If a response is seen and deemed to be maximal, the androgen dose can be slowly tapered but not usually stopped. Until recently the exact mechanism of action of androgens was unclear. However there is evidence that androgens control telomerase

expression in prostate cancer cells²⁰ and normal reproductive tissues.²¹ For these reasons, it is hypothesized that androgens might act similarly on hematopoietic cells.

Growth Factors

There appears to be potential benefit from cytokine therapy in selected patients with DC while waiting for HSCT or who are not eligible for transplant. G-CSF and GM-CSF have been used alone or in conjunction with erythropoietin and have produced transient increase in blood counts.

Hematopoietic Stem Cell Transplantation

HSCT is the only curative option in DC. To date, 25 patients with DC have reportedly undergone HSCT.²² In most cases standard conditioning regimens were used.

SHWACHMAN-DIAMOND SYNDROME

Shwachman-Diamond syndrome is an autosomal recessive disorder characterized by exocrine pancreatic insufficiency, bone marrow failure and other somatic abnormalities (particularly metaphyseal dysostosis).²³ Features of pancreatic insufficiency are apparent early in infancy. The spectrum of hematologic abnormalities includes neutropenia, pancytopenia (~20%), myelodysplastic syndrome and leukemia (~25%). The majority (>90%) of patients with Shwachman-Diamond syndrome have been found to have mutations in the *SBDS* gene.²⁴ The *SBDS* gene product (*SBDS*) has an important role in the maturation of the 60s ribosomal subunit and, therefore, in ribosome biogenesis.

Clinical Features

Hematological Manifestations

The most common hematologic abnormality affecting 88 to 100 percent of patients with SDS is neutropenia, defined as an absolute neutrophil count less than $1,500 \times 10^9/L$.²⁵ Anemia, either normochromic-normocytic or macrocytic, with reticulocytopenia has also been described in 42 to 82 percent of patients.²⁵ Thrombocytopenia (platelet count $<150 \times 10^9/L$) has been reported in 24 to 88 percent of patients and can lead to fatal bleeding.²⁵ Similar to patients with other marrow failure syndromes, around 80 percent of patients with SDS have elevated levels of hemoglobin F which is likely a sign of 'stress' hematopoiesis. Roughly 10 to 65 percent of patients have pancytopenia with some patients developing aplastic anemia.²⁶ Bone marrow findings are variable and may reveal a hypocellular, normocellular, or hypercellular marrow. Marrow cellularity must be interpreted in the context of the patient's peripheral blood counts as cellularity may be patchy and is subject to sampling variation.

Nonhematological Manifestations

Multisystem involvement may be seen in the form of:

- *Infections and immune abnormalities:* Patients with SDS are susceptible to recurrent bacterial, viral, and fungal infections, in particular, otitis media, sinusitis, mouth sores, bronchopneumonia, septicemia, osteomyelitis, and skin infections.²⁷ Neutropenia is likely a contributing factor, as well as possible defects in neutrophil chemotaxis.^{28,29}
- *Gastrointestinal features:* One of the hallmarks of SDS is exocrine pancreatic dysfunction of varying severities caused by absence of acinar cells. Patients classically present in early infancy with malabsorption, steatorrhea, failure to thrive, and low levels of fat soluble vitamins A, D, E, and K. Low serum pancreatic trypsinogen and low isoamylase are useful markers for pancreatic insufficiency in patients with SDS and fecal elastase levels may also be low. Imaging studies with ultrasound, computed tomography, or magnetic resonance imaging (MRI) often demonstrate a small, structurally abnormal pancreas composed mainly of fat.³⁰
- *Skeletal abnormalities:* The primary skeletal defects are related to abnormal development of the growth plates, in particular, the metaphyses. Metaphyseal dysostosis has been reported in roughly 50 percent of the patients, is usually asymptomatic, and most commonly involves the femoral head.³¹
- *Cardiac features:* Several case reports have described neonatal cardiac manifestations associated with SDS.^{32,33} Myocardial necrosis or fibrosis has been primarily seen on histopathology.
- *Other features:* Insulin-dependent diabetes, growth hormone deficiency, hypogonadotropic hypogonadism and hypothyroidism have been described in patients with SDS. Failure to thrive is common and is likely multifactorial including pancreatic insufficiency, feeding difficulties, recurrent infections, and metaphyseal dysostosis.

Laboratory Evaluation and Diagnosis

Exocrine Pancreatic Insufficiency

Exocrine pancreatic insufficiency may be demonstrated by one of the following:

- Elevated fecal fat excretion following a 72-hour collection in the absence of concomitant intestinal or cholestatic liver disease with imaging studies showing a small or fatty pancreas
- Low serum trypsinogen in patients under the age of three years or low serum isoamylase testing in patients over the age of three years.³⁴ The use of fecal elastase as a marker for exocrine pancreatic dysfunction in SDS is currently under investigation. Pancreatic stimulation testing with intravenous pancreozymin with or without secretin has been used to evaluate levels of pancreatic

enzymes; however, with the advent of serum markers, this invasive procedure has been used less commonly.

Bone Marrow Failure

Signs of marrow failure may include any of the following findings:

- Intermittent or persistent neutropenia (absolute neutrophil count $<1,500/\mu\text{L}$) documented at least 3 times over a minimum of 3 months without an apparent cause
- Hypoproliferative anemia with a hemoglobin concentration below the age-related adjusted norms
- Unexplained macrocytosis
- Platelet count $<150,000/\text{mL}$ without alternative etiology
- Hypocellular bone marrow, aplastic anemia, MDS or leukemia may be the presenting hematologic abnormality of a patient with underlying SDS.

Additional supportive features include skeletal abnormalities, hepatomegaly with or without elevated serum aminotransferase levels, and immunologic abnormalities.

Genetic Testing

SDBS genetic testing provides corroborative data in a patient who has been clinically diagnosed with SDS and allows genetic testing to identify affected family members. Up to 10 percent of patients with clinical features of SDS lack *SDBS* mutations; therefore, the absence (negative test) of the *SDBS* gene mutation does not rule out the diagnosis.²⁴ It is presently not known whether patients lacking *SDBS* mutations have mutations in an additional as yet unidentified gene(s) for SDS or if they represent a separate distinct disorder.

Clinical Management

Hematology: All patients with SDS should be monitored by a hematologist. The general recommendation from a clinical consensus conference is to monitor peripheral blood counts for cytopenias every 3 to 4 months. Marrow evaluation with aspirate and biopsy including cytogenetics to assess for marrow cellularity, MDS, acute leukemia, or other clonal disease is recommended on a yearly basis or more often if clinically indicated. Such regular monitoring allows timely institution of therapy prior to the development of clinical complications. Hematopoietic cell transplantation (HCT) prior to the development of overt leukemia is associated with better outcomes.

For those neutropenic patients with recurrent or severe infections, granulocyte colony stimulating factor (G-CSF) may be considered. Data regarding malignant myeloid transformation into MDS or AML in SDS patients on G-CSF therapy are inconclusive; however, there is no strong evidence that links G-CSF directly to leukemic conversion. Therefore, G-CSF should not be withheld if clinically indicated to treat infection or to prevent recurrent bacterial or fungal infections.

Gastroenterology: Patients with SDS should also be followed by a gastroenterologist for management of exocrine pancreatic insufficiency. Most patients require oral pancreatic enzyme supplementation. However, steatorrhea resolves in roughly 50 percent of patients; therefore, assessment of continued need for pancreatic enzyme supplementation is indicated. Measurement of the fat soluble vitamins A, D, E, and K should occur with appropriate supplementation as indicated.

Skeletal: Measures to maximize bone density should be implemented including adequate calcium and vitamin D intake, and weight-bearing exercises. In addition, it is important to screen for and correct any underlying endocrine problems that may contribute to osteopenia such as hypothyroidism or hypoparathyroidism.

CONGENITAL AMEGAKARYOCYTIC THROMBOCYTOPENIA

Congenital amegakaryocytic thrombocytopenia usually presents in infancy and is characterized by isolated thrombocytopenia and a reduction or absence of megakaryocytes in the bone marrow, but usually no somatic abnormalities. Approximately 50 percent of patients develop aplastic anemia, usually by the age of 5 years. Congenital amegakaryocytic thrombocytopenia can also evolve into myelodysplastic syndrome or leukemia. In a subgroup of patients with congenital amegakaryocytic thrombocytopenia biallelic mutations in the gene encoding for the thrombopoietin receptor (*c-MPL*) have been identified.²⁵

Clinical Features

Hematological Manifestations

CAMT is an autosomal recessive disorder that presents at birth with severe thrombocytopenia. Mean platelet counts at diagnosis are 21,000/ μ l, and platelets are of normal size and morphology.²⁶ The hemoglobin levels and white blood cell counts are normal. Red cells may be macrocytic, and hemoglobin F can be increased. At diagnosis, bone marrow specimens show normal cellularity with markedly reduced or absent megakaryocytes. Aplastic anemia subsequently ensues in 39 to 75 percent of the patients at the age of 2 to 53 months.²⁶ Patients with CAMT are prone to MDS/AML.²⁶ The typical course is the development of early thrombocytopenia, aplastic anemia, and then marrow cytogenetic abnormalities (usually monosomy 7), MDS and AML.

Nonhematological Manifestations

Roughly a quarter of patients have characteristic physical anomalies. The most common manifestations in those with anomalies are neurologic and cardiac. Findings relating to cerebellar and cerebral atrophy are present frequently, and developmental delay is a prominent feature

in this group. Patients may also have microcephaly and an abnormal facies. Congenital heart disease with a variety of malformations can be detected, including atrial and ventricular septal defects, patent ductus arteriosus, tetralogy of Fallot, and coarctation of the aorta. Some of these can occur in combinations. Other anomalies include abnormal hips or feet, kidney malformations, eye anomalies, and cleft or high-arched palate.

Pathogenesis and Genetic Aspects

Congenital amegakaryocytic thrombocytopenia is an autosomal recessive disorder caused by mutations in the *c-MPL* gene.²⁷ The *c-MPL* gene encodes the thrombopoietin receptor. Thrombopoietin is important for megakaryocyte differentiation as well as for the maintenance of hematopoietic stem cells. Type I patients have complete loss of *c-MPL* function and typically have a more severe presentation earlier in life. Type II patients maintain partial *c-MPL* function and may follow a milder clinical course.²⁸

Laboratory Evaluation and Diagnosis

The median age of diagnosis is 1.3 months (range 0–110 months) in the nonsyndromic cases and 2 days (range 0–18 months) in the syndromic cases.¹³ The typical patient presents with isolated severe thrombocytopenia from birth. The gold standard procedure for determining cellularity and marrow megakaryocyte pool is bone marrow biopsy. All patients with suspected CAMT should be offered *MPL* mutation analysis.

Therapy and Prognosis

Thrombocytopenia in patients with CAMT can have a variable clinical course.²⁸ Whereas infants with type I receptor mutations generally remain thrombocytopenic and have a rapid progression to trilineage bone marrow failure (mean onset 1 year 11 months of age), infants with type II mutations may show transient modest improvement of platelet counts during the first year of life and have a delayed onset of marrow failure (mean onset 5 years of age).²⁸ Nevertheless, with rare exceptions most patients with CAMT go on to develop bone marrow failure. Importantly, patients with CAMT are also at increased risk for the development of myelodysplasia and acute myeloid leukemia.²⁹

Supportive care comprises of platelet transfusions which should be used as medically indicated and not just because of a low platelet count. Single donor platelets are preferred to minimize sensitization. All blood products should be irradiated and tested negative for CMV. Corticosteroids have been used with no apparent efficacy. For aplastic anemia, androgens in combination with corticosteroids may induce a temporary partial response but the effect is short-lived. Based on the *in vitro* studies, several clinical trials have been conducted with interleukin-3 (IL-3), GM-CSF, and the fusion cytokine PIX321. These

cytokines may result in temporary hematologic improvement, but clearly are not curative. IL-3 and PIX321 are not available for clinical use.

Currently, the only definitive treatment for the long-term management of patients with CAMT is hematopoietic stem cell transplantation. HLA typing for the patient and siblings should be obtained at the time of diagnosis to direct management decisions. Transplantation with a matched sibling donor is the treatment of choice.^{30,31} Siblings who are heterozygous carriers of the *c-MPL* mutation have been used successfully as stem cell donors. Outcomes are less favorable for patients without a matched sibling donor, with failures due to delayed engraftment, rejection, GVHD and regimen-related toxicity having been reported.³²

INHERITED MARROW FAILURE SYNDROMES PRESENTING WITH ISOLATED CYTOPENIAS

Diamond-Blackfan Anemia

Diamond-Blackfan anemia usually presents in early infancy, with features of anemia. The hallmark of classical Diamond-Blackfan anemia is a selective decrease in erythroid precursors and normochromic macrocytic anemia associated with a variable number of somatic abnormalities such as craniofacial, thumb, cardiac and urogenital malformations.³³ Myelodysplastic syndrome and acute myeloid leukemia have been reported in a few patients, suggesting an increased predisposition to hematologic malignancies. There are also cases in which the disease has evolved into aplastic anemia. Thus, although Diamond-Blackfan anemia has been regarded classically as a pure red cell aplasia, a more global hematopoietic defect can be observed.

Clinical Manifestations

The diagnosis of classic Diamond-Blackfan anemia (DBA), a congenital red blood cell aplasia, is made when all four of the following diagnostic criteria are met:³³

- Age less than 1 year
- Macrocytic anemia with no other significant cytopenias
- Reticulocytopenia
- Normal marrow cellularity with a paucity of erythroid precursors.

Other findings include:

- Growth retardation (observed in 30%)
- Congenital malformations (observed in ~30-50%), in particular craniofacial, upper-limb, heart, and genitourinary malformations which include:
 - *Face and head (50%)*: Microcephaly; ocular hypertelorism; epicanthus, ptosis; broad, flat nasal bridge; microtia, low-set ears; cleft lip/palate, high arched palate; micrognathia; low anterior hair line

- *Eye*: Congenital glaucoma, congenital cataract, strabismus
- *Neck*: Webbed neck, short neck, Klippel-Feil anomaly, Sprengel deformity
- *Upper limb and hand including thumb (38%)*: Absent radial artery; flat thenar eminence; triphalangeal, duplex, bifid, hypoplastic, or absent thumb
- *Genitourinary (19%)*: Absent kidney, horseshoe kidney; hypospadias
- *Heart (15%)*: Ventricular septal defect, atrial septal defect, coarctation of the aorta, other cardiac anomalies.

Laboratory Evaluation

The following laboratory findings are observed in most, but not all, individuals with DBA:³⁴

- Increased red cell mean corpuscular volume (MCV)
- Elevated erythrocyte adenosine deaminase activity (eADA) (observed in 80-85%)
- Elevated hemoglobin F (HbF) concentration
- Bone marrow aspirate shows normocellular bone marrow with erythroid hypoplasia, marked reduction in normoblasts and normal myeloid precursors and megakaryocytes.

Genetic Aspects

DBA is inherited in an autosomal dominant manner. Approximately 40 to 45 percent of affected individuals have inherited the mutation from a parent; approximately 55 to 60 percent have a *de novo* mutation.

The first Diamond-Blackfan anemia gene (*RPS19*) was identified in 1999³⁵ and in western populations accounts for approximately 25 percent of the cases of the disorder. Subsequently heterozygous mutations in other genes encoding for ribosomal proteins of the small (RPS24, RPS17, RPS7, RPS10, RPS26) and large (RPL5, RPL11, RPL35A) ribosomal subunits have also been reported; collectively the genetic basis of approximately 50 to 60 percent of cases of DBA can now be established.³⁵ These observations have demonstrated that Diamond-Blackfan anemia is a disorder of ribosome biogenesis.

Management

Treatment of Manifestations

Corticosteroid treatment, recommended in children over age twelve months, can initially improve the red blood count in approximately 80 percent of affected individuals. The recommended corticosteroid is prednisone with a starting dose of 2 mg/kg/day given orally once a day in the morning, beginning when the child is at least six months old. An increase in hemoglobin concentration is usually seen in two to four weeks. Following sustained response corticosteroids may be slowly tapered to the minimal effective

dose. Monitoring of blood counts is needed to ensure that the red cell hemoglobin concentration remains at 80 to 100 g/L, the minimum required for transfusion independence. The corticosteroid maintenance dose varies and can be extremely low in some individuals. The recommended maximum maintenance dose is ≤ 0.5 mg/kg/day or ≤ 1 mg/kg every other day. If the recommended steroid dose cannot sustain the red cell hemoglobin concentration in an acceptable range (usually one month), the corticosteroids should be tapered and discontinued.

Side effects of corticosteroids include osteoporosis, weight gain, cushingoid appearance, hypertension, diabetes mellitus, growth retardation, pathologic bone fractures, gastric ulcers, cataracts, glaucoma, and increased susceptibility to infection.

Chronic transfusion with packed red blood cells is initially necessary while the diagnosis is made and in those not responsive to corticosteroids. Hematopoietic stem cell transplantation (HSCT), the only curative therapy for the hematologic manifestations of DBA, is often recommended for those who are transfusion-dependent or develop other cytopenias. Treatment of malignancies should be coordinated by an oncologist. Chemotherapy must be given cautiously as it may lead to prolonged cytopenia and subsequent toxicities.

Prevention of Secondary Complications

Transfusion-related iron overload is the most common complication in transfusion-dependent individuals. Iron chelation therapy with deferasirox orally or desferrioxamine subcutaneously is recommended after 10 to 20 transfusions. Steroid-related side effects must also be closely monitored, especially as related to risk of infection, growth retardation, and bone density in growing children. Often patients will be placed on transfusion therapy if these side effects are intolerable.

Thrombocytopenia Absent Radii Syndrome

Thrombocytopenia absent radii (TAR) is a clinically-defined syndrome characterized by thrombocytopenia and bilateral radial aplasia with thumbs present.^{36,37} At birth thrombocytopenia may be of variable severity, with platelet counts ranging from 10 to 100,000/ μ L and platelets that are normal in size and granularity.

Bone marrow examination typically demonstrates a reduction in the size and number of bone marrow megakaryocytes, and if obtained plasma TPO levels are usually elevated.^{38,39}

Although bilateral radial aplasia is the defining skeletal feature in TAR, additional skeletal abnormalities are frequently observed, including more extensive upper limb malformations, phocomelia, and lower limb malformations in as many as 50 percent of the patients. Nonskeletal abnormalities are also common, including gastroenteritis

and cow's milk intolerance in 47 percent, renal malformations in 23 percent, cardiac defects in 15 percent, facial dysmorphism in 53 percent, short stature in 95 percent, macrocephaly in 76 percent and capillary hemangiomata in 24 percent.⁴⁰

Severe Congenital Neutropenia (Including Kostmann Syndrome)

Severe congenital neutropenia, as its name indicates, is characterized by profound peripheral neutropenia ($<0.2 \times 10^9/L$).⁴¹ Patients with the congenital disorder usually present with recurrent, life-threatening infections in infancy. Bone marrow examination usually reveals a maturation arrest in the myeloid lineage. The disease can progress to myelodysplasia and leukemia, usually with acquisition of secondary mutations including mutations in the granulocyte colony-stimulating factor receptor. Heterozygous mutations in the neutrophil elastase gene (ELA2) have been demonstrated in the majority of patients.⁴² These mutations are thought to lead to the accumulation of a nonfunctional protein which in turn triggers an unfolded protein response leading to maturational arrest. The original family described by Kostmann, had autosomal recessive severe congenital neutropenia, which has been shown to be associated with biallelic mutations in the *HAX1* gene predicted to lead to defects in cell death.

Life-long treatment with G-CSF is currently the mainstay of management of patients with KS, and should be initiated as front-line treatment when the diagnosis is established. The daily starting dose is 5 μ g/kg subcutaneously, and this can be escalated by 5 to 10 μ g/kg/day every 14 days until the desired neutrophil number is achieved. Neutrophils $>0.5 \times 10^9/L$ generally provide protection from infection, but target counts of about $1\text{--}2.5 \times 10^9/L$ are clearly safer.

Cyclic neutropenia is an autosomal dominant disorder characterized by a regular, repetitive decrease in peripheral blood neutrophils at approximately 21-day intervals.⁴³ Patients usually present in infancy or childhood, and have a less severe infectious course compared with Kostmann syndrome. Diagnosis requires the demonstration of regular neutrophil cycles of 19 to 23 days, during which the neutrophil count typically fluctuates from normal/nearly normal for 16 to 19 days to moderately/severely low for 3 to 4 days. Daily treatment with G-CSF at doses of 1 to 5 μ g/kg typically improves symptoms in most patients.

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Aplastic Anemia

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Acquired bone marrow failure or acquired aplastic anemia (AA) is a rare but heterogenous disorder characterized by pancytopenia with a hypocellular bone marrow in the absence of an inherited bone marrow syndrome. The majority (70–80%) of these cases are categorized as idiopathic because their primary aetiology is unknown. In a subset of cases, a drug or infection can be identified that precipitates the bone marrow failure, although it is not clear why only some individuals are susceptible. In approximately 15 to 20 percent of patients the disease is constitutional/ inherited, where the disease is familial and/ or presents with one or more somatic abnormalities.

The history of AA is long; the earliest description of this disease entity was given by Ehrlich¹ at the end of the 19th century. Erythrocytes, granulocytes, and platelets, which are normally produced in the bone marrow, decrease to dangerously low levels. Blood cell counts determine presentation and prognosis. Anemia leads to fatigue, dyspnea, and cardiac symptoms; thrombocytopenia to bruising and mucosal bleeding; and neutropenia to sharply increased susceptibility to infection.

The incidence of acquired aplastic anemia in Europe and North America is around 2 per million population per year.² The incidence is 2 to 3 times higher in East Asia and in some parts of north India it may be as high as 6.8 per million population. The strong inverse association between incidence of disease and socioeconomic standing in Thailand³ supports an environmental etiology. The age distribution is biphasic with peaks from 10 to 25 years and >60 years. There is no significant difference in incidence between males and females.⁴

CLASSIFICATION OF APLASTIC ANEMIA

The International Agranulocytosis and Aplastic Anemia Study has defined aplastic anemia as hemoglobin ≤ 100 g/dL, platelet count $\leq 50 \times 10^9/L$, granulocytes ≤ 1.5

Table 1: Definition of severity of aplastic anemia

Severe AA (SAA) ⁵	BM cellularity <25%, or 25–50% with <30% residual hemopoietic cells* 2/3 of the following: Neutrophil count $<0.5 \times 10^9/L$ Platelet count $<20 \times 10^9/L$ Reticulocyte count $<20 \times 10^9/L$
Very severe AA (vSAA) ⁶	As for severe AA but neutrophils $<0.2 \times 10^9/L$
Non-severe AA	Patients not fulfilling the criteria for severe or very severe aplastic anemia

*Cellularity should be determined by comparison with normal controls⁷

$\times 10^9/L$, and a bone marrow biopsy demonstrating a decrease in cellularity and the absence of significant fibrosis or neoplastic infiltration. Table 1 summarizes the classification of AA on the basis of Figure 1 severity.

ETIOLOGY OF A PLASTIC ANEMIA

Acquired AA can be classified into “idiopathic” and “secondary”. Secondary AA can be attributed to a definable cause including:

- Drugs and toxins
- Viral infections
- Hepatitis-associated AA, notably seronegative hepatitis
- Immune disorders, e.g. thymoma
- Paroxysmal nocturnal hemoglobinuria.

Seventy to eighty percent of the AA cases are idiopathic.⁸ In a large prospective study by the French Cooperative Group,⁸ the suspected etiology was recorded for 243 cases of AA in children and adults: 74 percent were

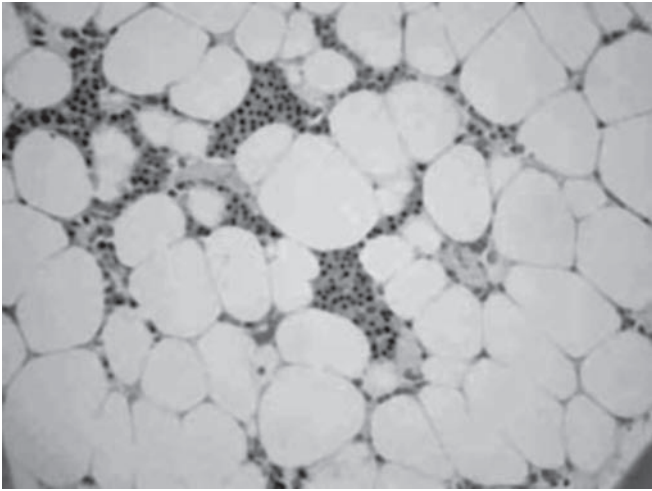


Fig. 1: Bone marrow biopsy specimen from a patient with severe aplastic anemia showing active hematopoiesis in less than 25 percent of the bone marrow space

idiopathic, 13 percent were associated with drugs, 5 percent with hepatitis, 5 percent with toxins, and the rest were categorized as miscellaneous including two cases that were pregnancy related.

Many drugs and chemicals have been implicated in the etiology of aplastic anemia, but for only very few is there reasonable evidence for an association from case control studies, and even then it is usually impossible to prove causality (Table 2). A careful drug history should be obtained, detailing all drug exposures for a period beginning 6 months and ending 1 month prior to presentation.⁹

A number of viruses have been implicated in the development of AA in a small portion of the patients. However, attributing causality to some viral agents may be difficult due to their ubiquitous nature. Implicated viruses include

Ebstein-Barr virus,¹² cytomegalovirus,¹³ human herpesvirus¹⁴ human immunodeficiency virus,¹⁵ parvovirus B,¹⁶ hepatitis A,¹⁷ and B¹⁸ measles, mumps, rubella,¹⁹ varicella, and flaviviruses.²⁰

Hepatitis-associated AA occurs several weeks to several months after the onset of acute hepatitis of variable severity.²¹ Most commonly, the hepatitis is sero-negative for any known hepatitis viruses. Preceding hepatitis is seen in 2 to 5 percent of patients with AA in studies from the West,²² but is much higher in the East, where it was implicated in up to 24 percent of the cases.²³ It appears to be more common in young males. The hepatitis may follow a relatively benign course; however, the aplasia is associated with high mortality if untreated or refractory.

Immunologic disorders are occasionally associated with acquired AA, albeit rarely. AA has been reported in patients with eosinophilic fasciitis,²⁴ thymoma,²⁵ Graves' disease,²⁶ systemic lupus erythematosus,²⁷ rheumatoid arthritis,²⁸ Sjögren syndrome,²⁹ and transfusion-related graft-versus host disease (GVHD).³⁰

Paroxysmal nocturnal hemoglobinuria (PNH) is very uncommon in childhood, particularly before adolescence. It is characterized by episodic hemolysis, thrombosis, AA, and myelodysplastic syndrome (MDS). It is an acquired clonal disorder of hematopoietic stem cells due to an X linked somatic mutation of the PIGA gene.³¹ This results in abnormal biosynthesis of the cell membrane-anchoring phospholipid, glycosylphosphatidyl inositol, and an absence of glycosylphosphatidyl inositol-linked proteins, including the complement regulatory proteins, CD55 and CD59. Approximately 25 percent of adult patients with PNH present with or develop AA, and about 15 percent of adult patients with AA develop PNH in the recovery phase after immunosuppressive therapy (IST).³²

PATHOPHYSIOLOGY

Three main mechanisms have been implicated in the pathophysiology of acquired AA: an "autoimmune attack" on hematopoietic progenitor cells; inherent stem cell defects; and defects of the bone marrow stroma or micro-environment.

Immune Physiology of Aplastic Anemia

Most cases of acquired aplastic anemia can be pathophysiologically characterized as T-cell-mediated, organ-specific destruction of bone marrow hematopoietic cells.³³ In an individual patient, the aberrant immune response can sometimes be linked to a viral infection or to drug or chemical exposure. There is also an overrepresentation of HLA-DR2 in patients with AA as in other autoimmune diseases.³⁴

Stem Cell Defects

Primary hematopoietic stem cell abnormalities have been demonstrated in acquired AA, including reduced numbers

Table 2: Currently licensed drugs which have been reported as a rare association with aplastic anemia. Evidence based on case reports or uncontrolled series¹⁰ or case control studies^{2,3,9}

Antibiotics	Chloramphenicol*, Sulphonamides, Cotrimoxazole, Linezolid
Anti-inflammatory	Gold, Penicillamine, Phenylbutazone, Indomethacin, Diclofenac, Naproxen, Piroxicam, Sulphasalazine
Anti-convulsants	Phenytoin, Carbamazepine
Anti-thyroids	Carbimazole, Thiouracil
Anti-depressants	Dothiepin, Phenothiazines
Anti-diabetics	Chlorpropamide, Tolbutamide
Anti-malarials	Chloroquine
Others	Mebendazole, Thiazides, Allopurinol

*No association with chloramphenicol tablets was observed in recent study from Thailand.² There is no evidence for an association between chloramphenicol eye drops and aplastic anemia.¹¹

of CD34+ cells,³⁵ reduced multipotent and committed colony forming cells. Several investigators have recently reported shortened telomere lengths in peripheral blood leukocytes from patients with AA compared with normal age-matched controls.³⁶ Telomere length improved after successful treatment with IST.³⁶ Like hemoglobin F, this might reflect “stress” hematopoiesis. However, telomere shortening might also be due to telomerase dysfunction.

Defects in Bone Marrow Stroma or Microenvironment

Abnormalities of the marrow stroma have been reported in a small proportion of the patients with AA. Abnormal stromal secretion of hematopoietic growth factors has been found in patients with AA.

DIAGNOSIS OF APLASTIC ANEMIA

The following investigations are required to (i) confirm the diagnosis, (ii) exclude other possible causes of pancytopenia with a hypocellular bone marrow, (iii) exclude inherited aplastic anemia, (iv) screen for an underlying cause of aplastic anemia and (v) document or exclude a co-existing abnormal cytogenetic clone or a PNH clone. See Table 3 for a summary of investigations required for the diagnosis of aplastic anemia.

Full Blood Count, Reticulocyte Count, Blood Film and Percent HbF

The full blood count (FBC) typically shows pancytopenia although usually the lymphocyte count is preserved. Anemia

is usually severe (hemoglobin of about 3 g/dl). In most cases the hemoglobin level, neutrophil and platelet counts are all uniformly depressed, but in the early stages isolated cytopenia, particularly thrombocytopenia, may occur. In about 40 percent of cases erythrocytes are macrocytic. Reticulocytes are usually decreased, but occasionally are inexplicably excessive for the anemia. The first sign of recovery is a rise in reticulocyte count, followed by increase in hemoglobin, then neutrophils, with platelets slowest to recover; if at all.

Marrow

Both a bone marrow aspirate and trephine biopsy are required. Erythropoiesis is reduced or absent, dyserythropoiesis is very common and often marked, so this alone should not be used to make a diagnosis of MDS. Megakaryocytes and granulocytic cells are reduced or absent; dysplastic megakaryocytes and granulocytic cells are not seen in aplastic anemia lymphocytes, macrophages, plasma cells and mast cells appear prominent. Hypoplasia may be patchy, especially early in the disease. Thus, a good quality trephine of at least 2 cm is essential to assess overall cellularity, to assess the morphology of residual hematopoietic cells and to exclude an abnormal infiltrate. Increased blasts are not seen in aplastic anemia, and their presence either indicates a hypocellular MDS or evolution to leukemia.^{37,38}

Other Tests

Other tests include Vitamin B₁₂ and folate levels to exclude megaloblastic anemia which, when severe, can present with pancytopenia, an autoantibody screen as rarely SLE may occur with a hypocellular marrow. Liver function tests should be performed to detect antecedent hepatitis, but in post-hepatitic aplastic anemia the serology is most often negative for all the known hepatitis viruses. Blood should be tested for hepatitis A antibody, hepatitis B surface antigen, hepatitis C antibody and Epstein-Barr virus (EBV). Cytomegalovirus (CMV) and other viral serology should be assessed if BMT is being considered. Human immunodeficiency virus (HIV) is not a recognised cause of aplastic anemia, but it can cause isolated cytopenias. Paroxysmal nocturnal hemoglobinuria should be excluded by performing flow cytometry.³⁹ The Ham test and sucrose lysis test have been abandoned by most centres as diagnostic tests for PNH. Analysis of glycosylphosphatidyl inositol (GPI)-anchored proteins, such as CD55 and CD59 by flow cytometry, is a sensitive and quantitative test for PNH enabling the detection of small PNH clones which occur in up to 50 percent of patients with aplastic anemia, the proportion depending on the sensitivity of the flow cytometric analysis used.⁴⁰

Differential Diagnosis of Pancytopenia and A Hypocellular Bone Marrow

- Hypocellular MDS/acute myeloid leukemia (AML) can sometimes be difficult to distinguish from aplastic

Table 3: Summary of investigations required for the diagnosis of aplastic anemia

1. FBC and reticulocyte count
2. Blood film examination
3. HbF% in children
4. Bone marrow aspirate and trephine biopsy, including cytogenetics
5. Peripheral blood chromosomal breakage analysis to exclude Fanconi anemia
6. Flow cytometry for GPI-anchored proteins
7. Urine hemosiderin if Ham test positive or GPI-anchored protein deficiency
8. Vitamin B₁₂ and folate
9. Liver function tests
10. Viral studies: Hepatitis A, B and C, EBV, HIV (CMV, 5)
11. Anti-nuclear antibody and anti-dsDNA
12. Chest X-ray
13. Abdominal ultrasound scan and echocardiogram
14. Peripheral blood gene mutation analysis for dyskeratosis congenital DKC1, TERC-TERT) if clinical features or lack of response to immunosuppressive therapy

anaemia. The following features of MDS are not found in aplastic anemia: dysplastic cells of the granulocytic and megakaryocytic lineages, blasts in the blood or marrow.

- Hypocellular acute lymphoblastic leukemia (ALL) occurs in 1 to 2 percent of cases of childhood ALL. Overt ALL usually develops within 3 to 9 months of the apparent bone marrow failure.
- Hairy cell leukemia classically presents with pancytopenia but the accompanying monocytopenia is a constant feature of this disorder.
- Lymphomas, either Hodgkin lymphoma or non-Hodgkin lymphoma and myelofibrosis may sometimes present with pancytopenia and a hypocellular bone marrow.
- Mycobacterial infections can sometimes present with pancytopenia and a hypocellular bone marrow, this is seen more commonly with atypical mycobacteria.

MANAGEMENT OF APLASTIC ANEMIA

Supportive Care

Supportive modalities include chronic transfusion programs that treat and prevent major bleeding episodes and maintain hemoglobin, and antibiotics to treat infections. The provision of phenotypically matched red blood cell transfusions and single-donor platelet units would reduce alloimmunization, particularly for the chronically transfused patients. Donation of blood products from members of the patient's family is not advisable, as HSCT using related donors might be warranted in the future. CMV-negative recipients should receive CMV-negative blood products wherever possible. Filtration and irradiation of all blood products is recommended.

Maintaining hemoglobin with transfusion of red blood cells allows for normal activities. Children better tolerate a greater degree of anemia than adults and can generally handle transfusion thresholds of between 60 and 70 g/L. Platelet transfusion support to treat and prevent life-threatening bleeding has probably resulted in the largest impact on the survival of patients with SAA. It has changed the leading cause of death from bleeding to infections. Reducing the transfusion threshold to $10 \times 10^9/\text{L}$ in a stable patient has been found to be safe.⁴¹ Other measures to prevent bleeding include avoidance of antiplatelet agents (e.g. NSAIDs) and avoidance of trauma.

The risk of serious bacterial and fungal infections correlates with the neutrophil count and duration of severe neutropenia. This risk is exacerbated during immunosuppressive therapy (IST) or hematopoietic stem cell transplantation (HSCT). Prophylaxis for *Pneumocystis carinii* and fungal infections should be considered during IST. Neutropenic patients with fever should be treated aggressively with broad-spectrum antibiotics and with antifungal agents when clinically appropriate. Ceftazidime with

Aminoglycoside is the usual antibiotic regimen and systemic antifungal therapy should be introduced into the febrile neutropenia regimen early if fevers persist.

Hemopoietic Growth Factors

The routine use of rHuEpo (recombinant Erythropoietin) in aplastic anemia is not recommended as there may be severe and or sudden worsening of anemia due to red cell aplasia from anti-rHuEpo antibodies.⁴² A short course of G-CSF may be considered for severe systemic infection that is not responding to intravenous antibiotics and anti-fungal drugs, but should be discontinued after 1 week if there is no increase in the neutrophil count.

Definitive Therapy

The following options are available:

- A. Hematopoietic stem cell transplantation
- B. Immuno-modulation
 - Anti-thymocyte globulin (ATG)
 - Cyclosporine-A (CA)
 - High dose corticosteroids
- C. Androgens

Hematopoietic Stem Cell Transplantation (HSCT)

Matched Sibling Donor HSCT

The first successful HSCT in a patient with SAA was reported in 1970.⁴³ During the 1970s, HSCT was established as the best therapy for AA. For children and young adults afflicted with SAA, early HSCT from an HLA-matched sibling donor is widely considered as the gold standard of care. Matched unrelated donor (MUD) BMT may be considered when a patient has severe aplastic anemia, has no matched sibling donor but a matched unrelated donor, is <50 years old (or 50–60 years old with good performance status), and has failed at least one course of ATG and cyclosporine.

Immunosuppressive Therapy

Immunosuppressive therapy is recommended for: (i) patients with non-severe aplastic anemia who are transfusion dependent, (ii) patients with severe or verysevere disease who are >40 years old and (iii) younger patients with severe or very severe disease who do not have an HLA-identical sibling donor. The standard immunosuppressive regimen is a combination of antithymocyte globulin (ATG) and cyclosporine. ATG must only be given as an in-patient. Cyclosporine should be continued for at least 12 months after achieving maximal hematological response, followed by a very slow tapering, to reduce the risk of relapse.

Equine ATG (e.g. Atgam; Pharmacia and Upjohn, Milton Keynes, UK) is more commonly used, and is

usually administered at 100 to 160 mg/kg, in divided doses over 4 to 10 days. Rabbit ATG (e.g. Thymoglobuline; Intix-Sangstat, Lyon, France) has also been shown to be effective, at doses of 2.5 to 3.5 mg/kg daily for 4 to 5 days.⁴⁴ Acute allergic reactions are common. Immune complex-mediated serum sickness typically manifests 10 to 14 days after initiation of therapy. These adverse effects have largely been ameliorated by the concurrent administration of prednisone, usually at 1 to 2 mg/kg/day, and premedication with antihistamines and acetaminophen (paracetamol). Cyclosporine is administered at 6 mg/kg per dose twice daily to maintain blood levels of 150 to 200 µg/L.

Patients who failed to respond to the initial course of ATG treatment still have a substantial chance of response to repeated courses, using ATG from the same or an alternative animal source.

Androgens and Growth Factors

Androgens have no role as a single treatment agent for SAA, unless other modalities are unavailable. Androgen treatment can induce remission in 38 percent of children with non severe AA.

High Dose Corticosteroids

Popular in Europe and probably effective in patients treated within few weeks of diagnosis, this therapy is reserved for occasional patients due to tremendous toxicity. The dose of methylprednisolone is 100 mg/kg for a week tapered over a month. We use it only for the patients, who cannot afford ATG/ALG.

Other Immunosuppressive Agents

High dose cyclophosphamide and Mycophenolate mofetil are other agents which have been evaluated in the management of AA but have not been found to be useful. High dose cyclophosphamide without stem cell support was associated with prolonged neutropenia and high mortality. Alemtuzumab (Campath-1H) is currently under evaluation for the treatment of refractory aplastic anemia in prospective trials at NIH in USA, and retrospectively by the EBMT, following reports of its efficacy in patients with autoimmune cytopenias, particularly autoimmune neutropenia.⁴⁵

Response to Therapy

Response to therapy should be confirmed by two or more blood counts at least 4 weeks apart, and should ideally be measured in patients who are not receiving hemopoietic growth factors. The criteria for response to immunosuppressive therapy are summarized in Table 4.

Table 4: Criteria for response to immunosuppressive therapy in AA

<i>a. Response criteria for severe aplastic anemia</i>	
None	Still severe
Partial	Transfusion independent No longer meeting criteria for severe disease
Complete	Hemoglobin normal for age Neutrophil count $>1.5 \times 10^9/l$ Platelet count $>150 \times 10^9/l$
<i>b. Response criteria for non-severe aplastic anemia</i>	
None	Worse or not meeting criteria below
Partial	Transfusion independence (if previously dependent) or doubling or normalization of at least one cell line or increase of baseline hemoglobin of >30 g/l (if initially <6) or increase of baseline neutrophils of $>0.5 \times 10^9/l$ (if initially <0.5) or increase of baseline platelets of $>20 \times 10^9/l$ (if initially <20)
Complete	Same criteria as for severe disease

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Immune Thrombocytopenic Purpura: Treatment Guidelines

Raj Warriar, Aman Chauhan

INTRODUCTION

All pediatricians come across cases of immune thrombocytopenia especially in these days of coulter counters and automated platelet counts. Immune thrombocytopenia (ITP) was called idiopathic thrombocytopenia until recently when the pathophysiology of the disease was unraveled by several elegant clinical and basic research studies.

ITP follows a benign course in most children but has the potential to be life threatening. Risk of intracranial bleeding, soft tissue and mucosal bleeding secondary to trauma can cause morbidity and mortality. Lack of evidence based management protocol¹ is a potential cause for poor management of ITP. ITP is reported approximately in 5 per 100,000 children and 2 per 100,000 adults.² We would like to discuss in brief about the various presentations of an ITP case and more importantly the management guidelines.

PATHOPHYSIOLOGY

At present our understanding of pathophysiology of ITP leads us to two main mechanisms. It is either immune mediated increased destruction of platelets or decreased production of platelets which results in overall decrease in circulating platelet number.

Dr Harrington was the first person who highlighted the role of immunity in destruction of platelets in ITP patients. In an unusual experiment he injected himself and other test subjects with blood from ITP patients and to his and everybody's surprise he found that there was a rapid decline in circulating platelet quantities of the test subjects.³ It was this experiment which gave birth to hypothesis of antiplatelet factor, which was later confirmed to be an antibody against platelets.⁴ B and T cells are an integral part of the cascade involved in platelet

destruction. Antiplatelet antibodies opsonize the platelets and then are attached to antigen presenting cells with the help of Fcγ receptors. Opsonized platelets are finally phagocytosed by the macrophages. T cells at the same time stimulate B cells to produce more antiplatelet antibody and new research shows that some cryptic epitopes from platelet antigens stimulate platelet specific T cells.⁵

Reduced platelet production is another important mechanism which explains pathophysiology of ITP in some of the patients. Recent discovery of thrombopoietin (TPO) and its role in thrombopoiesis helped us understand role of reduced thrombopoiesis in ITP. Increase in platelet quantity after administering TPO mimetics in some study populations consolidated the fact that TPO has a definitive role in ITP.⁶

Most of the cases of ITP are self limiting and require no treatment. Commonly the event responsible for antiplatelet antibody production is a viral illness. At present most of the treatment protocols are concentrating on reduction of platelet destruction and for this the drugs used are usually immunosuppressives. This might change in near future if the TPO mimetic prove to be safe and effective in various trials which are currently in progress. Nevertheless splenectomy is regarded treatment of last resort due to morbidity and mortality associated with the procedure.

CLINICAL PRESENTATION AND DIAGNOSIS

The spectrum of disease fluctuates from asymptomatic state to dreaded intracranial hemorrhage (Fig. 1). Inter-continental childhood ITP study group (ICIS) found the mean age of presentation of ITP in cohort of children to be 5.7 years.⁷ Boys especially below 10 years are found to have higher incidence of ITP⁸⁻¹⁰. Physical examination is mostly positive for cutaneous manifestations such as petechiae and bruising. One fourth of children present

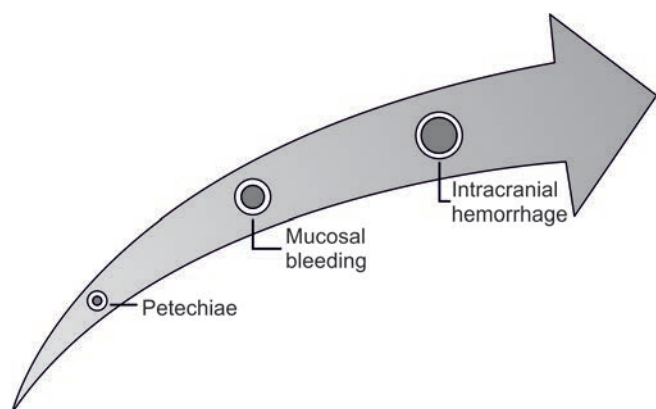


Fig. 1: Clinical manifestations in increasing order of severity

with epistaxis though hematuria is less frequent¹¹. Other rare atypical findings may include lymphadenopathy and hepatosplenomegaly.^{11,12}

Clinical impression of ITP is confirmed by finding of thrombocytopenia in blood smear. More than 50 percent of acute ITP cases present with platelet count less than $20 \times 10^9/L$. Chronic ITP is defined as platelet count less than $150 \times 10^9/L$ for more than 6 months after the diagnosis.¹³ Presence of mild eosinophilia is a common finding along with few megathrombocytes.

PERIPHERAL SMEAR

Bone marrow examination is not routinely performed in children unless their are atypical; clinical or lab findings. General pediatrician often get a marrow done and interpreted by pathologists to rule out the possibility of acute leukemia which may go into a temporary remission on steroids with disastrous consequences. Retic count, ESR, ANA, blood group, coombs, EBV may be needed in selected cases based on associated symptoms. Close and continued monitoring of the clinical status and hematological picture is the most important step in the management of ITP.

Differential Diagnosis

Primary ITP is a diagnosis of exclusion. It can be satisfactorily diagnosed by carefully ruling out causes of pseudothrombocytopenia, secondary ITP and inherited ITP. An accurate history combined with a complete blood count and a thorough evaluation of the smear is the first and most important step according to this old fashioned hematologist. Acute onset of bruising and petechiae in an otherwise healthy child often with a recent history of viral infection associated with isolated thrombocytopenia and large platelets in the smear is suggestive of acute ITP. Prolonged fever, weight loss, bone pain, significant lymphadenopathy and organomegaly, etc. are unusual and warrants careful

exam to rule out leukemia, aplastic anemia or other more serious illnesses.

Pseudothrombocytopenia is the result of clumping of platelets in the presence of ethylenediaminetetraacetic acid (EDTA) anticoagulant. It is essential that a smear be evaluated to rule out a false count and for morphology of RBC's, WBC's and platelets themselves. Isolated thrombocytopenia with normal RBC morphology and absence of any immature WBC series and larger than usual platelets fits the classic description of ITP.¹⁴ Abnormalities in RBCs or WBC series are unusual in the "garden variety" ITP in children. Other common causes of secondary thrombocytopenia can be ruled out by investigating for EBV, SLE, Hep C, HIV based on history and clinical exam findings.¹³ Detailed family history is essential to rule out inherited causes of thrombocytopenias like Wiskott-Aldrich syndrome. The inherited thrombocytopenias are classified on the basis of platelet size and gene mutations.¹⁵ Other miscellaneous conditions to be kept in mind are thrombocytopenia secondary to drugs, infections (like HIV, EBV, and CMV, etc.), preeclampsia, HELLP syndrome, DIC, large hemangiomas, aplastic anemia, metabolic disorders and marrow infiltration.

Treatment

A sound understanding of pathophysiology is the backbone of management of ITP. Rapid strides in pharmacotherapy have added to the preexisting predicament of when to treat and how to treat? This section would highlight commonly used treatment protocols with special emphasis on Indian scenario along with newer drugs and alternative therapies. It is essential to clearly understand that there is no study that has shown that any specific treatment regimen decreases mortality or alters the risk of the disease process from becoming chronic. Personalization of treatment based on platelet count, age, clinical picture, duration, lifestyle issues, economic consideration and parental, patient and may be doctor anxiety is the need of the hour. Any standard treatment protocol especially in Indian scenario for all ITPs would be a step backward.

Treatment of ITP can be divided into medical and surgical management. Medical management is further divided into first line and second line pharmacotherapy. Supportive therapy by a team experienced in the variable course and outcome of ITP is crucial. Education of the patient, teachers, siblings, parent and primary care physician is of need for close monitoring for any acute bleed especially intracranial or intra-abdominal can significantly decrease mortality and morbidity. The child and family also require psychosocial support, trauma prevention advice including nonparticipation in contact sports.

Medical options for front line drug therapy are corticosteroids, IV Ig and IV Rh Anti-D.

CORTICOSTEROIDS

Sartorius in 1984 was the first one to report benefit of prednisolone in ITP.¹⁶ Another study by Buchanan and Holtkamp in the same year reaffirmed that prednisolone boosts platelet counts by day 7th of the treatment.¹⁷ There is a well established consensus regarding initial benefit from oral prednisolone. Corticosteroids act by impairing the clearance of opsonized platelets in bone marrow and peripheral organs. It also reduces autoantibody levels in the body.¹⁸ Many prospective, randomized studies confirm that corticosteroids increase the platelet levels more rapidly than no treatment.¹⁹ High dose prednisone at approximately 4 mg/kg per day for 4 days or the shortest period possible can minimize the side effects as well as maintain the therapeutic significance in treatment of ITP.²⁰⁻²⁴ The duration of treatment and dose of drug is determined by the response and side effects. Some of the common complications associated with corticosteroid treatment are avascular necrosis, diabetes, gastritis, ulcers, growth retardation, hypertension, insomnia, osteoporosis (adults), personality changes, risk of opportunistic infections, etc. It is important to taper down the dose and terminate the drug on either stoppage of bleeding or on achieving a platelet count higher than $20 \times 10^9/L$. There are many doctors who stop the treatment after 2 to 3 weeks irrespective of the response.

INTRAVENOUS IMMUNOGLOBULIN G

Imbach et al were the first one to propose the role of IV immunoglobulin G in reversal of thrombocytopenia.²⁵ IV Ig G acts by impairing the clearance of opsonized platelets¹⁸ probably mediated through Fc γ RIIb receptor.²⁶ Some studies also suggest that IV Ig G might cause increased clearance of antiplatelet antibodies via saturation of the FcRn salvage receptor for IgG.²⁷ Our present knowledge of IV immunoglobulin G is mostly contributed by two Canadian clinical trials.^{28,29} These studies concluded that IV Ig G had a faster response rate as compared to corticosteroids when the target platelet count was $50 \times 10^9/L$, also single dose IV Ig G 0.8 g/kg was as effective and safer than larger dose of 1g/kg for 2 days. IV Ig G was also found better than IV Anti-D to achieve the platelet count of $20 \times 10^9/L$. IV Ig G although more expensive is definitely one of the safer options available and may shorten the length of the hospital stay due to the rapid response usually within 24 to 48 hours. Some of the common infusion related side effects are headache, fever, chills and nausea. Other worrisome but rare side effects include aseptic meningitis, renal impairment or failure and thromboembolic events.

INTRAVENOUS ANTI-D

Salama et al in 1983 reported increase in platelet counts in ITP patients who were also positive for rhesus D antigen

after infusion of IV Anti-D.³⁰ Current wisdom favors the notion that IV Anti-D coats the RBC which are positive for D antigen, these opsonized RBC in turn competes with opsonized platelets in spleen for sequestration.³¹ Recent reports suggest that dose of 75 $\mu\text{g/kg}$ over 3 to 5 minutes is more efficacious than 50- $\mu\text{g/kg}$ dose though the side effects are more common with higher dose. Some of the commonly encountered infusion related side effects are fever, chills, nausea and headache. Another important adverse effect is fall in hemoglobin secondary to hemolysis, usually the fall in hemoglobin is not more than 2g/dl^{32,33} but rarely hemolysis can be severe and can lead to renal failure and DIC.^{34,35}

Second-Line Pharmacotherapy

Second-line pharmacotherapy comprises of mainly immunosuppressants and rituximab. These drugs come into role when first-line of drugs have failed or have become intolerant. Immunosuppressants primarily act at level of T cells. Azathioprine, cyclophosphamide and cyclosporine are the main drugs in use. Dapsone, MMF, danazol, vinca alkaloids, etc. are few other second-line drugs with unproven efficacy and these agents are used rarely in children at physician's own discretion.

RITUXIMAB

Rituximab is a monoclonal antibody used in treatment of lymphoma. It acts by reducing the number of B cells which produce auto antibodies. Rituximab is a human murine monoclonal antibody against CD 20 antigen on B lymphocytes. Results of a systemic review conducted by Arnold et al³⁶ from 19 studies were promising and instill a hope in use of rituximab. Severe side effects after rituximab therapy are fortunately rare but there is potential of neutropenia and reactivation of chronic infections like tuberculosis. Presently, rituximab seems to be the most promising drug for treatment of refractory ITP. The response to rituximab was complete and most frequently used dose was 375 mg/m² for 4 weeks. Recent studies suggest a superior response rate if dexamethasone is given with rituximab also there is evidence in favor of rituximab being used before resorting to splenectomy in a refractory case of ITP.³⁷

DAPSONE (Diphenyl sulfone, Avlosulfon, DDS)

Recently some studies have reported reversal of thrombocytopenia in 40 to 50 percent of patients taking dapsone. The dose recommended is 25 mg to 100 mg per day and it takes about a month for response to be noticed. The effect of drug is expected to stay for few months before relapse occurs, which demands continuation of therapy again. Few people believe that dapsone in addition to prednisolone should be recommended for those patients who require low dose steroids for maintenance of high platelet count.

SURGICAL MANAGEMENT

Splenectomy is not a favored option for treating ITP in children and this is reflected in various guidelines which prefer medical treatment over surgical management. Few indications which justify splenectomy are severe menorrhagia, life threatening hemorrhage and relentless life style limitation. A major factor which deters most of the physicians to take surgical route is risk of developing overwhelming postsplenectomy sepsis and life time risk of sepsis from encapsulated organisms. Despite all odds if decision is made in favor of performing splenectomy, a laparoscopic approach is preferred and effort is made to identify and remove accessory spleen at the time of surgery. It is also important to immunize the child with *Haemophilus influenzae* type B, pneumococcal and meningococcal vaccines. Some physicians recommend prophylactic penicillin up to 5 years of age (or even later ages) as vaccines do not immunize against all pneumococcal serotypes. Education of the patient, parent, primary care MD and emergency room MDs about the risk of sepsis is also essential.

Acute ITP in children spontaneously resolves irrespective of any treatment in 80 percent of cases. Of the 20 percent that are truly chronic 80 percent get remission following splenectomy but a few will relapse over a period of years. The explanation given for relapse is that patients with significant antibodies will have the liver or other macrophages continue to destroy sensitized platelets and that the defective production is unable to compensate for the sustained destruction. Adolescents and older patients are more likely to be chronic and it is important to look for antibody mediated destruction due to collagen vascular diseases and or bone marrow failure syndromes in adults.

TREATMENT SELECTION

The factors which influence the selection of treatment regimen in a given patient are quality-of-life impact, adverse events, likelihood of response, bleeding risk, patient/parent anxiety and economic issues. It is very important to take a detailed clinical history and perform a thorough physical exam. Clinical history has important implications not only in diagnosing the disease but also in deciding the treatment regime. Based on clinical history patients can be subclassified into following groups:

- Emergent
- Acute responsive
- Acute refractory
- Chronic persistent
- Chronic refractory.

Treatment of Emergent Disease

The goal of treatment here is immediate cessation of bleeding. This can be achieved by either platelet directed interventions or ancillary interventions. Platelet directed interventions rely on IV corticosteroids, IV Ig G, IV Rh Ig, combination therapy and platelet infusion. Platelet

infusions by themselves are not of any use due to immediate antibody mediated destruction. Ancillary interventional options include cessation of antiplatelet agents, antifibrinolytic therapy and use of recombinant factor VIIa. Emergency splenectomy under cover of medical therapy may be very rarely indicated in extreme cases.

Management of Acute ITP (Table 1) (Figs 2 and 3)

Whether to treat or not to treat is the most important and perhaps the most difficult question faced by a pediatric hematologist. Many believe in observation alone while others consider early initiation of therapy. Those who believe in observation, justify their judgment since severe hemorrhage is rare and drug therapy may not prevent severe hemorrhage. It may add to the financial burden and expose the child to severe drug associated side effects. Proponents of early initiation of therapy argue that platelet count certainly increases faster than without treatment thus decreasing the likelihood of severe bleeding. Quality of life issues may be less with the quicker and better maintained response following drug treatment.

Table 1: American Society of Hematology 2011 Guidelines³⁸

Bone marrow exam is not required for initial workup of a typical ITP patient and in IV Ig treatment failure.

No treatment required for minor bleeds (Petechiae/ bruise) irrespective of platelet count.

Corticosteroids are preferred first line treatment, IV Ig reserved for fast platelet response if required, anti-D contraindicated if patient has anemia secondary to blood loss or autoimmune RBC destruction.

Rituximab and high dose dexamethasone if failed first line treatment (Corticosteroids, IV Ig and anti-D) or inadequate response to splenectomy.

Splenectomy if failed first line treatment.

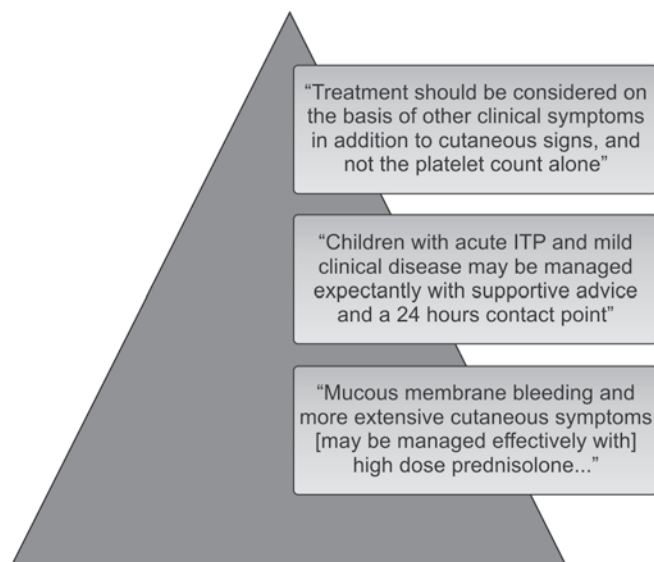


Fig. 2: British guidelines (2003) British committee for standards in Haematology general haematology task force. Br J Haematol 2003; 120:574-96

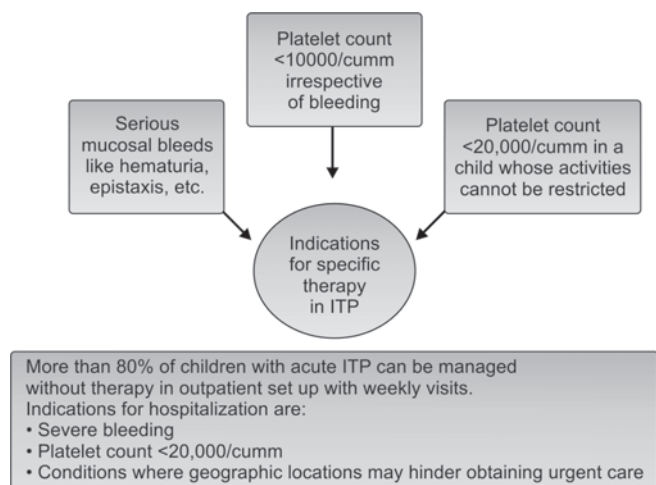


Fig. 3: Indian Association of Pediatrician Guidelines 2006 on management of ITP in children

Treatment of Chronic ITP

Chronic ITP includes all patients who have platelet count less than $150 \times 10^9/l$ persisting for more than 6 months from the time of diagnosis. Currently there is no universally effective regimen. These are the patients where second-line pharmacotherapy can be considered as a serious option. Treatment may be withheld in many cases if the platelet counts are maintained above 20,000 without any bleeding symptoms. Azathioprine \pm prednisone, vincristine or vinblastine, cyclophosphamide, cyclosporin, dapsone and combination chemotherapy are few treatment options for chronic ITP. These patients are also suitable candidates for splenectomy as discussed before. A conservative approach is still the first-line of choice with observation alone or combination of drugs used as when indicated. Any plans for use of immunosuppression or splenectomy in a child with chronic ITP should be carefully reviewed with experienced pediatric hematologists and then discussed at length with parents and the child.

Thrombopoietin (TPO) Mimetics and ITP

Gernsheimer in late 80's reported reduced platelet production in ITP patients and subsequent studies in both animals and human subjects confirmed that the phenomenon of ineffective thrombopoiesis was real and was largely due to the effect of antiplatelet antibodies on megakaryocytic apoptosis. Decreased platelet production is now considered to play a significant role especially in refractory chronic ITP patients and opens up a new avenue to try novel therapies like TPO receptor agonists. TPO receptor agonists have been shown to produce a statistically significant positive short term platelet response compared to placebo in many studies. TPO receptor agonists have also been found to be effective in reduction in WHO Grade

1 to 4 bleeding events. Evaluation of clinical response for life threatening or severe bleeding has not shown a statistically significant reduction as compared to placebo. The cochrane data base in their review (July 2011) of 6 RCTS with 808 patients concluded that there was no evidence to demonstrate that bleeding events are significantly improved. They also concluded that effect on overall survival needs further studies.

Six weeks and six months trials have shown that it is more effective than placebo in increasing platelet counts and decreasing bleeding episodes. Long term data (median duration of 100 weeks) supports the above conclusion. Splenectomy did not affect the response.

Review of literature suggests that it is a viable option in chronic, refractory adult patients with immune mediated thrombocytopenia who have failed standard therapy possibly including splenectomy. It may be worthwhile doing a well conducted multicenter trial looking at the role of using TPO mimetics earlier in the course or as part of a multiagent protocol even before splenectomy. There is minimal data regarding long term safety with the use of TPO. Small studies in Europe and USA have shown that it is safe and efficient in raising platelet counts and decreasing the risk of bleeding. Short term use of TPO receptor agonists is considered safe, especially in comparison to long term use of immunomodulatory agents and the side effects especially risk of infections, hypertension, etc. Dr George Buchanan from Dallas, Texas and a pioneer in the field of ITP in children has commented that there may be a role for TPO mimetics even in cases not considered chronic. An example would be a child with low platelets not responding to IV Ig G or steroids and having acute bleeding episodes. This may be an indication for a course of TPO mimetics (e.g. eltrombopag) while waiting for the ITP to resolve. The lack of long term toxicity data, cost and some limitations on oral use with respect to diet and timing of oral medications also need to be considered before wide spread use of this agent in children. The very low incidence of intracranial hemorrhage and other major complications make it very difficult to study valid endpoints in ITP treatment options in children. Limitations related to timing of oral intake and dietary interactions could hamper wide spread use of the drug in children. Pediatric hematologists loath splenectomy and only use it only as a last resort if IV Ig G, steroids, Win; Rho and Rituxan as well as "father time" have all failed to increase platelet counts to a level compatible with the patient's life style. Refractory ITP may need to be treated by combination therapy targeting increased destruction combining efforts to increase production. It would certainly be an option to consider TPO mimetic prior to splenectomy or prolonged heavy immunosuppression. The option of using it to obtain a short term reprieve from acute significant bleeding while waiting for response from other drugs or self resolution even in "nonchronic" cases is worth

looking into side effects seem to be minimal and mostly related to hepatobiliary system.

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Disseminated Intravascular Coagulation

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INTRODUCTION

Although the first clinical observations on disseminated intravascular coagulation (DIC) were reported in the 19th century, this condition of widespread and disordered coagulation has probably afflicted mankind for as long as trauma and infection have beset us¹. Disseminated intravascular coagulation (DIC) is an acquired syndrome characterized by hemorrhage and microvascular thrombosis. It is a complex pathophysiological disorder which is characterized by activation of coagulation pathways which leads to organ failure and consumption of platelets and coagulation factors leading to clinical bleeding. Patients with DIC could present with bleeding or thrombosis induced organ failure depending on which point of time in the disease spectrum they present to the clinician. Since there is no single laboratory test to rule out or establish DIC scoring systems have been evolved. The International Society of Thrombosis and Hemostasis (ISTH) standardization subcommittee has therefore, proposed working definitions to facilitate earlier detection and treatment.² Several advances have been made over time in the management of this disease but the cardinal rule remains to treat the underlying disorder.

PATHOGENESIS

Pathogenesis is primarily due to an uncontrolled and excessive production of thrombin as shown in Flow chart 1.

Activation of Hemostasis

This begins with exposure of blood to procoagulants, primarily mediated by the extrinsic pathway involving tissue factor (TF) and Factor VII ultimately leading to thrombus formation. When the antithrombotic mechanisms are overwhelmed by the markedly increased production of thrombin, thrombin may circulate and lead to DIC. The

fine homeostatic balance of controlled thrombin production is lost in DIC. The widespread deposition of fibrin results in tissue ischemia and consumption of platelets, fibrinogen, prothrombin, Factor V, Factor VIII, which leads to bleeding.

Secondary Fibrinolysis

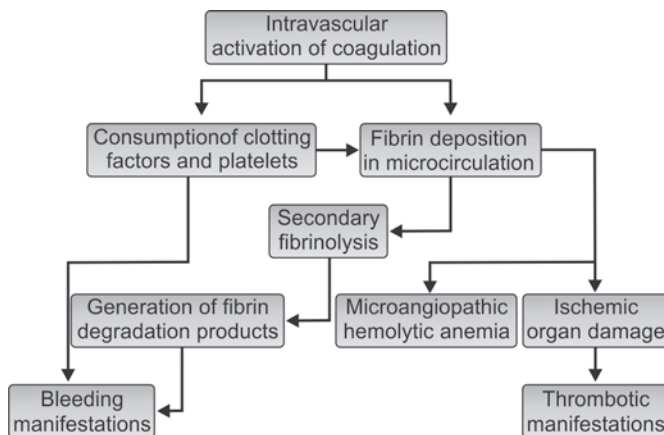
The release of tissue plasminogen activator with subsequent generation of plasmin from plasminogen produces a secondary fibrinolysis and the release of fibrinogen degradation products (FDPs). When there is widespread systemic fibrin deposition as in DIC these byproducts may interfere with normal fibrin polymerization and enhance bleeding and also bind to platelet surface glycoproteins IIb/IIIa receptor interfering with platelet aggregation. Excessive plasmin leads to proteolytic degradation of fibrinogen and other clotting factors causing consumption coagulopathy.

ETIOLOGY

The most common causes of DIC in older infants and children include sepsis, trauma and malignancies. The common causes in newborns include sepsis and perinatal complications. Other causes include acute hemolytic transfusion reaction, Kasabach-Merritt syndrome, snake bites and liver disease. The common etiologies are listed in Table 1.

CLINICAL PRESENTATION

The perturbed coagulation of DIC can manifest clinically at any point in the spectrum from bleeding to thrombosis. Hemorrhage is the most common presentation followed by the skin manifestations of purpura and acral gangrene. In mild cases, bleeding may be seen at venipuncture sites. Purpura fulminans is a potentially life-threatening

Flow chart 1: Pathophysiology of disseminated intravascular coagulation**Table 1:** Causes of disseminated intravascular coagulation

<i>Infection</i>	Meningococcus, gram-positive and negative bacterial sepsis, human immunodeficiency virus, varicella-zoster, cytomegalovirus (CMV), dengue fever, malaria
<i>Injury</i>	Brain injury, crush injury, massive burns, extensive surgery
<i>Malignancy</i>	Acute promyelocytic leukemia, acute lymphoblastic leukemia
<i>Microangiopathic disorders</i>	Giant hemangioma—Kasabach-Merritt syndrome
<i>Gastrointestinal disease</i>	Acute and chronic liver disease, Reye's syndrome
<i>Neonatal causes</i>	Birth asphyxia, respiratory distress syndrome, meconium aspiration, amniotic fluid aspiration, necrotizing enterocolitis, congenital infections—Neonatal CMV, herpes simplex virus, bacterial or fungal infections
<i>Congenital thrombotic disorders</i>	Homozygous deficiencies of proteins C and S, antithrombin III deficiency

disorder seen in newborns with homozygous protein C or S deficiency occurring 7 to 10 days after a benign skin infection or gram-negative septicemia.³

Acute DIC develops when blood is exposed to large amounts of tissue factor over a brief period of time, with massive generation of thrombin, resulting in the acute triggering of coagulation. This overwhelms control mechanisms, and compensatory mechanisms do not have sufficient time to recover. Compensated or chronic DIC develops when blood is continuously or intermittently exposed to small amounts of tissue factor and compensatory

Table 2: Acute vs chronic DIC

<i>Parameter</i>	<i>Acute</i>	<i>Chronic</i>
Platelet counts	↓	Variable
PT	↑	N
aPTT	↑	N
TT	↑	N
Fibrinogen	↓	N-↑
FV	↓	N
FVIII	↓	N
FDP	↑	↑
D-dimer	↑	↑

mechanisms in the liver and bone marrow are largely able to replenish the depleted coagulation proteins and platelets. The laboratory findings used to confirm DIC are different in acute and chronic disease as shown in Table 2.

DIAGNOSIS

In patients with DIC a variety of abnormal coagulation parameters may be detectable, such as thrombocytopenia, prolonged coagulation times, reduced levels of coagulation inhibitors or high levels of fibrin split products. There is not a single test that is accurate to establish or reject a diagnosis of DIC. A combination of widely available tests and recently developed diagnostic algorithms can be helpful in selecting the group of DIC patients which require specific interventions.

DIC is an extremely dynamic situation and the tests are a snapshot of this dynamic state. An analysis of five reports of patients groups with DIC, with a total of 900 patients suggest that the laboratory abnormalities reported, in decreasing order of frequency are, thrombocytopenia, elevated fibrin degradation products, prolonged PT prolonged aPTT and a low fibrinogen.⁴⁻⁸

Platelet Count

Thrombocytopenia or a downward trend of platelet count is a sensitive but not specific indicator of DIC. Thrombocytopenia is a feature in up to 98 percent of patients with DIC with a platelet count of $<50 \times 10^9/L$ in about 50 percent.⁷ Thrombocytopenia correlates strongly with increased thrombin generation. It is the most sensitive indicator in DIC. A continuous drop even within a normal range indicates active generation of thrombin.⁹

PT and aPTT

The PT or aPTT is prolonged in about 50 to 60 percent of cases of DIC at some point during the course of illness.¹⁰ This is mainly due to the consumption of coagulation factors but can also be attributed to impaired synthesis or loss of coagulation proteins due to massive bleeding.

In about 50 percent of patients the PT, aPTT are normal due to the presence of circulating activated clotting factors. To be noted is that INR is not to be monitored as it is only used for oral anticoagulant monitoring.⁹

Fibrin Related Markers

Fibrinolytic activity can be measured as FDP by specific enzyme linked immunosorbent assay (ELISA) or by latex agglutinations assays. It is important to remember that many other conditions such as trauma, recent surgery and venous thromboembolism are associated with elevated FDPs including D-dimer. FDPs are metabolized by liver and secreted by kidneys, liver and kidney impairment can influence levels.⁹

Soluble fibrin monomers (SF) measurement offers theoretical advantage in DIC in reflecting thrombin action on fibrinogen. Most studies have shown 90 to 100 percent sensitivity for diagnosis of DIC but low specificity.¹¹ A major problem is of quantitation.

Fibrinogen

Measurement of fibrinogen is not very helpful in the diagnosis of DIC fibrinogen acts as an acute phase reactant and can remain well within the normal range for a long time. In a consecutive series of patients the sensitivity of a low fibrinogen level for the diagnosis of DIC was only 28 percent and hypofibrinogenemia was detected in very severe cases of DIC only.¹²

Natural Inhibitors of Coagulation

The natural anticoagulants such as antithrombin III or protein C are reduced in about 90 percent of all DIC patients. Plasma levels of antithrombin have been shown to be potent predictors for survival in patients with sepsis and DIC. Antithrombin levels are markedly decreased not only due to consumption but also impaired synthesis and degradation by elastase from activated neutrophils.¹³ Levels of protein C may also indicate the severity in DIC. In physiologic conditions protein C is activated by thrombin bound to endothelial cell membrane associated thrombomodulin. This binding results in about a 100 fold increase in activation of protein C and also blocks the thrombin mediated conversion of fibrinogen to fibrin. During severe inflammation and DIC the protein C system is defective due to downregulation of thrombomodulin. Nonetheless the general availability of these tests is limited and single determinations are neither sensitive nor specific for DIC.

Blood Film

Fragmented RBCs do not constitute >10 percent cells in DIC. Though they are not sensitive or specific for DIC, in some cases of chronic DIC with normal coagulation studies they may prove to be useful.⁹

Point of Care Tests

Thromboelastography (TEG) is a method that provides an overall picture of *ex vivo* coagulation. The theoretical advantage of TEG over conventional coagulation assays is that they provide an idea of platelet function as well as fibrinolytic activity. The diagnostic sensitivity and specificity is unclear.¹³ A new method that has proved sensitive and specific for hypercoagulability is the partial thromboplastin time biphasic waveform analysis. This test detects the presence of precipitates of very low density lipoprotein and C- reactive protein that appears very early in DIC.¹⁴

Scoring System

The ISTH has developed a five step diagnostic algorithm to calculate the DIC score using simple laboratory tests that are available in most hospital laboratories. The presence of an underlying disorder known to be associated with DIC is a prerequisite for the algorithm.⁹ The ISTH overt DIC score has shown to be sensitive of infective and noninfective etiologies.¹⁵ Bakhtiari et al found the sensitivity of the ISTH overt DIC score to be about 91 percent with a specificity of 97 percent.¹⁶ Several studies have confirmed that the presence of overt DIC by the ISTH algorithm is an independent predictor of mortality (Table 3).

MANAGEMENT

The basic tenet in the management of DIC is treatment of the underlying disorder. In many cases the DIC will resolve spontaneously when the underlying disorder is treated. However, supportive care measures are required to reduce the mortality and morbidity associated with DIC. There is no consensus on how supportive therapy should be used due to the paucity of data. In general, supportive care is

Table 3: ISTH diagnostic scoring system for DIC

Scoring system for overt DIC

Risk assessment: Does the patient have an underlying disorder known to be associated with overt DIC?

If yes: Proceed

If no: Do not use this algorithm

Order global coagulation tests: (PT, platelet count, fibrinogen, fibrin related marker)

Score the test results

- Platelet count ($>100 \times 10^9/L=0$, $<100 \times 10^9/L = 1$, $<50 \times 10^9/L = 2$)
- Elevated fibrin marker (e.g. D-dimer, fibrin degradation products) (no increase = 0, moderate increase =2, strong increase=3)
- Prolonged PT (<3 s=, >3 but <6 s =1, >6 s=2)
- Fibrinogen level (> 1 g/l=0, <1 g/l=1)

Calculated score

> 5 compatible with overt DIC: Repeat score daily
 < 5 suggestive for nonovert DIC repeat next 1–2d

divided into component replacement and anticoagulation therapy.

Role of Plasma and Platelets

Blood component therapy should be instituted only in cases of active bleeding, those going for an invasive procedure or at an increased risk of bleeding. Platelet transfusion is generally given to patients with active bleeding and a platelet count of $<50 \times 10^9/L$.⁹ Fresh frozen plasma (FFP) can be used if there is a coagulation defect and the patient is bleeding in the dose of 15 ml/kg. Specific deficiencies in fibrinogen despite FFP replacement may be corrected by cryoprecipitates or fibrinogen concentrates.

Role of Anticoagulants

Though there are no randomized controlled trials that show the clinical benefit of heparin cases of DIC, in cases where thrombosis is the primary feature there is a definite role of heparin in therapeutic doses. In patients who are at a high-risk of venous thromboembolism (like recent surgery, prolonged immobilization or indwelling vascular catheters) prophylactic anticoagulation is of benefit.¹⁷

In patients who have a coexisting increased risk of bleeding unfractionated heparin is of greater value due to its short half-life.

Role of Anticoagulant Factor Concentrates

The levels of both antithrombin and protein C are decreased in DIC. It is reasonable to think that administration of these anticoagulants may have a beneficial effect in management as restoration of these proteins may reduce microthrombus formation.

Antithrombin concentrates have been available for some years now. A large multicentric randomized controlled trial to assess the effect of antithrombin on mortality of septic patients showed no significant reduction in those that received antithrombin concentrate.¹⁸ In the absence of prospective data from randomized controlled trials confirming a beneficial effect of antithrombin concentrates in patients with DIC and not receiving heparin their use is not recommended.

Activated protein C (APC) inactivates FVa and FVIIa and inhibits thrombin formation. It also binds to plasminogen activator inhibitor (PAI) and stimulates fibrinolysis. Drotrecogin alfa (DrotAA) (recombinant activated ProC) decreased mortality (risk ratio 0.71 in overt DIC and RR of 0.81 in nonovert DIC) in PROWESS study with trend to more bleeding but less overt thrombosis.¹⁹ Patients with severe sepsis with DIC maybe treated with recombinant human activated protein C (continuous infusion $24 \mu g/kg/h$). However, patients with platelet counts of $<30 \times 10^9/L$ should not be given this product.

Role of Antifibrinolytics

Antifibrinolytic agents like tranexamic acid are usually not indicated in patients with DIC where inhibition of the fibrinolytic system seems inappropriate. Its only use maybe in coagulopathy associated with acute promyelocytic leukemia where hyperfibrinolysis predominates.

Investigational Therapy

Recombinant human soluble thrombomodulin, a new agent which inactivates coagulation by binding to thrombin and activates protein C, is being investigated in patients with DIC. A phase III clinical trial in Japanese patients greater than 15 years of age with DIC from infection or malignancy, showed promising results in comparison to heparin therapy.²⁰

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von Willebrand's Disease

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INTRODUCTION

Erik von Willebrand first reported an autosomally inherited mucocutaneous bleeding disorder in a large family from the Aland Islands off the coast of Finland in 1926. The disease was termed von Willebrand's disease (vWD), named after this original report. vWD is the most common inherited bleeding disorder in humans. It is genetically and clinically heterogeneous and is caused by a deficiency or dysfunction of the protein termed von Willebrand's factor (vWF). Consequently, primary hemostasis is impaired because of defective interaction between platelets and the vessel wall.

Von Willebrand factor (vWF) circulates in blood plasma at concentrations of approximately 10 mg/mL. In response to numerous stimuli, vWF is released from platelets and endothelial cells. It performs two major roles in hemostasis. First, it mediates platelet-plug formation as an adhesion protein that diverts circulating platelets to the sites of vascular injury, particularly through larger multimers. Second, it forms a non-covalent complex with the procoagulant protein factor VIII (FVIII) in plasma, thereby stabilizing and protecting it from inactivation and clearance.

vWD is divided into three major categories:

1. Partial quantitative deficiency (type I)
2. Qualitative deficiency (type II)
3. Total deficiency (type III).

Qualitative vWD type II is further divided into four variants, i.e. IIA, IIB, IIN, and IIM, based on the characteristics of the dysfunctional vWF. These categories correspond to distinct molecular mechanisms, with corresponding clinical features and therapeutic requirements.

PATHOPHYSIOLOGY

The vWF gene is located near the tip of the short arm of chromosome 12. The gene is composed of 52 exons and spans a total of 180 kb of the human genome; therefore,

it is similar in size to the FVIII gene. Expression of the vWF gene is restricted to megakaryocytes, endothelial cells, and, possibly, placental syncytiotrophoblasts. A partial nonfunctional duplication (pseudogene) is present on chromosome 22.

vWF is synthesized in megakaryocytes and endothelial cells as pre-pro-vWF. Sequential cleavage releases mature vWF which undergoes multimerization and exists as a series of multimers, varying in molecular weight between 0.5 (dimer) and 20 million kd (multimer). The building block of these multimers is a dimer, held together by disulfide bonds located near the C-terminal end of each subunit. It is stored in specific cellular storage granules such as the Weibel-Palade body in endothelial cells and the α -granule in platelets.^{1,2}

CLASSIFICATION³ (Table 1)

vWD type I: It causes a mild-to-moderate quantitative deficiency in vWF (i.e. ~20-50 percent of normal levels).

vWD type II: It is due to qualitative abnormalities of vWF and is subdivided into types IIA, IIB, IIM and IIN.

vWD type IIA: It is the most common qualitative abnormality of vWF and is associated with the selective loss of large- and medium-sized multimers.

vWD type IIB: It is characterized by the loss of large multimers through a mechanism distinct from that of type IIA. Observations to date have identified a critical region of vWF involved in the binding of vWF to the platelet receptor glycoprotein Ib (GPIb). Each of these single amino acid substitutions is thought to result in a gain of function, leading to spontaneous binding of vWF to platelets. Normally, plasma vWF is inert in its interaction towards platelets until it encounters an exposed subendothelial surface. vWF binding to collagen or other ligands within the injured vessel wall presumably results in a secondary

conformational change, which then facilitates binding to the GPIIb receptor.

In vWD type IIB, the mutant vWF is capable of spontaneously binding GPIIb in the absence of sub-endothelial contact. The large multimers have the highest affinity for GPIIb and are rapidly cleared from the plasma along with the bound platelets, resulting in thrombocytopenia and the characteristic loss of large multimers.

Platelet type vWD (PT-vWD) is a condition caused by mutations in the GPIIb gene that affect the region of the receptor that binds to vWF.⁴ Its clinical and laboratory results are indistinguishable from vWD IIB, however, they can be differentiated either by specialized tests that distinguish enhanced ristocetin-induced binding of vWF to washed patient platelets or by genetic analysis.

vWD type IIM (M for multimer) refers to qualitative variants with decreased platelet-dependent function that is not due to the absence of high molecular weight multimers.

vWD type IIN, sometimes referred to as vWD Normandy (after the province of origin of one of the first families identified with the disease), is characterized by a defect residing within the patient's plasma vWF that interferes with its ability to bind FVIII. This has important implications in the differential diagnosis of hemophilia.

Patients with vWD type III, a severe quantitative deficiency associated with very little or no detectable plasma or platelet vWF, have a profound bleeding disorder. vWD type III appears to result from the inheritance of a mutant vWF gene from both parents. In the most straightforward model, vWD type I would simply represent the heterozygous form of type III vWD; however, inheritance patterns indicate greater complexity. vWD type III is much rarer than the predicted frequency of 1 case per 40,000 persons based on this model and is closer to 1 case per 1 million persons. Although few mutations have been identified in families with pure vWD type I, some vWD type I cases have been suggested to be due to a mutant vWF subunit that interferes in a dominant negative way with the normal allele, accounting for the autosomal dominant inheritance (Table 1).

FREQUENCY

Internationally

Clinically significant vWD affects approximately 125 persons per million population, with severe disease affecting approximately 0.5 to 5 persons per million population. Reports from screening unselected individuals indicate a higher prevalence of vWD abnormalities, i.e. close to 1 percent of the population. In surveys in which the higher prevalence figures have been noted, affected individuals have been documented to have some, albeit mild, clinical evidence of a hemostatic defect.⁷

Table 1: Classification and frequency of von Willebrand disease^{5,6}

Type	Description	Frequency of cases
I	Partial quantitative deficiency of normal vWF	70-80%
II	Quantitative defects of vWF	15-20%
IIA	Decreased platelet dependent vWF function with lack of HMWM*	10-20%
IIB	Increased binding affinity for platelet glycoprotein Ib	3-5%
IIM	Decreased platelet dependent vWF function with normal vWF multimers	1-2%
IIN	Decreased vWF affinity for F VIII	1-2%
III	Complete deficiency of vWF	~1 per 1 million

* HMWM: High molecular weight multimers

A rare *acquired form of vWD* exists and is due to antibodies to vWF (acquired vWD).

Mortality/Morbidity

For most affected individuals, vWD is a mild manageable bleeding disorder in which clinically severe hemorrhage manifests only in the face of trauma, menses (in women) or invasive procedures. However, significant variability of symptomatology exists between family members.

- In individuals with types II and III, bleeding episodes may be severe and potentially life-threatening.
- Individuals with type III disease who have correspondingly low F VIII levels may develop arthropathies, as is more common in patients with F VIII deficiency, with comparable F VIII levels.

Race

No racial predilection exists for vWD, although several localized concentrations of severe disease have been documented in, Israel, Sweden and Iran.

Sex

- Males and females are affected equally; however, the phenotype maybe more pronounced in females because of menorrhagia and the visibility of easy bruising.
- During pregnancy, the vWF level increases in most patients with non-type III disease. Thus, in patients with functionally normal vWF, labor and delivery usually proceed normally. However, patients with type II disease may experience hemorrhagic problems. In particular, patients with type IIB may experience thrombocytopenia due to the increased plasma levels associated with abnormal vWF. All patients should be monitored for excessive bleeding, particularly during the first week postpartum.⁸

Age

This is an inherited condition. Bleeding related symptoms may occur at a young age, even just after or during birth. Females often present with heavy periods at menarche. Some reports suggest a decreased bleeding tendency as patient's age.

GENETICS

vWD I

The phenotype is postulated to be most commonly due to various missense mutations in the vWF gene. A tyrosine to cysteine mutation at codon 1584 that is present in 10 to 20 percent of type 1 patients is probably the most common.⁹ Other transcriptional and splicing mutants have also been documented in type 1 patients. On the other hand, mutations at other loci influencing vWF biosynthesis may be responsible for some type 1 vWD patients who have no obvious mutations in their vWF.

vWD IIA

This subtype accounts for ~15 percent of vWD cases and is inherited as an autosomal dominant trait most commonly. The majority of mutations in type IIA vWD have been well characterized, with are missense changes in the region of the vWF gene encoding the A2 protein domain.¹⁰ Most of the other mutations disrupt the generation of dimers or multimers.

vWD IIB

This shows an interesting gain-of-function mutation and represents a variety of different missense mutations in the region of the VWF gene encoding the GPIb binding region of the protein, the A1 domain.¹¹ Platelet type-vWD (PT-vWD) is a rare subtype with identical clinical and laboratory findings to vWD IIB and in this form mutations in platelet GPIb cause a phenotype similar to that of vWD IIB. Genetic analysis of the A1 domain-encoding region of the VWF gene (exon 28) and the GpIb α gene can ascertain the genetic diagnosis.

vWD IIM

A missense alteration in the same region of the vWF gene (the A1 domain) in which the type IIB mutations are localized has been identified in cases with a definitive genetic diagnosis.¹² Thus, type IIM vWD represents the result of loss-of-function mutations that adversely influence the binding of vWF to the platelet GPIb receptor.

vWD IIN

Unlike the other forms of vWD II, this subtype exhibits a recessive mode of inheritance. The disease-causing mutations are in the regions of the gene encoding the

N-terminal D'D3 F VIII-binding domain of the protein (exons 18–25).

vWD III

Molecular genetic studies in this phenotype demonstrate a variety of null mutations including gross deletions, frame shift and nonsense mutations in their vWF genes.

HISTORY¹³

- The most common symptoms include nosebleeds, skin bruises, and hematomas. Prolonged bleeding from trivial wounds, oral cavity bleeding, and excessive menstrual bleeding are common. Gastrointestinal bleeding is rare.
- A common but nonspecific symptom is easy bruising.
- Prolonged bleeding after minor trauma to skin or mucous membranes is characteristic of vWD.
- Severe hemorrhage after major surgery is less common, but delayed bleeding may occur up to several weeks after surgery.
- Heavy bleeding is common after tooth extraction or other oral surgery, such as tonsillectomy and adenoidectomy.
- Menorrhagia is a common presenting complaint in women.
- Bleeding symptoms are often exacerbated by the ingestion of aspirin and are ameliorated by the use of oral contraceptives.

PHYSICAL EXAMINATION

Physical examination findings are usually normal. However, patients may have physical sequelae, such as bleeding or bruises.

DIFFERENTIAL DIAGNOSES

- | | |
|----------------------------------|-----------------------------|
| • Hemophilia A | • Hemophilia B |
| • Bernard-Soulier syndrome (BSS) | • Platelet function defects |
| • Antiplatelet drug ingestion | • Fibrinolytic defects |
| • Platelet-type pseudo-vWD | • Acquired vWD |

Laboratory Studies

The ideal screening test for vWD would be a simple laboratory test with adequate sensitivity to most types of vWD and also have a low false positive rate. However, that ideal test does not exist as yet. Screening tests typically include complete blood counts (for evidence of iron deficiency anemia due to bleeding), bleeding time, prothrombin time (PT) and activated partial thromboplastin time (aPTT). Although, bleeding time and aPTT may be prolonged, normal results may be seen in patients with vWD. The PFA-100, an analyzer that evaluates platelet function under conditions of high shear stress that has also been incorporated into the screening investigations for vWD diagnosis.¹⁴

The aPTT is mildly prolonged in approximately 50 percent of patients with vWD. The prolongation is secondary to low levels of FVIII because one of the normal functions of vWF is to protect FVIII from degradation.

The PT should be within reference ranges. Prolongations of both the PT and the aPTT signal a problem with acquisition of a proper specimen or a disorder other than or in addition to vWD.

Bleeding time is discussed as follows:

- Historically, the template bleeding time is a test used to help diagnose vWD. This test is subject to wide variation and, with the availability of tests that provide more specific results, is not currently essential for making the diagnosis of vWD.
- A prolonged bleeding time is not specific for vWD and does not help predict whether patients without a bleeding disorder will have problematic bleeding during surgery. The test is difficult to perform, and results are difficult to confirm (i.e. reproducibility); results frequently are normal in patients with vWD type I.

Specific Laboratory Work-up for vWD (Table 2)

Laboratory studies are directed towards documenting a vWF deficiency. vWF levels vary with physiologic stress. In particular, plasma levels increase with estrogens, vasopressin, growth hormone, and adrenergic stimuli. Thus, vWF levels may be normal intermittently in patients with vWD, and measurements should be repeated to confirm abnormal results. Repeating tests at intervals of more than 2 weeks is advisable to confirm or definitively exclude the diagnosis, optimally at a time remote from hemorrhagic events, pregnancy, infections, and strenuous exercise.

FVIII level, ristocetin cofactor (RCoF) activity, and vWF antigen (vWF:Ag) are some of the commonly used tests.

vWF levels correlate with ABO blood type. Individuals with type O blood normally have the lowest levels of vWF, i.e. approximately 50 to 75 percent of the vWF levels found in persons with other blood types. vWF levels should be compared to an ABO blood group type-specific range from the laboratory where the test is performed.¹⁵

vWD may be evaluated using the following:

- *vWF:Ag:* This assay is usually performed (with the use of rabbit antibody to vWF) using either a quantitative immunoassay or an enzyme-linked immunosorbent assay. A discrepancy between the vWF:Ag value and RCoF activity suggests a qualitative defect that should be further investigated by characterization of the vWF multimeric distribution. Several important genetic and environmental influences must be kept in mind when interpreting the results of vWF plasma estimations, especially ABO blood type, as mentioned above.
- *Ristocetin activity:* Ristocetin, an antibiotic causes platelet aggregation by inducing vWF to bind to the GPIIb

receptor on platelets. It is used in the laboratory to quantify the functional activity of plasma vWF in the ristocetin cofactor assay (vWF:RCo).¹⁶ The test for RCoF activity is good for evaluating vWF function, although results are difficult to standardize and the test is difficult to perform. Thus, the validity of test results should be verified when the test is performed at centers with personnel who are not accustomed to performing this test. Ristocetin is added to a suspension of washed formalin-or paraformaldehyde-fixed platelets in the presence of the patient's plasma (as a source of vWF). The rate of aggregation is then measured using an aggregometer, a device specifically designed to monitor this activity.

- *RIPA:* The ristocetin-induced platelet agglutination (RIPA) assay that assesses platelet sensitivity to low-dose ristocetin and is very useful in identifying type 2B vWD. In this subtype of vWD platelet membranes are overloaded with the high-affinity mutant vWF resulting in increased sensitivity to ristocetin concentrations below 0.6 mg/mL. Low-dose RIPA is carried out in platelet-rich plasma, using a low concentration of ristocetin. This low concentration of ristocetin does not cause vWF binding and aggregation of platelets in samples from normal individuals, but in patients with either type 2B vWD or mutations in the platelet vWF receptor it does cause vWF binding and aggregation of platelets. The latter defects have been termed pseudo-vWD or PLT-vWD, and they can be differentiated from type 2B vWD by vWF:PB assay. At higher concentrations of ristocetin (1.1–1.3 mg/mL),¹⁷ RIPA is reduced in persons with type 3 vWD. However, the test is not sufficiently sensitive to reliably diagnose other types of vWD.
- *vWF FVIII-binding (vWF:FVIIIb) assay:* It measures the ability of vWF to bind added exogenous FVIII and is used to diagnose type 2N vWD.
- *FVIII assay:* FVIII coagulant assay is a measure of the cofactor function of the clotting factor, FVIII, in plasma. In the context of vWD, FVIII activity measures the ability of vWF to bind and maintain the level of FVIII in the circulation.
- *vWF multimer analysis:* The vWF multimer test is usually performed after the initial vWD testing indicates an abnormality. It is a qualitative assay that depicts the variable concentrations of the different-sized vWF multimers and is usually done if the initial vWD testing suggests an abnormality. vWF circulates in the plasma in the form of a heterogeneous mixture of multimers ranging in size from 500 to 20,000 kDa. The high molecular-weight multimeric forms of the protein are the most effective in mediating the platelet interactive functions of vWF and it is these forms that are absent in some type II forms of vWD. The molecular weight profile of plasma vWF is most often evaluated using a

Table 2: Classification and results of laboratory studies in the common forms of von Willebrand disease ¹⁸

	<i>I</i>	<i>III</i>	<i>IIA</i>	<i>IIB</i>	<i>IIM</i>	<i>IIN</i>
vWF:Ag	↓	↓↓↓	↓	↓	↓	↓→
vWF:RCo	↓	↓↓↓	↓↓	↓↓	↓↓	↓→
FVIII:C	↓→	0.05-0.1	↓→	↓→	↓→	0.1-0.4
vWF:RCo/vWF:Ag ratio	>0.6	-	<0.6	<0.6	<0.6	>0.6
Multimers	Normal	-	Abnormal	Abnormal	Normal	Normal
RIPA	Normal	-	↓	↑	↓	N

RIPA: Ristocetin-induced platelet agglutination; VWF: von Willebrand factor; VWF:Ag: VWF antigen; VWF: RCo: VWF ristocetin cofactor assay.

sodium dodecyl-sulfate electrophoretic assay followed by detection of the vWF multimers in the gel, using a radiolabeled polyclonal antibody or a combination of monoclonal antibodies. Alternatively, the protein is transferred to a membrane (Western blot), and the multimers are identified by immunofluorescence or other staining techniques.

- *vWF platelet binding (PB) assay:* This assay measures the vWF binding to normal paraformaldehyde-fixed platelets using low concentrations of ristocetin. Both type IIB vWD and PLTvWD have agglutination of platelet-rich plasma to low-dose ristocetin, but the vWF:PB assay can differentiate type IIB vWD from PLT-vWD. Only vWF from persons with type IIB vWD has increased vWF:PB, while vWF from persons with PLT-vWD has normal vWF:PB with low doses of ristocetin.
- *vWF collagen-binding (CB) assay:* The vWF:CB assay measures vWF binding to collagen. Patients with defects in collagen binding may have a normal vWF:RCo and thus escape clinical diagnosis unless a vWF:CB assay is performed.
- *vWF FVIII-binding assay:* This test is used to diagnose type IIN vWD and measures the ability of vWF to bind added exogenous FVIII.
- *DNA sequencing analysis:* DNA can be used to make a molecular diagnosis of variants of type II vWD.
- *vWD type I:* vWD type I can be diagnosed in a patient with significant mucocutaneous bleeding, laboratory test results compatible with vWD type I, and a positive family history for vWD type I. These criteria are impossible to satisfy in many patients for various reasons. Therefore, physicians must acknowledge this diagnostic uncertainty and should not deny patients treatment, especially when patients' laboratory test results are compatible with vWD type I and they have either a significant history of mucocutaneous bleeding or a positive family history for vWD type I. The variability in vWF levels due to acute-phase influences is especially noticeable in this subtype.

A less common problem is the misdiagnosis of vWD type I in patients who actually have a qualitative defect. The results of screening tests recommended for patients with vWD type I often show proportionally decreased RCoF activity and vWF:Ag in patients with vWD type IIB, although classic teaching is that a discrepancy should exist between the two. In this scenario, ristocetin-induced platelet aggregation test results should demonstrate an exaggerated affinity of the mutant vWF for platelets in the presence of ristocetin.

- *vWD type II:* Disproportionately low RCoF activity relative to vWF:Ag may reflect a decreased affinity of vWF for platelets. The most common cause of such loss of function is the absence of hemostatically effective large vWF multimers, characteristic of vWD type IIA. This subtype is diagnosed based on the combination of markedly reduced RCoF activity relative to the vWF:Ag (ratio <0.6) and compatible multimer gel analysis results. The FVIII levels may be normal or low.

In type IIB, brisk platelet agglutination occurs at low concentrations of ristocetin that have little or no effect on platelet-rich plasma from normal controls. Positive results from this test are found in only one other extremely rare disease, platelet-type or pseudo vWD. Due to the resultant thrombocytopenia this subtype should be considered in the differential diagnosis of cases with inherited forms of thrombocytopenia.

vWD IIM includes variants in which binding to platelets is impaired but the vWF multimer distribution is normal. Screening laboratory test findings are similar to those found in vWD type IIA, but multimer gel analysis results show that large multimers are present. Also, ristocetin-induced platelet agglutination is reduced.

In vWD type IIN platelet-dependent functions of vWF are preserved, but FVIII levels are low (often <10%). This condition is an autosomal mimic of hemophilia A, and a careful family history helps distinguish the two. The bleeding tendency is relatively mild and on laboratory investigation often the only abnormality is a low FVIII level of 0.10 to 0.40 units/mL.

Multimeric examination of the vWF is particularly important in the diagnosis of type II vWD. Results from this laboratory test reveal the multimeric distribution of vWF, thus allowing classification of type II disease depending on the specific absence of large multimers (type IIB) or both intermediate and large (type IIA) multimers.

- *vWD type III:* This is a recessive disorder in which vWF protein is virtually undetectable. The absence of vWF causes a secondary deficiency of F VIII and a subsequent severe combined defect in blood clotting and platelet adhesion. Results from screening assays show absent RCoF activity and vWF:Ag and a prolonged aPTT. These patient's also have very low levels of F VIII (<0.10 units/mL).
- *Testing for therapeutic options:* A laboratory evaluation of a patient's response to administrations of desmopressin (DDAVP) is commonly performed to assess whether or not a patient can receive this product either therapeutically or prophylactically before surgery.

Rule out whether the patient has type IIB prior to testing, particularly in patients with risk factors for thrombotic complications, because case reports suggest that this drug may be contraindicated in this setting.

Medical Care

An early and important problematic area of management is definitive diagnosis of the disorder. While type III and type II forms of the disorder should be readily identifiable (with access to an experienced coagulation laboratory), the diagnosis of type I disease still poses significant problems.¹⁹ The two main treatment options for patients with vWD are DDAVP and transfusion therapy.

Type I vWD

Desmopressin (DDAVP) is the treatment of choice for individuals with vWD type I.

Type II vWD

Responses to DDAVP are variable in patients with type II disease. A trial infusion may be performed to evaluate the potential efficacy for a particular patient.

Many individuals with vWD type IIA have a response to DDAVP, with peak vWF and FVIII levels at 30 to 60 minutes. This is similar to responses observed in patients with vWD type I; however, rapid loss of vWF, FVIII, and, particularly, RCoF activity, occurs as the high molecular weight multimers are degraded, with return to baseline levels at four hours post-infusion. Although the response is transient, it may be adequate therapy in certain clinical situations.

For prophylaxis in major surgery or for treatment of serious bleeding episodes, vWF-containing FVIII concentrates are the treatment of choice.

Desmopressin (DDAVP) trials may be contraindicated in patients with type IIB because of thrombocytopenia and possible thrombotic complications.

Desmopressin (DDAVP) is probably not effective in patients with type IIM and is rarely effective in patients with type IIN.

Type III vWD

Individuals with vWD type III have a virtually complete deficiency of vWF; thus, the fact that DDAVP, an agent which causes release of stored vWF, has no effect in patients with vWD type III is not surprising.

The treatment of choice for patients with vWD type III (and other vWD types unresponsive to DDAVP) is virus-inactivated, vWF-containing FVIII concentrates that contain a near-normal complement of high molecular weight vWF multimers. Most experience reported in the literature has been with the use of Humate-P, a plasma derived product of intermediate purity. Two other FVIII concentrates, Alphanate and Koate-HP, have been reported to be efficacious in the treatment of vWD. Too little vWF is present in monoclonally purified FVIII concentrates and recombinant FVIII concentrates to allow their use in the treatment of vWD.

Cryoprecipitate, the standard component used for vWD therapy during the 1970s and 1980s, is no longer the material of choice. There have been successful pre-clinical trials of recombinant vWF and interleukin-11 preparations, but at this stage it is too early to assess the relative advantages and likely clinical application of these compounds.

Alloantibody formation occurs in 10 to 15 percent of patients with type III disease.²⁰ Therefore, the possibility of this complication must be managed appropriately because patients are at increased risk for life-endangering anaphylactic reactions to vWF-FVIII preparations. With hemostatic stress in emergency situations, infusion of FVIII preparations devoid of vWF, while adjusting for the markedly decreased FVIII half-life, may be necessary.

Platelet Transfusions

These may be helpful in some patients with vWD whose disease is refractory to other therapies. Cryoprecipitate and fresh frozen plasma contain functional vWF but should be avoided whenever possible because of the potential transmission of viral disease. An additional drawback of fresh frozen plasma is the large infusion volume required.

SURGICAL CARE

Particular attention to hemostasis is advised once the hemostatic defect has been corrected medically.

ACTIVITY

Patients should be wary of any physical activity associated with an increased risk of hemorrhage. The two principal drug categories include non-transfusional compounds (e.g. DDAVP, antifibrinolytics) and transfusional compounds. Whenever possible, avoid transfusions.

THERAPEUTICS USE

Desmopressin²¹

Desmopressin (DDAVP) is a synthetic analog of the antidiuretic hormone vasopressin; it has enhanced antidiuretic activity and no pressor activity related to vasopressin. The infusion of DDAVP into healthy individuals and individuals with vWD type I results in a rapid increase in circulating levels of vWF:Ag and FVIII and RCoF activity.

Typically, a maximal rise of vWF and FVIII is observed in 30-60 minutes. The typical maximal rise is 2- to 4-fold for vWF and 3- to 6-fold for FVIII. Additionally, hemostatic levels of both factors are usually maintained for at least 6 hours. DDAVP can also be administered via a highly concentrated nasal spray; 300 µg intranasally produces levels comparable to those observed with an intravenous infusion. Intranasal therapy is particularly useful for home therapy of menorrhagia and recurrent epistaxis. Treatment of choice for individuals with vWD type I. Causes a rapid (~30 min; peaks in 90-120 min) 3 to 5-fold increase in release of vWF and FVIII from endothelial cells.

DDAVP: 0.3-0.4 µg/kg IV in 10 to 50 mL NS over 10 to 30 min.

- SC: 0.3 µg/kg
- IN: 2 puffs (300 µg) for individuals >50 kg
- DDAVP: Administer as in adults
- < 50 kg: 1 puff (150 µg) IN
- >50 kg: Administer as in adults

Precautions

Documented hypersensitivity; platelet-type vWD; patients with type IIB disease with thrombotic risk factors. *Interactions with other drugs.*

Co-administration with demeclocycline and lithium decreases effects; fludrocortisone and chlorpropamide increase effects.

Caution is warranted in patients with severe cardiovascular disease; adverse effects include facial flushing, headache, mild decrease in blood pressure, and slight increase in heart rate; hyponatremia and seizures reported in children (usually < 2 years).

Fluid restriction to maintenance levels for 24 hour is advised following a single infusion, along with careful monitoring of sodium levels if repetitive dosing is used in children or elderly patients.

Drug Category—Antihemorrhagic

For use in patients with blood-product deficiencies; platelets may be a valuable option in treatment of patients with type III disease.

Antihemophilic Factor (Human)

When DDAVP cannot raise vWF level to hemostatically acceptable levels, a blood product containing vWF may

be required. It is found in normal plasma necessary for clot formation. Antihemophilic factor (AHF) can temporarily correct coagulation defect of patients with classic hemophilia (hemophilia A) in which a deficiency of FVIII exists. Specific activity of different brand products varies. Humate-P is a product containing both FVIII and vWF. Dose depends on patient's weight, severity of hemorrhage, severity of deficiency, presence of inhibitors, and desired FVIII level. Clinical effect on patient is most important determinant of therapy. When inhibitors are present, dose requirements are extremely variable and determined by clinical response. Length of treatment and loading dose depend on extent and location of hemorrhage.

- *Type 1 disease:* Minor bleeding 40 to 50 U/kg (1 or 2 doses).

Major bleeding: Loading dose of 40 to 75 U/kg, then 40-60 U/kg q8-12h for 3 d to keep RCoF activity nadir >50 percent; then 40 to 50 U/kg qd for up to 7 days.

- *Types 2 and 3 Disease:* Minor bleeding 40 to 50 U/kg (1 or 2 doses).

Major bleeding: Loading dose of 60-80 U/kg, then 40-60 U/kg q8-12h for 3 d to keep RCoF activity nadir >50 percent; then 40 to 50 U/kg qd for up to 7 d. Monitor FVIII levels.

Problems: Documented hypersensitivity; safety for use during pregnancy has not been established.

Signs or symptoms of any allergic reactions must always be assessed. Rate of administration of AHF concentrate should be reduced or discontinued if a significant change in vital signs occurs and is thought to be due to allergic reaction and not to continuing active bleeding; immune tolerance regimens can be associated with nephrotic syndrome, which would require discontinuation of product. Alloantibody formation in type III disease is a rare complication in patients receiving multiple transfusions; recombinant FVIII or recombinant FVIIa may be indicated for patients with a history of allergic reactions.

Drug Category: Antifibrinolytics²²

They may be used to prevent breakdown of formed blood clots to temper hemorrhage. They block formation of plasmin and may be used to manage mucosal bleeding, particularly in the nasopharynx and in the GI and GU tracts. These drugs are most often used concomitantly with other medications for dental extractions and oral surgery.

Aminocaproic Acid

It inhibits fibrinolysis via inhibition of plasminogen activator substances and, to a lesser degree, through antiplasmin activity. Main disadvantage is that thrombi that form during treatment are not lysed and effectiveness is uncertain. It has been used to prevent recurrence of subarachnoid hemorrhage.

Dosage: 50-60 mg/kg PO/IV q4-6h

Precautions: Documented hypersensitivity; evidence of active intravascular clotting process; because aminocaproic acid can be fatal in patients with DIC, differentiating between hyperfibrinolysis and DIC is important. The drug should not be administered unless a definite diagnosis of hyperfibrinolysis is made and caution is warranted in cardiac, hepatic, or renal disease.

Co-administration with estrogens may cause increase in clotting factors, leading to a hypercoagulable state. Safety for use during pregnancy has not been established.

Tranexamic Acid

It is an alternative to aminocaproic acid and acts by inhibiting fibrinolysis by displacing plasminogen from fibrin.

Dosage: 20 to 25 mg/kg PO q8-12h

Precautions: Similar to those advised with aminocaproic acid.

Drug Category: Estrogens²²

Estrogens may be helpful in reducing menorrhagia. Even in type III disease in which case vWF and FVIII levels are not necessarily increased, they may mediate changes in endometrium, which lessen menstrual bleeding severity.

Ethinyl Estradiol (Estinyl)

It reduces secretion of LH and FSH from pituitary by decreasing amount of gonadotropin-releasing hormones.

DRUGS TO BE AVOIDED

- ASA, Ibuprofen, Antihistaminics
- Anti-platelet agents—Dipyridamole, Ticlopidine
- Anti-microbials—High dose penicillin, Cefalosporin Nitrofurantoin, Hydroxychloroquin
- Cardiovascular drugs—Propranolol, Furosemide, Ca⁺ channel blocker, Quinidine
- Misc—Caffeine, Tricyclic antidepressants, Phenothiazines, Valproate, Heparin.

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Hemophilia

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Hemophilia results from deficiency of one of the clotting factors. Hemophilia A (Classic hemophilia) and B (Christmas disease) are inherited, X-linked, recessive disorders resulting in deficiency of functional plasma coagulation factor VIII and IX respectively and are more common, besides other factor deficiencies (Factor VIII and IX are required for synthesis of thrombin through intrinsic pathway), which are rarest. They account for 90 to 95 percent of severe congenital coagulation deficiencies. The two disorders are considered together because of their similar clinical pictures and similar patterns of inheritance.

HISTORY^{1,2}

Hemophilia is one of the oldest described genetic diseases. An inherited bleeding disorder in males was recognized in Talmudic records of the second century. Hemophilia has often been called “The Royal Disease”. This is because Queen Victoria, Queen of England was a carrier and many generations of this family suffered from hemophilia. They passed the disease on to the Spanish, German and Russian Royal families. The modern history of hemophilia began in 1803 with the description of hemophilic kindred by John Otto, followed by the first review of hemophilia by Nasse in 1820. Wright demonstrated evidence of laboratory defects in blood clotting in 1893; however, FVIII was not identified until 1937 when Patek and Taylor isolated a clotting factor from the blood, which they called anti-hemophilia factor (AHF).

A bioassay of FVIII was introduced in 1950. Although the intimate relationship between FVIII and von Willebrand factor (vWF) is now known, it was not appreciated at the time. In 1953, decreased factor FVIII in patients with vWF deficiency was first described. Further research by Nilson and coworkers indicated the interaction between these two clotting factors.

In 1952, Christmas disease was described and named after the surname of the first patient who was examined in detail. This disease was distinct from “hemophilia” because mixing plasma from a patient with “true hemophilia” and one with Christmas disease, corrected the clotting time; thus, hemophilia A and B were differentiated.

In the early 1960s, cryoprecipitate was the first concentrate available for the treatment of patients with hemophilia. In the 1970s, lyophilized intermediate-purity concentrates were obtained from a large pool of blood donors. The introduction of concentrated lyophilized products that are easy to store and transport has dramatically improved the quality of life of patients with hemophilia and facilitated their preparation for surgery and home care.

In the 1980s, the risk of transmitting viral contaminants in commercial FVIII concentrates was well recognized. Most patients with severe hemophilia became infected with hepatitis B and C viruses. By the mid-1980s, most patients with severe hemophilia had been exposed to hepatitis A, B, and C viruses and human immunodeficiency virus (HIV). New virucidal techniques have been effective in eliminating new HIV transmissions and virtually eliminating hepatitis B and C exposures. The present standard of using recombinant products in the treatment of hemophilia virtually eliminates the risk of viral exposure.

PATHOPHYSIOLOGY

The role of the coagulation system is to produce a stable fibrin clot at sites of injury. The clotting mechanism has two pathways: intrinsic and extrinsic.

The intrinsic system is initiated when factor XII is activated by contact with damaged endothelium. The activation of factor XII can also initiate the extrinsic pathway,

fibrinolysis, kinin generation, and complement activation. In conjunction with high-molecular-weight kininogen (HMWK), factor XIIa converts prekallikrein (PK) to kallikrein and activates factor XI. Activated factor XI, in turn, activates FIX in a calcium-dependent reaction. Factor IXa can bind phospholipids. Then, factor X is activated on the cell surface; activation of factor X involves a complex (tenase complex) of factor IXa, thrombin-activated FVIII, calcium ions, and phospholipid.

In the extrinsic system, the conversion of factor X to factor Xa involves tissue factor (TF), or thromboplastin; factor VII; and calcium ions. TF is released from the damaged cells. It is thought to be a lipoprotein complex that acts as a cell surface receptor for FVII, with its resultant activation. It also adsorbs factor X to enhance the reaction between factor VIIa, factor X, and calcium ions. Factor IXa and factor XII fragments can also activate factor VII.

In the common pathway, factor Xa (from intrinsic or extrinsic pathways) forms a prothrombinase complex with phospholipids, calcium ions, and thrombin-activated factor Va. The complex cleaves prothrombin into thrombin and prothrombin fragments 1 and 2. Thrombin converts fibrinogen into fibrin and activates FVIII, factor V, and factor XIII. Fibrinopeptides A and B, the results of the cleavage of peptides A and B by thrombin, cause fibrin monomers to form and then polymerize into a meshwork of fibrin; the resultant clot is stabilized by factor XIIIa and the cross-linking of adjacent fibrin strands. Because of the complex interactions of the intrinsic and extrinsic pathways (factor IXa activates factor VII), the existence of only one *in vivo* pathway with different mechanisms of activation has been suggested.

FVIII and FIX circulate in an inactive form. When activated, these two factors cooperate to cleave and activate factor X, a key enzyme that controls the conversion of fibrinogen to fibrin. Therefore, the lack of either of these factors may significantly alter clot formation and clinical bleeding.

Frequency

Hemophilia has prevalence of approximately 1:10,000 males for hemophilia A and 1:35,000 for hemophilia B. The overall prevalence of hemophilia is usually estimated at between 1:5,000 and 1:10,000 males. Of this 80 to 85 percent have hemophilia A and 10-15 percent have hemophilia B, i.e. the combined incidence for both hemophilia was estimated to be approximately 1:5,000 live male births.³ The number of affected persons worldwide is estimated to be about 400,000.

Race

Hemophilia shows no apparent racial predilection and appears in all ethnic groups.

Sex

Both hemophilia A and B are X-linked recessive disorders; therefore, they affect males almost exclusively. Reports of affected females are rare, and these cases are attributed to extreme lyonization or the presence of 2 independent mutations.

Age

Significant deficiency in FVIII or FIX may be evident in the neonatal period and continue through the life of the affected individual. The absence of hemorrhagic manifestations at birth does not exclude hemophilia.

Clinical Manifestation of Hemophilia^{4,5}

Approximately 30 to 50 percent of patients with severe hemophilia present with manifestations of neonatal bleeding (e.g. after circumcision). Approximately 1 to 2 percent of neonates have intracranial hemorrhage. At birth, other neonates may present with severe hematoma and prolonged bleeding from the cord or umbilical area.

After the immediate neonatal period, bleeding is uncommon in infants until they become toddlers. When trauma-related soft-tissue hemorrhage occurs, young children may have oral bleeding when their teeth are erupting. Bleeding from gum and tongue lacerations is often troublesome because the oozing of blood may continue for a long time despite local measures. As physical activity increases in children, hemarthrosis and hematomas occur. Chronic arthropathy is a late complication of recurrent hemarthrosis in a target joint. Traumatic intracranial hemorrhage is a serious life-threatening complication that requires urgent diagnosis and intervention. Petechiae usually do not occur in patients with hemophilia because they are manifestations of capillary blood leaking, which typically is the result of vasculitis or abnormalities in the number or function of platelets.

Hemophilia has been classified in three types as:

- Severe disease, defined as less than 1 percent factor activity (<0.01 IU/ml), generally presents in children younger than 1 year and accounts for 43 to 70 percent. Bleeding episodes includes spontaneous bleeding (1-2 episodes/week), predominantly in joints and muscles.
- Moderate disease, defined as 1 to 5 percent factor activity (0.01-0.05 IU/ml), generally presents in children aged 1-2 years and accounts for 15 to 26 percent. Bleeding episodes includes occasional spontaneous bleeding (1-2 episodes/year). Severe bleeding with trauma, surgery.
- Mild disease, defined as greater than 5 percent factor VIII activity (>0.05 IU/ml), generally presents in children older than 2 years and accounts for 15 to 31 percent. Severe bleeding only with major trauma or surgery (Table 1).

Table 1: Severity, factor activity, and hemorrhage type

Classification	Factor activity (%)	Cause of hemorrhage
Mild	>5	Major trauma or surgery
Moderate	1-5	Mild-to-moderate trauma
Severe	<1	Spontaneous, hemarthrosis

Causes

Both of these disorders are inherited in an X-linked recessive pattern. The genes for FVIII and FIX are located on the long arm of the X chromosome in bands q28 and q27, respectively. Numerous mutations in the gene structure have been described. Genetic abnormalities include genetic deletions of variable size, abnormalities with stop codons, and frame-shift defects. Recent data suggest that 45 percent of the cases of severe hemophilia A result from an inversion mutation.⁶ Several hundred mutations with different amino acid substitutes have been described in hemophilia B. These mutations include partial and total deletions, missense mutations, and others that result in the decreased or absent production of FIX or the production of an abnormal molecule. Evaluation and knowledge of the specific gene defect in families with severe hemophilia enables accurate gene tracking, carrier analysis, and prenatal diagnosis.

DIAGNOSIS^{7,8}

Accurate diagnosis is important and essential for effective management. Hemophilia should be suspected in patients presenting with a history of:

Easy bruising in early childhood;

- Spontaneous bleeding (particularly into the joints and soft tissues; and
- Excessive bleeding following trauma or surgery.
- Family history is very important in the diagnosis, majority diagnosed at birth because of family history, although 30 percent new mutations occur in case of hemophilia.

If any child presents with mucous membrane bleeding, ecchymosis, or excessive bleeding during and after surgery screening should be done.

The accurate diagnosis of hemophilia requires the following:

- Detailed history with particular emphasis on
 - Age of onset of bleeding
 - Site of bleeding
 - Whether bleeding spontaneous/ trauma related (number of episodes/ month or year)
 - Target joints, if any
 - Other affected members in the family
- Complete physical examination with particular care to record range of motion, deformities (if any) and muscle strength at the knees, hips and elbows.

Laboratory Studies

- Usually, the activated partial thromboplastin time (aPTT) is prolonged; however, normal aPTT does not exclude mild or even moderate hemophilia because of the relative insensitivity of the test. Severe hemophilia is easily identified with a significantly prolonged aPTT.
- Bleeding times, prothrombin times, and platelet counts are normal.
- The diagnosis is based on functional assay results for FVIII and FIX. Usually, immunoassay of these factors is not required for diagnosis, but it assists in identifying dysfunctional coagulation problems in some patients with hemophilia.
- Usually, vWF is also measured. The combination of low FVIII and low vWF may indicate vWF deficiency as the primary diagnosis.
- Because FVIII and FIX are large molecules that do not cross the placenta, the diagnosis can be made at birth by means of quantitative assay of coagulation factors in the cord blood.
- Early diagnosis of FIX deficiency is complicated by the physiologic reduction of vitamin K-dependent factors in young infants.

Other laboratory evaluations in the patient with hemophilia are a periodic screening for the presence of FVIII or FIX inhibitor and screening for transfusion-related or transmissible diseases such as hepatitis and HIV infection. This may be less important in populations who receive only recombinant product.

This is essential to avoid missing the diagnosis of common platelet disorders, von Willebrand disease and combined factor deficiencies. For patients with definite history of bleeding and normal results of tests listed above, screening for defects in factor XIII should be done.

MANAGEMENT OF HEMOPHILIA

Medical Care

Current treatment of patients with hemophilia requires a comprehensive multidisciplinary approach.⁹ A comprehensive team includes medical specialists in hematology, orthopedics, dentistry, and surgery; nurses; physiotherapists; social workers; and related allied health professionals. Comprehensive care clinics are supported by evidence of better access to care, less morbidity, and better overall outcome.

Ambulatory replacement therapy for bleeding episodes is essential for preventing chronic arthropathy and deformities. Home treatment and infusion by the family or patient is possible in most cases. Prompt and appropriate treatment of hemorrhage is important to prevent long-term complications and disability. For most mild hemorrhages, dose calculations are directed toward achieving an FVIII activity level of 30 to 40 percent or

FIX activity level of 30 percent and clotting factor activity of at least 50 percent in severe bleeds (e.g. major dental surgery, major surgery, trauma) and 80 to 100 percent in life-threatening hemorrhage.

Hospitalization is reserved for severe or life-threatening bleeds, such as large soft tissue bleeds; retroperitoneal hemorrhage; and hemorrhage related to head injury, surgery, or dental work. Patients are treated with prophylaxis or intermittent, on-demand therapy for bleeding events. Prophylaxis has been shown in many studies to prevent or at least reduce the progression of damage to target sites, such as joints.

In most countries with access to recombinant product, prophylaxis is primary, i.e. therapy is started in patients as young as 1 year and continues into adolescence. A cost-benefit analysis indicates that this approach reduces overall factor use and significantly reduces morbidity. In situations in which this is not feasible, secondary prophylaxis, i.e. therapy after a target joint has been established to prevent worsening of the joint is instituted for a defined period. Dosing is designed to maintain trough levels greater than 2 percent. This requires the administration of FVIII 3 times per week or FIX 2 times per week.

The treatment of hemophilia may involve the management of hemostasis, management of bleeding episodes, use of factor replacement products and medications, and treatment of patients with factor inhibitors.

FUNDAMENTALS OF TREATMENT

Nonpharmacological Method

Do not

- IM injections
- Contact sports
- Aspirin and other NSAIDs

To Do

- Local treatment—ice application and local pressure
- Early factor correction
- All procedure under factor cover
- Use of DDAVP/ EACA/Tranexamic acid
- Hepatitis A and B immunization
- Educate parents/teachers

Principles of Care^{10,11}

The general principles of care for hemophilia management include:

- Prevention of bleeding should be the goal;
- Acute bleeds should be treated as early as possible (within two hrs, if possible);
- Home therapy should be used to manage only uncomplicated mild/moderate bleeding episodes.
- All severe bleeds should be hospitalized.

- Prior to any invasive procedure, clotting factor or concentrate/DDAVP should be given to achieve appropriate factor level. (blood products should be avoided as far as possible).
- As much as possible; patients should adjust lifestyle to avoid trauma.
- Patients should be advised to avoid use of drugs affecting platelet function, particularly acetylsalicylic acid (ASA) and nonsteroidal anti-inflammatory drugs (NSAIDs), except certain COX-2 inhibitors. Paracetamol/acetaminophen are safe alternative to analgesia.
- Intramuscular injections, difficult phlebotomy, and arterial punctures must be avoided.
- Regular exercise should be encouraged to promote strong muscle, protect joints, and improve fitness.
- Contact sports should be avoided, but swimming and cycling with appropriate gear should be encouraged.

MANAGEMENT OF HEMOSTASIS

Hemostasis is achieved with replacement therapy aimed at correcting the coagulation factor deficiency.

Hemophilia A

Dose of factor is calculated as per formula of Abildgaard and colleagues:

Dose factor VIII (units) = units/dl (percent) desired rise in plasma factor VIII \times body weight (kg) \times 0.5 (To be given 12 hourly)

Hemophilia B

Dose of factor IX (units) = units/dl (percent) desired rise \times body weight (kg) (To be given 24 hrly)

The half-life of factor IX (18-24 hours) is much longer than that of factor VIII (10-12 hours), and therefore factor IX does not need to be administered as often. Whereas the minimal hemostatic level of factor VIII is 30 to 40 units/dl, that of factor IX appears to 25 to 30 units/dl.

For recombinant factor IX concentrate, the dose must be increased to 1.2 to 1.5 times owing to the poorer recovery of the recombinant factor IX in some patients. It is recommended that the recovery of factor IX after an infusion be determined for each patient to accurately determine subsequent therapeutic doses.

The dose and frequency of administration are calculated as outlined in Table 2.

Prophylactic Factor Therapy^{12,13}

Most centers initiate prophylactic therapy as soon as joint bleeding occurs. Best is to administer when child starts crawling or as soon as baby diagnosed in case of severe hemophilia. This therapy is usually administered through subcutaneous access port after the insertion of a central venous line; can be administered through peripheral venous access. In general, a dose of 20 to 40 units/kg of

Table 2: Replacement therapy dose calculations

Factor	Half-life hour	Increase after 1 U/ kg (%)	Required activity for common bleeding (%)
VIII	8-12	2	40
IX	24	1	30

factor VIII is administered every other day or three times a week; and 30 U/kg factor IX concentrate every 2 to 3 days (in each case to achieve trough level >1%).

The dose and rate are adjusted to ensure that the nadir before the next infusion is 1 units/dL. The levels attained by use of this regimen usually prevent spontaneous bleeding, although hemorrhages caused by trauma may still require additional replacement therapy. The goal is to prevent recurrent hemarthrosis and associated chronic hemophilic arthropathy and thereby promote a normal lifestyle.

MANAGEMENT OF BLEEDING EPISODES

- During an episode of acute bleeding an assessment should be performed to identify the site of bleeding and treatment should be given early.
- Early signs of bleeding, e.g. tingling sensation in joint or “aura” can be felt by the patient, and early treatment in form of factor concentrate (ideally) should be instituted earliest.
- Identification should be with the patient always, including diagnosis, severity, inhibitor status; type of product used, and contact information of treating physician to avoid delay in treatment and also unnecessary investigations.
- Life-threatening bleeds particularly, head, neck, chest, and GIT should be taken serious consideration always, and treatment instituted earliest possible (DDAVP can be considered in minor or moderate bleeds and always in case of mild to moderate hemophilia).
- If bleeding not controlled inhibitor assay assessment should be made.

TREATMENT OF SPECIFIC HEMORRHAGES IN HEMOPHILIA

Hemarthrosis ¹⁴⁻¹⁶

The most typical manifestation of hemophilia is articular bleeding (hemarthrosis). When hemarthrosis becomes frequent and/or intense, the synovium may not be able to reabsorb the blood, and to compensate for such reabsorptive deficiency the synovium will hypertrophy, resulting in what is called chronic hemophilic synovitis. Thus, it is very important not only to avoid acute hemarthrosis, but also to manage it as efficiently as possible, with the aim of avoiding the development of synovitis. The best way to

avoid articular bleeds is to begin hematological prophylactic treatment from the age of two to the end of skeletal maturity. However, it is not always possible.

TREATMENT OF HEMARTHROSIS

Acute Hemarthrosis

The objectives of treatment are to avoid muscular atrophy, maintain an adequate degree of articular mobility, control the recurrence of hemarthrosis, and recover joint function if possible. Hence, optimal treatment of hemarthrosis involves a combination of factor replacement, rest (with or without splinting), ice, appropriate analgesia, and supervised rehabilitation once the acute phase has been controlled and the risk of bleeding reduced.

Joint Aspiration

Joint aspiration is not commonly performed, but in cases of severe bleeding it may relieve the patient's pain and speed up rehabilitation. Before deciding on joint aspiration, the presence of a circulating inhibitor must be investigated to determine the best treatment. In any case, three to four days of joint rest is recommended. When hemarthrosis does not respond to medical treatment, septic arthritis must be suspected, especially if the patient is immunosuppressed. Another possibility could be hemophilic synovitis, which can be detected by clinical examination. Ultrasonography and magnetic resonance imaging will help confirm the occurrence of synovitis. Synovial bleeding secondary to synovial hypertrophy requires aggressive treatment. Synovitis may be controlled with early prophylactic treatment or by synovectomy. Joint aspiration may provide dramatic pain relief and early joint rehabilitation. However, it is not recommended in all cases as raised intrarticular pressure may contribute to femoral head necrosis in adults, or to Perthes' disease in children. Though arthrocentesis of the elbow, knee, and ankle are quite simple procedures that can be performed in outpatient clinic, both hip and shoulder joint aspirations require sedation and radiographic control by an image intensifier.

Adjunctive Management and Preventive Care

Following treatment considerations are important when adjunct with the factor replenishment, or can be more important when factor availability is hardened; also these may reduce the factor requirement, and also lessens the duration of treatment:

- RICE (rest, ice, compression, and elevation) is an important adjunctive management, besides factor replenishment either in form of concentrates or DDAVP (in case of hemophilia A). Bleeding muscle and joints can be kept at rest by splinting, casting, or using crutches, or a wheelchair. For the upper limb, usually a sling (for the shoulder) or a long-arm posterior plaster splint

(for the elbow) will provide sufficient rest, support, and protection. Lifting and carrying heavy items should be avoided until the bleeding has resolved, which usually takes four to five days application of cold/ice packs is useful to decrease inflammation (should be wrapped in a towel and not applied directly to skin). Ice should be applied for 20 minutes, every 4 to 6 hours, until swelling or pain decreases (not valuable after 48 hour).

- **Analgesia:** Depending on the degree of pain, paracetamol or a combination of paracetamol and dextropropoxyphene should be administered. NSAIDs should be avoided. Certain COX-2 inhibitors may be used judiciously for joint inflammation after an acute bleed and in chronic arthritis.

Following is the factor replacement therapy for hemarthrosis:

Hemophilia A: 20 to 50 u/kg factor VIII concentrate; 15 u/kg if treated early. If hemorrhage is severe, repeat the dose the following day and consider additional treatment every other day for 1 week.

Hemophilia B: 30 units/kg factor IX concentrate; 20 units/kg if treated early. If hemorrhage is severe, repeat the dose the following day and consider additional treatment every other day for 1 week.

Subacute Hemarthrosis

It should be treated with hematological substitutive therapy, with two to three weeks of immobilization by means of a semiflexible splint. The deficient factor should be administered thrice a week, to obtain 20 to 30 percent of the normal level. After each transfusion the patient should complete an exercise program focusing on active joint mobility, under the surveillance of an expert physiotherapist. If such mobility exercises are painful, only isometric exercises should be done. When a flexion contracture appears, it should be treated aggressively and early by conservative means to avoid it's becoming irreversible. Conservative measures include Oxford's inverted dynamic splints, extension-desubluxation hinged casts, dynamic splints, and traction followed by polypropylene orthosis. A flexion contracture with a duration ranging from weeks to months may require surgery: hamstring release and/or supracondylar extension osteotomy. A flexion contracture associated with osseous or fibrous ankylosis may also require a patellofemoral osteotomy.

Muscle or Significant Subcutaneous Hematoma

Muscle hemorrhages should be considered as severe as hemarthrosis, appropriate factor replacement therapy is crucial as mentioned below to reduce size of hematoma and restore normal range of motion and to prevent fibrosis of the muscle and contracture, and also atrophy or pseudotumor formation as muscle weakness can also predispose to joint hemorrhage.

Iliopsoas bleeding is particularly troublesome form of intramuscular hemorrhage and can be life-threatening due to large volume of blood lost into retroperitoneal space, aggressive plan is mandatory consisting of at least 10 to 14 days or longer of replacement, followed at least by several months of prophylactic therapy until clinical and radiologic evidence demonstrates resolution.

Muscle involvement may result in:

Iliopsoas: Femoral nerve damage and loss of function of the quadriceps muscle.

Gastrocnemius: Bleeds can lead to contracture in plantar flexion at the ankle.

Forearm compartment: Can lead to Volkmann's ischemic contracture.

Neck/throat: May compromise the airways.

Management

- Diagnosis is clinically obvious but ultrasonography/CT scan may be occasionally needed to confirm the presence of bleed
- Factor replacement as mentioned below
- Other measures—as described for hemarthrosis.

Factor Replacement Therapy

Hemophilia A: 20 units/kg factor VIII concentrate; may need every other day treatment until well resolved.

Hemophilia B: 30 units/kg factor IX concentrate; may need every 2 to 3 day treatment until well controlled.

Iliopsoas Hemorrhage

Hemophilia A: 50 units/kg factor VIII concentrate, then 25 u/kg every 12 hour until asymptomatic, then 20 u/kg every other day for total 10 to 14 days.

Hemophilia B: 80 u/kg factor IX concentrate, then 20 to 40 u/kg every 12 to 24 h to maintain factor IX >40U/dl until asymptomatic then 30U every other day for total 10 to 14.

Mouth, Deciduous Tooth, or Tooth Extraction

A common presentation of hemophilia is oral bleeding, whether from a torn frenulum in a young child or after tooth extraction in an older patient.

Clinical Features

- Swallowed blood may be vomited or passed as malena
- May result in severe anemia.
- Associated gingivitis/trauma may be seen.

Management

- Minor bleeding often controlled with antifibrinolytic drugs (dose described below)
- Major/persistent bleeding often requires factor replacement as described below

- Once bleeding has stopped, underlying cause must be treated:
 - Improve dental hygiene by regular brushing (2-3 times/day) with a soft tooth brush (NOT fingers) soon after applying antifibrinolytic drugs
 - Antiseptic mouth washes (chlorhexidine) 3 to 4 times/day for about a week.
 - Antibiotics, if necessary, to treat gingivitis (ampicillin/amoxicillin/metronidazole)
 - Dental scaling under factor replacement cover (single dose for 20 percent level, repeat after 24 hours, if necessary) and antifibrinolytic drugs.
- If anemia is severe ($Hb < 5$ g%) and symptomatic, blood transfusion may be needed. Iron and folate supplements should be given for 3-6 months)

Replacement therapy to achieve a factor level of 30 to 40 u/dl is adequate for initial therapy. As oral cavity contains abundant fibrinolytic activity, antifibrinolytic therapy with ϵ -aminocaproic acid or tranexamic acid¹⁷ is useful to stabilize the clot until the wound is healed.

Hemophilia A: 20 u/kg factor VIII; antifibrinolytic therapy; remove loose deciduous tooth.

Hemophilia B: 30 u/kg factor IX concentrate; antifibrinolytic therapy remove loose deciduous tooth.

Dental Care—Guidelines

- Brushing of teeth done in proper manner (paste should contain fluoride) at least twice daily (with soft brushes—dental floss or interdental brushes help reduce plaques).
- Mouthwashes containing chlorhexidine/triclosan should be used.
- Dental consultation as soon as teeth erupts then at age of around 12 or 13 years of age to decide for difficulties arising from overcrowding/malocclusion.

- In case of mild hemophilia any surgical dental procedure (even plaque removal or regional block anesthesia) can be done under cover of desmopressin; in case of severe hemophilia factor replacement is the key treatment (nonsurgical procedures can be done under antifibrinolytic agents in case of mild to moderate hemophilia—but hematologist consultation should be taken always).¹⁸
- Before any surgical procedure antibiotic cover should be given.
- Local use of fibrin glue/tranexamic acid swish-and-swallow after dental extraction are safe and cost-effective method to help control bleeding (tranexamic acid used topically—10 ml of a 5 percent solution used as mouth rinse for two minutes, four-five times daily for a week is recommended, it may be used concomitantly with oral tranexamic acid table for a week.¹⁹⁻²¹
- Pain can be controlled with NSAIDs preferably paracetamol, indomethacin, and codeine which are safe.
- After dental surgery, diet of cold liquid and minced solids should be taken for 5 to 10 days, smoking and tobacco chewing should be avoided.

Epistaxis: Clinical features:

- May be spontaneous or related to trauma
- Most often bleeding is anterior (from the Little's area)
- Anemia can be significant.

Management (Table 3)

- Sit patient upright and advise breathing from mouth.
- Apply firm pressure to both nostrils with two ice cubes wrapped in cloth/gauze pieces for 5 to 15 minutes.
- When bleeding stops, lightly pack the bleeding nostril with cotton/gauze soaked in a solution of antifibrinolytic drugs (500 mg of tranexamic acid in 10 ml of clean water).

Table 3: Replacement therapy for hemorrhage in hemophilia A and B

Site of bleeding	Required factor level %	Dose in hemophilia A	Dose in hemophilia B
Joint	30-50	20-40 U/kg/d	30-40 U/kg q2d
Muscle	40-50	20-40 U/kg/d	40-60 U/kg q2d
Oral mucosa	50, add EACA	25 U/kg	50 U/kg
Epistaxis	80-100, then 30 until healed	40-50 U/kg, then 30-40 U/kg/d	80-100 U/kg, then 70-80 U/kg q2d
GI tract	100, then 30 until healed	40-50 U/kg, then 30-40 U/kg/d	80-100 U/kg, then 70-80 U/kg q2d
G-urinary tract	100, then 30 until healed	40-50 U/kg, then 30-40 U/kg/d	80-100 U/kg, then 70-80 U/kg q2d
CNS	100, then 50-100 for 10-14 day	50 U/kg, then 25 U/kg q12h or continuous infusion	100 U/kg, then 50 U/kg/d
Trauma or surgical site	100, then 30-50 until healed	50 U/kg, then q12h or continuous infusion	100 U/kg, then 50 U/kg/d

- *Calcium alginate.* Calcium alginate is a polysaccharide that can be extracted from brown seaweed and made into fibers for swabs. When this material comes into contact with biological fluids, calcium alginate exchanges its Ca^{++} ions with Na^{+} ions from the blood and gels. Several studies have shown a hemostatic effect of this material, which can be used for epistaxis.^{22,23}
- Nasal packing, if bleeding persists and factor replacement as described below.

Hemophilia A: 20 units/kg factor VIII concentrate if above fails.

Hemophilia B: 30 units/kg factor IX concentrate if above fails (4 hour after antifibrinolytic dose).

Major surgery:^{24,25} Preparation of patient for surgery includes a careful history, and physical examination, measurement of an inhibitor titer, careful measurement of the increment and half-life after infusion of the appropriate clotting factor (VIII or IX), and assurance that adequate amounts of coagulation factor. Before surgery, the replacement factor infused to achieve a level of 80 u/dl for factor IX and 100 u/dl for factor VIII, the levels should be maintained greater than 50 to 60 u/dl for 7 to 10 days postoperatively. Lower doses to maintain levels at greater than 20 to 30 u/dl for an additional 1 to 2 weeks may then be used and continued until healing has occurred. Following is the treatment plan: *Hemophilia A:* 50 to 75 u/kg factor VIII concentrate, then initiate continuous infusion of 3u/kg per hour to maintain factor VIII > 100 U/dl for 24 hour; then give 2 to 3 units/kg continuously for 5 to 7 days to maintain the level greater than 50 U/dl and an additional 5 to 7 days at a level > 30 U/dl. (May switch to bolus dosing when patient ready for discharge)

Hemophilia B: 80 units/kg IX concentrate, then 20 to 40 u/kg every 12 to 24 h to maintain factor IX > 40 U/dl for 5 to 7 days and then > 30 U/dl for 5 to 7 days.

Hematuria

Clinical Features

- Uncommon but can occur spontaneously or following trauma
- May be associated with pain/dysuria
- Often due to local lesion
- Anemia may be significant

Management

- If mild (not causing significant anemia); Bed rest and adequate hydration with good urine output—one and half times the normal maintenance, and watching for 2 days may be sufficient
- If bleeding persists more than 2 days factor replacement as described below
- Cystoscopy/IVP/Ultrasonographic examination of the kidney may be required (rule out common causes of hematuria).

- Blood transfusion may be needed if anemia is severe. Iron and folate replacement for 3 to 6 months should be given.
- No antifibrinolytic drugs should be used.

Hemophilia A: 20 u/kg factor VIII concentrate; if not controlled, prednisone if human immunodeficiency negative.

Hemophilia B: 30 u/kg factor VIII concentrate; if not controlled, prednisone if human immunodeficiency negative.

GIT Hemorrhage

Occasional complication, acute episode should consider high doses of concentrate if substantial blood loss has occurred as per life-threatening hemorrhage, and revise your diagnosis and cause of hemorrhage after prompt investigations.

CNS Bleeding—Most Serious Complication

Clinical Features

- Often following minor trauma but may occur spontaneously. Trauma may be unrecognized, particularly in children.
- Onset of clinical presentation may be delayed (up to several days) after the injury
- Headache, vomiting, irritability, confusion, lethargy, drowsiness
- Focal neurological deficits
- Seizures.

Management

- Maintain airway, breathing and circulation. Therapy should be initiated before the radiological evaluation of lumbar puncture. Treatment involves replacement therapy to achieve a factor level of 100 units/dl for factor VIII and 80 units/dl for factor IX, the maintenance of adequate hemostatic levels (>50 to 60 units/dl) for a minimum of 14 days, and a more prolonged period of prophylactic therapy for an additional 1 to 2 weeks or longer.
- CT scan of the head to assess type and extent of bleeding
- Urgent referral to a center with facilities for intensive care and surgery, if needed
- Anticerebral edema measures and antiepileptic medications.

Soft Tissue Hemorrhage

- For most superficial soft tissue bleeding, factor replacement therapy is not necessary. The application of firm pressure and ice may be helpful.
- Evaluate the patient for hemorrhage severity and possible muscular or neurovascular involvement. Rule out possible trauma to spaces containing vital organs, such as the head or abdomen. Open compartment hemorrhage,

such as in the retroperitoneal space, scrotum, buttocks, or thighs, can result in extensive blood loss. Treat with factor immediately if this situation is suspected.

Lacerations and Abrasions

- Treat superficial lacerations by cleaning the wound, then applying pressure and steristrips.
- Treat abrasions with cleaning and pressure.
- For deep lacerations, raise the factor level, and then suture. Suture removal occasionally requires another infusion of factor.

Life-threatening Hemorrhage (Other than Central Venous System, e.g. Gastrointestinal Airway)

Life-threatening hemorrhages includes CNS hemorrhages, bleeding around airways, and is most common cause of life-threatening hemorrhages into hemophilia. Management is early replacement of factor as mentioned in CNS hemorrhage above.

Factor Replacement Products and Medications

FVIII Products^{26,27}

- A variety of products are available for replacement therapy. Fresh frozen plasma and cryoprecipitate are no longer used in hemophilia A and B because of the lack of safe viral elimination and concerns regarding volume overload. Many plasma-derived FVIII concentrates are commercially available.
- Various purification techniques are used to reduce or eliminate the risk of viral transmission, including heat treatment, cryoprecipitation, and chemical precipitation.
- Many recombinant FVIII concentrates are now available. The advantage of such products is the elimination of viral contamination. The effectiveness of these products appears comparable to that of plasma-derived concentrates. Concerns regarding higher incidences of the presence of inhibitor appear to be unwarranted.
- With wider availability of improved products (stability, purity) use of continuous infusion of factors has increased incrementally. Continuous administration of antihemophilic factors prevents the peaks and valleys in factor concentrations that occur with intermittent infusion; this benefit is particularly important when treatment is required for prolonged periods of time.
- Besides improved hemostasis, continuous infusions decreases the amount of factor used, which can result in significant savings.
- The indications for this approach include intracranial hemorrhage, vascular compromise, iliopsoas bleeding, and preparation for surgery.
- In most minor-to-moderate bleeding episodes, intermittent boluses are adequate. Intermittent boluses can

also be used as prophylaxis, especially in the treatment of recurrent bleeding in target joints.

Cryoprecipitate²⁸

Cryoprecipitate is prepared by a few blood banks in India. It should have at least 80 IU of factor VIII activity in 30 to 50 ml of the product and should be used for replacement therapy in factor VIII deficiency and von Willebrand disease. Stored at or below -30°C . Needs to be thawed before use and should be infused as soon as it reaches room temperature ($20-30^{\circ}\text{C}$) using blood-giving set.

Cryosupernatant/Lyophilized Prothrombin Complex Concentrate (PCC)

Left over plasma after preparation of cryoprecipitate contains factors II, VII, IX, X (the prothrombin complex). Can be used for replacing any of the above-mentioned factors. Can be stored at 4 to 8°C . Lyophilized PCC not commonly available.

Fresh Frozen Plasma (FFP)/Fresh Plasma

If plasma is used within 6 hours of bleeding from a donor, it is considered to be fresh plasma and contains all clotting factor in near normal quantities. If this plasma is frozen and stored at or below -30°C , then it is called FFP. FFP contains both factor VIII and IX in concentration of 1 IU/ml. Each bag of FFP should be between 100 to 200 ml (or 100-200 if of factor VIII/IX). Needs to be thawed and infused over 15 to 30 minutes as soon as it reaches room temperature ($20-30^{\circ}\text{C}$) using a blood-giving set.

Fresh Whole Blood

When no other product is available, fresh whole blood may have to be used. If it has to be used, then "screened" donors should be used to donate blood. 1 IU of factor VIII/IX will be present in about 2 ml of whole blood.

Since blood bank products are not virus inactivated at present, there is a significant risk of transmission of HIV, hepatitis B and C viruses with the use of any of these products:

- *Desmopressin vasopressin analog, or 1-deamino (8-D-arginine) vasopressin (DDAVP)²⁹⁻³²*
 - DDAVP is considered the treatment of choice for mild and moderate hemophilia A. It is not effective in the treatment of severe hemophilia.
 - It stimulates a transient increase in plasma FVIII levels and results in sufficient hemostasis to stop a bleeding episode or to prepare patients for dental and minor surgical procedures.
 - It can be administered intravenously at a dose of $0.3\text{ }\mu\text{g}$ per kilogram of body weight.
 - Its peak effect is observed in 30 to 60 minutes.
 - A concentrated DDAVP intranasal spray is available. Its effectiveness is similar to that of the intravenous

preparation, although its peak effect is observed later, at 60 to 90 minutes after administration.

- Several doses of DDAVP may need to be infused every 12 to 24 hours before tachyphylaxis is observed.
- The major adverse effects of DDAVP are asymptomatic facial flushing and hyponatremia.
- *Antifibrinolytic drugs* (e.g. tranexamic acid and epsilon amino caproic acid) for 5 to 10 days are effective as adjunctive treatment for mucosal bleeds (e.g. epistaxis, mouth bleed) and are used to decrease the use of coagulation products in dental extraction. It neutralizes fibrinolytic activity in the saliva. These drugs should be avoided in renal bleeding as unlysed clots in the renal pelvis and ureter can behave like stones resulting in ureteric colic and obstructive nephropathy. Antifibrinolytic drugs should not be given concurrently with nonactivated or activated prothrombin complex concentrates because of potential thrombotic complications.

Preventive Care

Prevention of bleeding should be the goal, staying healthy also helps prevent bleeds. This includes:

- Getting regular exercise to promote strong muscles, protect joints, and improve fitness
- Wearing protection (helmets, protective padding) that is appropriate for the sport or activity
- Getting regular check-ups that include joint and muscle examinations
- Getting all vaccinations is recommended, including hepatitis A and B;
- Maintaining a healthy body weight to avoid extra stress on joints; and
- Avoiding contact sports, but swimming and cycling with appropriate gear should be encouraged. Physiotherapy to develop strong muscles and thereby prevent bleeding into the joints is an important component of hemophilia care in developing countries. All patients and their families should have a book of simple exercises and the child as he grows should learn that regular exercise, even when there is no bleeding, is the best prevention.

Gene Therapies ³³⁻³⁵

With the cloning of FVIII and FIX and advances in molecular technologies, the possibility of a cure for hemophilia with gene therapy is an area of intense research, and human trials are underway. Hemophilia A and B are ideal disease states to target for gene therapy since they are caused by mutations in single identified genes, a slight increase in clotting factor levels *in vivo* can convert severe hemophilia into milder disease, and current replacement therapies will always be considered suboptimal. Also, there is a wide range of safety if there is an “overshoot” of

desired level of coagulation activity. Unfortunately, to date the promise of gene therapy and a cure for the hemophilia patient have not been realized, primarily because a gene delivery system which is nonimmunogenic enough to allow for long-term expression of the clotting factor activity has not been achieved completely. Furthermore, strategies for gene therapy in general have been modified following a death experienced in a gene therapy trial for ornithine transcarbamylase deficiency, and due to cases of acute T cell leukemia reported in X-linked recessive SCID treated with retroviral vectors, attributable to insertional mutagenesis. Despite the relative safety and some indications of prolonged expression gained from the 6 trials conducted in the hemophilias, there are currently no gene therapy trials open for hemophilia, although additional trials are under review. If specific FVIII or FIX gene therapy cannot be immediately achieved, then other novel therapeutic approaches may offer alternative benefits, including:

- The use of gene delivery of engineered secreted, activated FVII
- Applications of new viral vector technology
- Use of nanoparticle technology for the delivery of genes to hepatocytes
- Gene “pharming”.

Any of these, if successful, could enhance the quality of life for the individual with hemophilia and potentially offer an approach to treatment of patients in developing countries where concentrate therapy is unavailable.

Pegylated Factor VIII³⁶

The current treatment for hemophilia A involves intravenous injection of recombinant or plasma-derived human FVIII, because injected FVIII has a short half-life *in vivo*, this strategy has major limitations for highly demanding regimens (e.g. prophylaxis, immune tolerance induction, surgery). Newer formulations of longer-acting FVIII are presently under investigation. The use of low molecular weight polyethylene glycol (PEG)-containing liposomes as carriers for recombinant FVIII (rFVIII) results in the prolongation of hemostatic efficacy. Data from preclinical experiments in mice, early clinical evaluations, and pharmacokinetics and pharmacodynamics results indicate that an rFVIII pegylated liposomal formulation may provide potential clinical benefit to patients with severe hemophilia A by prolonging the protection from bleeding. FVIII-Lip once-weekly prophylaxis is not inferior to rFVIII-water for injection thrice-weekly prophylaxis.

Bioengineered Clotting Factors to Increase Protein Expression and Bioactivity³⁷

Both recombinant protein replacement therapy and gene therapy could be facilitated by either the development of factors that demonstrate improved biosynthesis or through the generation of coagulation proteins with

enhanced biological properties. FVIII variants have been generated that either stabilize the molecule, increase the specific activity, or enhance production:

- B-domain deleted—FVIII yields higher mRNA levels, and targeted point mutations within the A1 domain reduce interactions with the endoplasmic reticulum (ER) chaperone immunoglobulin-binding protein. In order to increase ER-to-Golgi transport, several asparagine-linked oligosaccharides within a short B-domain spacer have been engineered within BDD-FVIII. A bioengineered FVIII incorporating a combination of these elements was secreted 15- to 25-fold more efficiently than full-length FVIII, both *in vitro* and *in vivo*.
- FVIIIa could be stabilized via the incorporation of a disulfide bond that prevents the spontaneous dissociation of the A2 domain from the activated FVIII heterotrimer following thrombin activation. This disulfide bond-stabilized FVIII showed prolonged FVIIIa activity and improved potency in whole blood clotting assays.
- Gain-of-function FVIII mutants have also been created by engineering out calcium-binding sites in the FVIII heavy chain, resulting in 2-fold increased activity.
- The specific activity of FIX could also be increased by protein engineering. In particular, replacing the first epidermal growth factor (EGF)-like domain of FIX with that of factor VII (designated FIX-EGFVII) resulted in a bioengineered FIX molecule with improved bioactivity in hemophilia B dogs.
- Engineering out the collagen IV-binding sites of FIX improved the bioavailability of FIX, resulting in higher circulating FIX levels when it was delivered via gene therapy.
- Alternatively, the half-life of FIX could be improved further by generating a fusion protein comprising FIX and the immunoglobulin (Ig) constant (Fc) region in a unique monomeric configuration. This FIX-Ig fusion protein exhibited improved pharmacokinetic properties and clotting activities in hemophilia B mice and dogs. Whether the use of bioengineered clotting factors alters the risk of inhibitors remains to be addressed. Some gain-of function mutations are buried, or conservative, and thus would not be expected to result in new epitopes recognizable by B-cells. In fact, some mutations may decrease the risk of inhibitor formation, permitting a longer-term strategy to develop more active, less immunogenic, molecules. Novel technologies that can affect the coagulation cascade.

CONSULTATIONS

A genetic counselor may be consulted. Genetic testing for hemophilia A and B is available and must be offered to potential carriers. Prenatal testing is performed by using amniocentesis or chorionic villus biopsy.

Annual dental evaluation is recommended. A neurologist and neurosurgeon should be consulted when necessary, and consultation with an orthopedic surgeon should be considered in situations involving significant or repeated hemarthrosis.

Activity

Generally, individuals with severe hemophilia should avoid high-impact contact sports and other activities with a significant risk of trauma. However, mounting evidence suggests that appropriate physical activity improves overall conditioning, reduces injury rate and severity, and improving psychosocial functioning.

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Inhibitors in Hemophilia and Management

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INTRODUCTION

In about 25 percent of severely affected hemophilia A and 1 to 3 percent in children with hemophilia B treatment is complicated by the formation of inhibiting antibodies (inhibitors) directed towards FVIII or Factor IX.¹ These inhibitory antibodies bind to infused FVIII, thereby reducing its half-life and neutralizing its coagulant activity,² resulting in an increased bleeding tendency that does not respond to FVIII replacement therapy. FIX inhibitors develop less frequently. When an inhibitor is suspected, testing should be done by Bethesda inhibitor assay (BIA). Inhibitor screening should be done before invasive procedures and at regular intervals during the initial 50 treatment days, as this is the highest risk period for inhibitor development. After factor replacement for 150 treatment days, the rate of inhibitor development is substantially reduced.

An inhibitor is usually detected during routine screening or when, suddenly and unexpectedly, bleeding does not stop as quickly as it should in response to treatment with factor VIII or IX. The Bethesda inhibitor assay measures the amount of antibody, reported as a number of Bethesda units, or a Bethesda titer, which is proportional to the amount of inhibitor present.

The mechanism of FVIII inhibitor development remains unresolved and complicated because no single factor can be counted as responsible. Risk factors for development of inhibitors³⁻⁵ are relatively young children, usually within their first 50 exposures to FVIII, both patient- and product-specific factors, specific molecular abnormalities (e.g. gene deletions, stop codon mutations, frame shift mutations) are associated with a higher incidence of inhibitor development (FVIII and FIX). Also, inhibitors are more likely to develop in black children. In addition, purified products (some no longer marketed) have been associated with increased inhibitor development. As

for recombinant FVIII products, no new inhibitors have been known to develop in previously treated patients, and inhibitors develop in as many as 30 percent of previously untreated patients (PUPs). In PUPs, the titer of the inhibitors is low in half and transient in one-third. A recent large open labeled randomized control trial study all across the world 'Survey of Inhibitors in Plasma-Product Exposed Toddlers' (SIPPET) would tell the better answer between correlation of inhibitor formation between plasma derived and recombinant factors. Results are awaited.

Clinically, these antibodies result in an increased bleeding tendency that does not respond to factor VIII replacement therapy. Patients that develop inhibitors suffer increased mortality and morbidity, although alternative (albeit expensive) hemostatic therapies are available. The development of inhibitory antibodies therefore, remains one of the greatest challenges in the treatment of hemophilia A patients. Inhibitory antibodies that develop in patients with hemophilia A are usually of mixed subclass with a dominant contribution of IgG4. Current evidence suggests that these antibodies recognize a restricted set of well-defined regions in factor VIII.

An inhibitor is usually detected in one of two ways. Although the person with hemophilia may have no symptoms, the inhibitor may be discovered during routine screening performed at a comprehensive evaluation. Alternatively, an inhibitor may be suspected when, suddenly and unexpectedly, bleeding does not stop as quickly as it should in response to treatment with factor. The presence of an inhibitor is usually confirmed using a specific blood test called the Bethesda inhibitor assay. The amount of antibody can be measured using this test, and is reported as a number of Bethesda units, or a Bethesda titer. Therefore, the higher the number of Bethesda units (or, the higher the Bethesda titer) the more inhibitor there is present.

When an antibody is detected, it will usually be classified as either high or low responding depending on how a person's immune system is stimulated upon repeated exposure to factor VIII or IX. If the immune system reacts briskly and strongly, the amount of inhibitor directed against factor VIII or IX can rise quickly to high levels (reflected in a high Bethesda titer). Without further exposure to the factor, the Bethesda titer may drop down to a low level, but this process could take many months to occur. When it has these characteristics, the inhibitor would generally be called high responding. Alternatively, the immune system may be stimulated in a different way such that its response to factor exposure is slower and weaker, and the Bethesda titer will remain low. This type of inhibitor is generally characterized as "low responding." Interestingly, the characteristics of an inhibitor can change over time, and at times the inhibitors have been noted to disappear spontaneously within several weeks or months without apparent treatment.

ACQUIRED AUTOANTIBODY INHIBITORS (ACQUIRED HEMOPHILIA)

Autoantibody inhibitors, predominantly targeting FVIII in individuals with previously normal coagulation, occur with an estimated incidence of 1 to 3 per million population per year. The mortality rate associated with acquired autoantibody inhibitors approaches 25 percent versus the substantially lower risk of death in those with alloantibodies. Compared to alloantibody inhibitor patients, acquired hemophilia is characterized by:

- A more severe bleeding pattern
- Higher incidence in older population
- Occurrence in conjunction with identifiable underlying autoimmune diseases, lymphoproliferative or solid tumor malignancies, pregnancy
- Use of certain antibiotics such as penicillin and sulfonamides in approximately 50 percent of cases.

The therapy of acquired autoantibody inhibitors is based primarily on the need to control or prevent acute hemorrhagic complications, which frequently are life- and limb-threatening and secondarily to eradicate the autoantibody to restore normal coagulation. While most bleeds associated with low titer autoantibody inhibitors (<5 Bethesda units) may be treated effectively with FVIII concentrates administered at high doses, the correlation between Bethesda unit titer and response to therapy is not as predictable as it is with alloantibody inhibitors.

Eradication of inhibitor is highly desirable and widely accepted goal of hemophilia care. The eradication of inhibitor is accomplished through immune tolerance induction (ITI) which typically involves the daily infusion of large doses of FVIII over many months to years as well as the use of immunosuppressive agents. The efficacy rate of ITI ranges from 63 to 83 percent.⁶ A major disadvantage of ITI is its high initial cost.

Management of Inhibitors in Hemophilia

General Rules

- Monitor all patients every 3 to 6 months for the development of inhibitors. This should be done specially in children in newly diagnosed children with hemophilia.
- Never undertake a surgical procedure or joint aspiration in a person with hemophilia without checking for inhibitors.
- If there is no response to appropriate replacement therapy, treat for inhibitors.

After initial diagnosis of a low titre inhibitor in a patient with Hemophilia A, routine doses of factor VIII may be as much as doubled and the clinical response and inhibitor titre monitored. Subsequent poor clinical response or rising titre levels indicate a non-transient inhibitor. The diagnosis of a high titer inhibitor which does not respond to factor VIII should be treated with an alternative product. There is an incidence of inhibitors in those with mild hemophilia A following treatment with factor VIII concentrates and the guidelines will also apply to those patients. DDAVP is occasionally used in mild to moderate hemophilia but is often ineffective.

CONTROL OF HEMORRHAGE

Product Options for Replacement Therapy

The major precept of hemophilia care consists of adequate replacement of the deficient coagulation factor protein so as to prevent or reverse acute bleeding episodes. This is most effectively and efficiently accomplished by the administration of clotting factor concentrates, which contain an abundance of the specific deficient coagulation factor. A multiple varieties of standard and modified factor VIII (FVIII), factor IX (FIX), and recombinant activated factor VII (rFVIIa) concentrates are available for the hemophilias and are categorized according to:

- Their source material, e.g. pooled normal plasma versus genetically engineered in "perpetual" mammalian cell lines.
- Their degree of purity, e.g. calculated on the basis of their specific activity (International Units [IU] of specific clotting factor activity/mg of total protein).
- The viral pathogen inactivation methods employed during manufacture, e.g. heat treatment, addition of solvent detergents, chromatographic separation steps, and nanofiltration, or combinations of the above.
- By whether they have been "activated" during manufacture, e.g. activated prothrombin complex concentrates (APCCs) and rFVIIa (used in allo- and autoantibody inhibitor patients) versus nonactivated PCCs (used for hemophilia B or low titer factor IX inhibitors).
- Finally, for rFVIIa, rFVIII, and rFIX, by the presence or absence of extraneous animal proteins or human albumin in the cell culture milieu as a nutrient source or in the final product as a stabilizer, e.g. first

generation FVIII products contain human and animal albumin in both the cell culture and the final product whereas third generation products have no animal or human protein present (except for the specific purified, recombinant human clotting factor protein) at any stage of production.

The choice of which replacement product to use is determined primarily by perception of safety from pathogen transmission and from alloantibody inhibitor development; however, other variables, including patient and/or physician preference, cost and reimbursement exigencies, product availability, and, interestingly, patient “value-added” features such as convenient vial sizes, innovative syringe delivery systems, etc. all contribute to the final decision. Fortunately, it is accepted that all of the currently available replacement products are equally effective for the treatment and prophylaxis of bleeding events (exclusive of inhibitors) and it is generally recognized that all products are virtually viral-safe. What is not so clear is what the tolerance of the patient or physician is to the extremely low but theoretical potential for transmission of non-lipid-enveloped pathogens, e.g. parvovirus B19, or prions, e.g. variant Creutzfeld-Jakob disease (vCJD), in plasma-derived products or the theoretical risk of pathogen transmission for the use of hamster cell cultures for the recombinant products. This also has become a major problem for individuals with von Willebrand disease, who are dependent on intermediate purity FVIII concentrates, some of which contain functional von Willebrand factor protein. No transmission of human immunodeficiency virus (HIV), hepatitis C virus (HCV), hepatitis B virus (HBV), or hepatitis A virus (HAV) has been documented for any replacement products licensed in the United States since the mid-1980s and no cases of vCJD have ever been reported anywhere with the use of any factor concentrate; however, because vCJD occurred in the UK in a recipient of packed red blood cells from a donor who was subsequently identified as being infected and because a plasma-derived FVIII concentrate was recalled recently in France because of a vCJD infected donor, recombinant products generally are perceived as potentially safer than plasma-derived products. There is general consensus that previously untreated patients with hemophilia should receive recombinant clotting factor concentrates, if at all possible. In the US, over 90 percent of clotting factor replacement therapy is recombinant in nature. These subtleties in the safety and purity of replacement products are particularly limited to patients in more developed countries since over 80 percent of the world’s hemophilia patients receive inadequate or no replacement therapy.

Factor VIII

In the case of life-threatening hemorrhage infusion of factor VIII in large doses can be used to swamp the inhibitor. This therapy is mostly used in patients with low responding

inhibitors. In patients who are high responders, this treatment may be effective provided the inhibitor level is less than 5 BU/mL. Factor VIII levels should be observed to assess and monitor response. Anamnesis can occur 5 to 7 days after therapy and make factor VIII ineffective. Recombinant and plasma-derived factor VIII are available.

Recombinant Factor VIIa

This product has been widely used and has proved to be highly effective in the management of spontaneous bleeding episodes which are life- or limb-threatening. Evidence in the literature suggests that it is effective in 79-92 percent of such episodes.⁷ In addition, there is evidence that it is effective in over 90 percent of cases of surgery.⁷ Recombinant factor VIIa is infused as a bolus. Continuous infusion of recombinant factor VIIa may reduce the quantity and cost of treatment but evidence is conflicting. A recent study suggests continuous infusion of 50 µg/kg/hr is effective in surgery.⁸ Antifibrinolytics are administered concurrently. The standard adult dose of recombinant factor VIIa is 90 µg/kg. However, in children the mean half-life is substantially reduced to 1.32 hours⁷ and thus higher doses of up to 200 to 250 µg/kg may be required. There is widespread evidence that recombinant factor VIIa is effective for treatment of all hemorrhage in patients with high responding factor VIII inhibitors. The use of rFVIIa potentially overcomes the significant drawbacks associated with conventional replacement therapy for the treatment of patients with inhibitors. It is a new concept of therapy based on the idea of compensating for an impaired FVIII/FIX-dependent coagulation pathway by driving the FVII/tissue factor-dependent pathway which is the normal initiator of hemostasis. The addition of exogenous rFVIIa is thus a pharmacological treatment instead of conventional substitution therapy. Other benefits include no risk of viral transmission, lack of anamnestic response and a more local hemostatic effect. Although the 35 mg/kg is probably suboptimal for postoperative management, at least in major procedures, 90 mg/kg is more effective for both minor and major procedures. More studies are needed to further define and refine an optimal dose schedule for surgical and nonsurgical patients with inhibitors. In conclusion, the availability of this product with its powerful and local hemostatic action is an important advance in the treatment available for the management of these challenging patients.

Activated Prothrombin Complex Concentrates (APCCs) e.g. FEIBA

Activated prothrombin complex concentrate, such as FEIBA VH, is effective in the treatment of 90 percent of bleeding episodes and has been effective in the management of bleeding during major surgery.⁷ An effective dose is 60 to 100 units/kg twice per day. The maximum daily dose of FEIBA is 200 units/kg/day.

Antifibrinolytic agents, such as tranexamic acid, should not be administered concurrently with FEIBA. It should be noted that FEIBA contains small amounts of factor VIII and therefore, may cause elevation of inhibitor titers in some patients. The 1997 Working Party Report⁹ did not recommend the use of these agents as first choice because they are plasma-derived rather than recombinant products; there is a reported high incidence of thrombosis associated with their use; and it is not possible to measure their activity in a standardized way. In patients who are having frequent bleeds, a trial of FEIBA as prophylaxis should be considered. The suggested dose is 75 to 100 units/kg three times a week.

Prothrombinex-HT

Despite general skepticism about the effectiveness of prothrombinex-HT in the management of joint hemorrhage, some patients report benefit and continue to be treated with this product. There are concerns about the incidence of thrombosis when using repeated high doses, particularly in the presence of liver disease and when used in combination with antifibrinolytics. There is no evidence of efficacy in serious hemorrhages in surgery.⁷

Antifibrinolytic Therapy

The recommended dose of tranexamic acid is 35 mg/kg/8 hour.

Plasmapheresis/Immunoadsorption

Plasmapheresis can be used to reduce inhibitor titers to allow effective therapy with factor VIII. Specific immunoadsorption using the Malmo protocol¹⁰ is available.

Immunosuppression

There is as yet little information on the use of immunosuppression in patients with factor VIII inhibitors but some experimental protocols are being proposed. Immunosuppression has been associated with side effects including delayed wound healing and increased susceptibility to infection. Rituximab (anti-CD 20 monoclonal antibody) therapy may be considered as an adjunct therapy to reduce inhibitor titers.

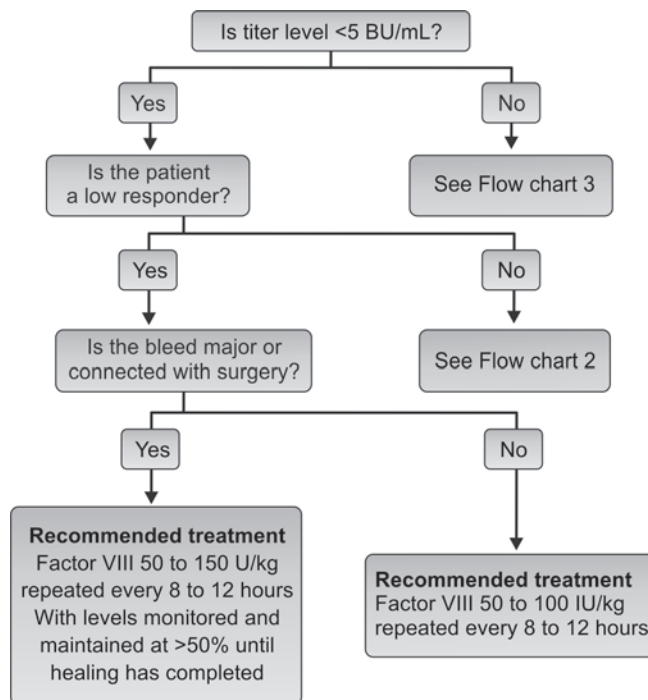
TREATMENT REGIMENS

Low Titer Inhibitor (< 5 BU/ml), Low Responder (Flow chart 1)

Minor Bleeding

The recommended dose of factor VIII is 50 to 100 IU/kg repeated every 8 to 12 hours. The response should be assessed clinically and factor VIII levels monitored.

Flow chart 1: Low titer low responder



Major Bleeding

The recommended dose of factor VIII is 50 to 150 IU/kg repeated every 8 to 12 hours. The response should be assessed clinically and factor VIII levels monitored and maintained at > 50 percent until healing has completed.

Low Titer Inhibitor (< 5 BU/ml) but History of High Responder (Flow chart 2)

Minor Bleeding

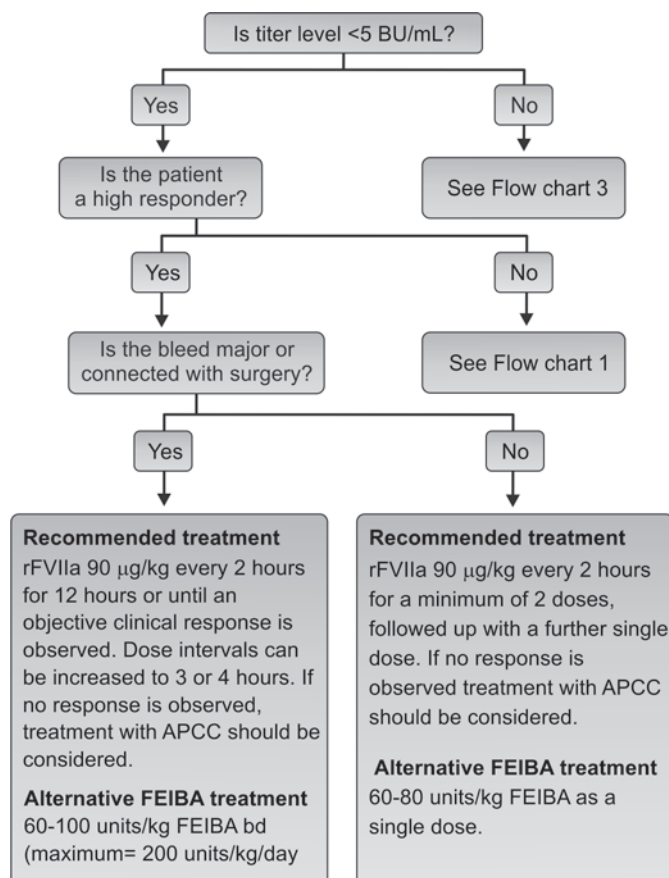
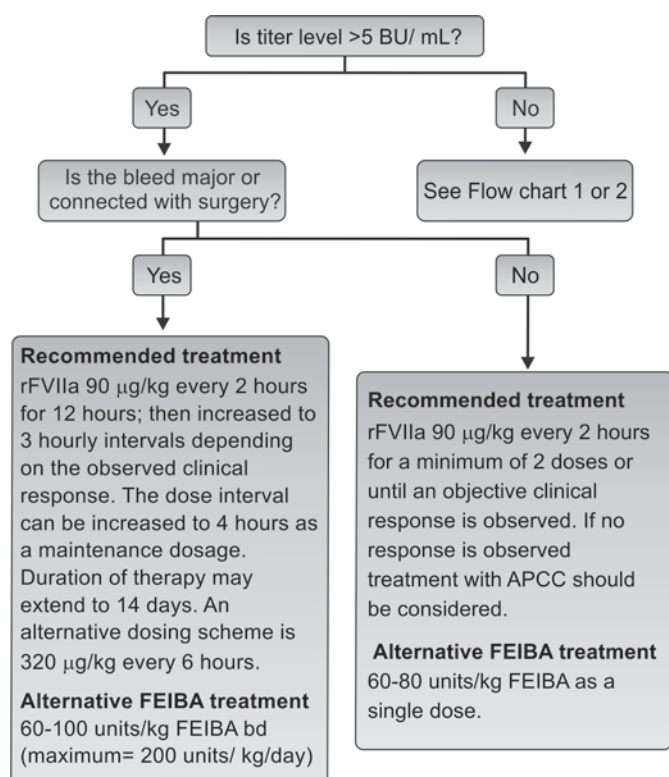
Infusions of factor VIII will cause an anamnestic rise of the levels of factor VIII inhibitor within 3 to 5 days rendering further therapy with factor VIII ineffective. The recommended adult dose of recombinant factor VIIa is 90 µg/kg (recommended pediatric dose may be up to 200 to 250 µg/kg) at 2 hourly intervals for a minimum of 2 doses or until an objective clinical response is observed. This should be followed up with a further single dose. If no response is observed treatment with APCC should be considered.

Guidelines for the treatment of inhibitors in hemophilia A. Australian Hemophilia Center Directors' Organization, September 2004¹¹

High Titer Inhibitor (>5 BU/ml) (Flow chart 3)

Minor Bleeding

The recommended adult dose of recombinant factor VIIa is 90 µg/kg (recommended pediatric dose may be up to 200 to 250 µg/kg) at 2 hourly intervals for a minimum of 2 doses or

Flow chart 2: Low titer high responder**Flow chart 3: High titer**

until an objective clinical response is observed. This should be followed up with a further single dose. If no response is observed treatment with APCC should be considered.

Major Bleeding

The recommended adult dose of recombinant factor VIIa is 90 µg/kg (recommended pediatric dose may be up to 200 to 250 µg/kg) at 2 hourly intervals for 12 hours; then increased to 3 hourly intervals depending on the observed clinical response. If appropriate, the dose interval can be further increased to 4 hours as a maintenance dosage. The duration of therapy is dependent on the severity of the hemorrhage. If major surgery has been performed, the duration of therapy may extend to 14 days. An alternative dosing scheme is 320 µg/kg every 6 hours. If no response is observed, treatment with APCC should be considered.

Guidelines for the treatment of inhibitors in hemophilia A, Australian Hemophilia Center Directors' Organization, September 2004.¹¹

ELECTIVE MAJOR SURGERY

Major surgery in patients with inhibitors carries a high degree of risk and should only be carried out in recognized HTC after careful consultation and agreement with at least one other Australian hemophilia specialist. All such discussions should be documented. It is recommended that a pharmacokinetic study be undertaken before surgery. The dosage regimen is based on the regimen for major bleeds. Dental surgery and the insertion of IV access devices require 3 to 5 days of therapy and antifibrinolytics.

EMERGENCY MAJOR SURGERY

The dosage regimen is based on the regimen for major bleeds. If time allows, there should be consultation and agreement with one other hemophilia specialist as in Elective Major Surgery. Any such discussion should be documented. The patient should be transferred to a recognized HTC as soon as practicable.

IMMUNE TOLERANCE

Tolerance should be considered in all those patients with recent persisting inhibitors. Eradication of the inhibitor will allow the patient with hemophilia to be treated with factor VIII, either on demand or prophylactically, with an optimal outcome and improved quality of life. Immune tolerance induction (ITI) is demanding for both patients and parents, and written informed consent should be obtained before starting. Intensive replacement therapy for immune tolerance usually requires central venous access. The International Registry on Tolerance¹² identifies better results in those patients with a lower age at

the start of ITI; shorter elapsed time of inhibitor presence before ITI; lower maximum pretreatment inhibitor titers and treatment with higher doses of factor VIII. There are a number of published tolerance protocols that describe a variety of doses of FVIII (e.g. 50 IU/kg three times a week up to 200 IU/kg daily) as well as the use of immune suppression. Tolerance should continue until eradication of the inhibitor demonstrated by a greater than 60 percent recovery and normal half-life of factor VIII. Tolerance should only be attempted in consultation with a physician experienced in the management of patients with hemophilia and inhibitors.

Immune tolerance induction using a desensitization technique is successful in up to 90 percent of patients with alloantibodies against factor VIII, with greatest success seen in patients with low titer inhibitors who are treated soon after detection of an alloantibody and in whom treatment includes administration of immunosuppression along with repeated infusions of high titer concentrates. Nonhemophiliac patients with acquired inhibitors represent a unique patient population that requires special management. These patients have a mortality rate that approaches 25 percent because of the association of acquired inhibitors with severe bleeding complications, occurrence in a largely elderly population, and the frequent presence of an underlying, often serious, primary medical condition. Typically, daily or bid FVIII or FIX concentrates are administered until the inhibitor titer is no longer detectable in the Bethesda Unit laboratory assay and the clotting factor recovery and circulating $t_{1/2}$ in plasma are normalized. Bypassing agents should be used to treat or prevent acute bleeding complications, which may become more frequent as anamnestic responses to ITI occur. The success of ITI approaches 90 percent usually over approximately 6 to 12 months for allo-FVIII antibody inhibitors and the following variables appear to be good prognostic indicators:¹³

- Initiation of ITI soon after detection of the alloantibody
- Initiation of ITI after reduction of antibody titer to a low level employing immunosuppression or mechanical means or waiting for the titer to decay from high to low level
- Low titer, low responder (nonanamnestic) inhibitor (<5 Bethesda Units)
- Use of plasma derived FVIII concentrates rich in von Willebrand factor
- Use of FVIII concentrates in amounts large enough (200 IU/kg/d) to achieve detectable FVIII activity in laboratory assays (for high titer inhibitors); low titer inhibitors may be suppressed with lower amounts of FVIII (25 IU/kg/d).

A large prospective randomized clinical trial is in progress to establish the validity of these variables. Once ITI is successfully achieved, a prolonged prophylaxis regimen with FVIII administered three times weekly should be instituted to consolidate inhibitor eradication. Several regimens are effective—the Dutch regime (25 IU factor/kg 3 times per week) is the most affordable.

ITI is less successful for FIX alloantibody inhibitors and may be associated with the development of severe anaphylaxis and nephrotic syndrome. Patients should be informed about the possibility of anaphylaxis if ITI is attempted in this setting. These individuals often have large FIX gene deletions and require rFVIIa to treat their acute bleeding episodes so as to avoid further exposure to any additional FIX antigen.

Eradication of autoantibody inhibitors depends on immunosuppressive measures, such as:

1. Administration of corticosteroids with 30 to 50 percent efficacy in 3 to 6 weeks.
2. Use of cytotoxic and myelosuppressive chemotherapeutic agents, e.g. cyclophosphamide, cyclosporine, 2-chlorodeoxyadenosine.
3. Immunomodulation with intravenous immunoglobulin.
4. Selective B-lymphocyte depletion with rituximab. Recent studies have been very promising although prospective controlled studies have not yet been performed. Some ITI regimens are complemented by extracorporeal plasmapheresis and/or immunoadsorption to reduce the inhibitor titers and thus improve the chances of ITI success.

Treatment of Resistant to Immunosuppressive Therapy

The management of patients with severe hemophilia A and inhibitors to factor VIII resistant to standard immune tolerance is challenging.

Rituximab (anti-CD 20 monoclonal antibody) therapy may be considered as an adjunct therapy to reduce inhibitor titers. Rituximab responders may require concurrent use of steroids and relapses may respond to retreatment.¹⁴ Recent immune tolerance induction regimens have successfully and rapidly eradicated the autoantibody inhibitor and this approach may emerge as preferable first-line therapy.¹⁵ A recent study¹⁶ used rituximab (375 mg/m² for 4 consecutive weeks) found to be useful as a part of rescue immune tolerance regimens if combined with FVIII. A total of 15 patients were reported of whom six (40%) achieved a negative inhibitor titer by Bethesda assay. Of the 12 patients treated with rituximab and FVIII, six (50%) achieved a negative inhibitor titer and none of the three patients treated without FVIII responded.

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Immunoglobulin G was first used in 1952 when Dr. Robert Good used it for treating X-linked agammaglobulinemia. Much of our current understanding of IgG has emerged from the research done in the late 1960s, which was mainly devoted to the assessment of the normal metabolic properties of IgG in humans.¹

The Y-shaped immunoglobulin G molecule is comprised of amino terminal end with two antigen-combining sites; the variable, or F(ab')₂, region; and the constant or crystallizable Fc region. Each molecule is specific to its antigen; this specificity resides within the variable region. Within the constant Fc region, common to all IgG molecules of that individual, reside multiple biological functions including binding to complement to cell-to-cell surface Fc receptors on the reticuloendothelial cells (FcR). FcR binding allows macrophages to phagocytize antigen-antibody reactions and cause mast cell and basophil activation and degranulation.

The exact mechanism of action of Immunoglobulin G is not known. Many of the immunomodulatory activities of the intravenous immunoglobulin (IVIG) may occur because of complementary interactions between autoantibody F(ab')₂ variable (V) regions (idiotypes) and V regions present in the administered IgG (anti-idiotypes) preparations. IgG dimers formed because of the id-anti-id complementarity, are plentiful in IVIG preparations and may function in several ways; to prevent auto antibody binding to antigen; when bound to FcR on phagocytic cells to act as superopsonins facilitating RE system clearance; when bound to FcR on B cells to inhibit autoantibody

In addition to a broad spectrum of autoantibodies based on donor number and population, pooled IVIG preparations contain antibodies to specific infectious antigens and super antigens. The infusion of large amounts of IVIG may change antigen-antibody ratios, thereby altering immune complex tissue deposition and solubilization. Fluctuations in serum levels change the catabolic rate of IgG, transiently altering the levels of both exogenous as well as endogenous immunoglobulins. Work by Dietrich, Kaveri, Kazatchkine, and others support the hypothesis that id-anti-id regulatory mechanisms predominantly account for the beneficial effects of IVIG administration. IVIG preparations may passively transfer autoantibody

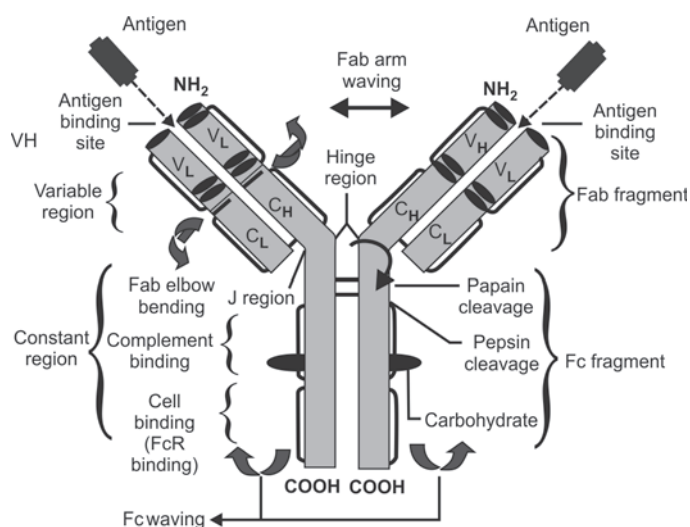


Fig. 1: Schematic representation of an immunoglobulin G molecule. CH indicates constant region of heavy chain; CL, constant region of light chain; VH, variable region of heavy chain; and VL, variable region of light chain.

anti idiotypes and actively alter endogenous regulation of autoantibody expression through id-anti-id interactions.² Prolonged benefit may also be attributed to Fc dependent changes in B cell and autoantibody production. Interactions with other cell surface antigens and alterations in cytokine secretion may additionally account for modulation of T and B cell activation and function.

Fc DEPENDENT INTERACTIONS

IVIG binds in the activated C3b and C4b components of the complement, inhibits their binding to target cells and solubilizes circulating immune complexes.

This mechanism is particularly important in the reversal of thrombocytopenia, hemolytic anemia and leukopenia.^{3,4} C3 and C4 bind to the Fc fragment of the IgG, forming heterodimers, which act as “superopsonins” sponging up activated complement; yet they are resistant to complement degradation.⁵ Consistent with the hypothesis, marked increases in the number of IgG molecules bound to RBC's have been observed in patients with autoimmune hemolytic anemia after treatment with IVIG. Decreased FcR binding on the RE cell's is often cited as a predominant mechanism in ITP and in cytopenias secondary to SLE. This response may be mediated by the competitive binding to FcR, which blocks binding of Ab-coated cells, as well as down regulation of FcR expression by small immune complexes present in the IVIG complexes. Another Fc mediated mechanism explaining the effect of IVIG infusions may be alteration of NK cell function. Following treatment of autoimmune neutropenia and ITP peripheral circulating numbers of NK cells is increased.⁶ F (ab')₂ or V region dependent interactions.

Passive infusion of anti-idiotypes in IVIG preparations may neutralize the effects of circulating autoantibody and down regulate its production when id-anti-id dimers bind to FcR on B cells. It may also stimulate the formation of regulatory IgG (and IgM) anti-id antibodies. Passive neutralization of antiphospholipid antibodies may result from id-anti-id interactions.

Clinical observation in patients with myasthenia gravis, SLE, ANCA positive vasculitides, GBS, and anti factor VIII autoimmune disease suggest that responders develop anti-idiotypic antibodies specific to the implicated autoantibody.

Similarly, specific down regulation of autoantibody production may account for the beneficial effects of IVIG treatment in patients with platelet and RBC alloimmunization.

Mechanisms Attributable to Fc- and F (ab')₂ Dependent Interactions

Modulation of cytokine secretion may be a primary or secondary effect. Several investigators have reported down modulation of monocyte secretion of proinflammatory

cytokines—IL-6, IL-1, TNF- α , IFN- γ , and IL-2 after *in vitro* incubation with PBMCs or stimulated macrophages with IVIG.⁷ Bendtzen et al first reported the presence of naturally occurring autoantibodies to IL-1 in the sera of normal individuals, another possible means of IVIG regulation of cytokine secretion.⁸ Recent publications have reported rapid increases in the plasma levels of IL-1 receptor antagonist and soluble TNF- α receptors as well as IL-6, IL-8, IFN- γ and/or TNF- α following IVIG infusion in patients with primary hypogammaglobulinemia or secondary epilepsy, suggesting agonistic as well as antagonistic effects on cytokine secretion.^{9,10}

The variable region dependent immunomodulatory effects of IVIG do not appear to be restricted to B cell activation and function. IVIG preparations contain antibodies to the first complementarity-determining region (cdr-1) of the T cell receptor (TcR) V β chain. Soluble MHC classes I and II including CD4 are present in the IVIG preparations. These molecules may directly down modulate specific T-B cell interactions. They also contain antibodies to CD5 cell surface antigen, which may function to regulate B cell production of auto-Abs.

Indications for Use

There are limited numbers of FDA labeled clinical indications for the use of IVIG in the US:

- As a replacement therapy for primary immunodeficiencies.
- As a treatment of idiopathic thrombocytopenic purpura
- As prophylaxis for bacterial infections in CLL
- Pediatric HIV infection
- For local and systemic infections
- Interstitial pneumonia
- Acute graft vs host disease after bone marrow transplantation.
- Renal transplants: In 2004, the FDA approved the Cedars-Sinai IVIG Protocol which has been 90 to 95 percent successful in removing antibodies from the blood of kidney transplant recipients so that they can accept a living donor kidney from any healthy donor no matter blood type (ABO incompatible) or tissue match
- Chronic inflammatory demyelinating polyneuropathy

However, based on the positive clinical experience on the treatment of ITP and Kawasaki disease, IVIG administration has been investigated in a number of autoimmune diseases and acquired immune deficiencies.

Prophylactic Use of IVIG in Acquired Immune Deficiencies

Following use as replacement therapy in patients with primary antibody deficiencies, IVIG administration has prevented infections in acquired immune deficiencies also in

Table 1: Use of IVIG as infection prophylaxis

- Hematological malignancies
 - CLL
 - Multiple myeloma
 - Low grade B cell lymphoma
- Immune deficiency following intensive chemotherapy and/or irradiation
- Prophylaxis of CMV infection
 - Bone marrow transplantation
 - Solid organ transplantation
 - HIV infection
- Prophylaxis in HIV positive adults and children
- Prophylaxis in hepatic insufficiency
- Prophylaxis in chronic renal insufficiency
- Prophylaxis in burns

Table 2: Effects of IVIG administration in Infections

- Binding and neutralization of infectious Ag toxins
- Restore normal levels of Ab to common organisms
- Blockade of binding of viruses and bacteria to target cells
- Neutralizing Abs vs superantigens
- Increased opsonization
 - PMN function requires normal levels of IgG
 - C3 + Fd of IgG = that acts as superopsonins
- Increased NK cell and bone marrow macrophage function
- Removal of circulating immune complexes in Ag excess, which are immunosuppressive
- Reduction in inflammatory cytokine levels.

the setting of hematological malignancies, solid tumors following intensive chemotherapy and/or irradiation, chronic renal or hepatic insufficiency, burns, and transplantation (Table 1).

Although IVIG treatment offers prophylaxis by passive administration of antibodies, additional effects are considered to mediate benefit Table 2.¹¹

Additionally

- Mori et al (2007) have found that intravenous immunoglobulin therapy does not change the course of Miller Fisher syndrome when used as treatment.¹²
- Korber et al (2007) have reported successful therapy of sclero-mixedema with low-dose intravenous immunoglobulin.¹³
- Zinman et al (2007), in a randomized trial of 51 patients with myasthenia gravis, found that IVIG had a positive effect in patients with worsening weakness due to myasthenia gravis.¹⁴

- Suchak et al found that intravenous immunoglobulin is effective as a sole immunomodulatory agent for treating pyoderma gangrenosum unresponsive to systemic corticosteroids.¹⁵
- Intravenous immunoglobulins are not recommended as a treatment of atopic dermatitis based on published data.
- Kerr and Ferguson have noted type II adult-onset pityriasis rubra pilaris successfully treated with intravenous immunoglobulin.¹⁶
- In febrile ulceronecrotic pityriasis lichenoides, high-dose IVIG combined with extracorporeal photochemotherapy can be an effective treatment.¹⁷

CLINICAL EVIDENCE FOR HIGH DOSE POLYCLONAL INTRAVENOUS IMMUNOGLOBULIN (IVIG) AS AN IMMUNOMODULATORY AGENT

High dose polyclonal IVIG is effective in the treatment of inflammatory disorders of the nervous system in adults. In randomized trials, IVIG reduced clinical disability in Guillain-Barre syndrome,¹⁸ chronic inflammatory demyelinating polyneuropathy,¹⁹ and multifocal motor neuropathy.²⁰ A systematic review of trials in multiple sclerosis suggests that IVIG reduced the relative risk of relapses by 21 to 28 percent (relative risk (RR) 0.79, 95 percent confidence interval (CI) 0.49 to 0.92; RR 0.72, 95 percent CI 0.54 to 0.97).²¹⁻²³ In randomized controlled trials evaluating serial magnetic resonance imaging in multiple sclerosis, brain lesions decreased in size and number after IVIG treatment.^{24,25} These studies suggest that IVIG can reduce cerebral inflammation and ameliorate pre-existing cerebral lesions.

In a systematic review of 11 randomized controlled trials with 492 patients of all ages with sepsis or septic shock, polyclonal IVIG reduced mortality by 36 percent, with a narrow confidence interval (RR 0.64, 95% CI 0.51 to 0.80).²⁶ This highly significant result may also, in part, reflect its multifactorial anti-inflammatory effects.

IVIG in ITP

The therapeutic dose of IVIG is set at 2 g/kg. Although some practitioners divide the total dose for infusion into five daily doses of 400 mg/kg each, it may be preferable to divide the total dose into two daily doses of 1 g/kg each, provided that the patient does not have such underlying conditions as congestive heart failure or renal (kidney) insufficiency.

Blanchette and the Canadian pediatric ITP group recently concluded 2 trials comparing IVIG, prednisolone and no treatment.²⁷ At least 6 other trials have demonstrated similar results that prednisolone leads to a faster increase in the platelets than no treatment at all. In the second trial by the same group, it was found that IVIG and prednisolone increased the platelet count significantly, but

marginally faster than IV Anti-D. The higher dose of IVIG did not increase the platelet count significantly faster than the lower dose IVIG arm.²⁸

IVIG in Kawasaki Disease

A Cochrane review of the effect of IVIG on the incidence of coronary artery aneurysms (CAA) was published in 2003.²⁹ A significant decrease in new CAA in favor of treatment with IVIG compared with placebo was seen at 30 days (relative risk 0.74; 95 percent CI 0.61 to 0.90). If the children with CAA found at enrolment were excluded, there was an improved benefit in children receiving IVIG (RR 0.67; 95 percent CI 0.46 to 1.00). There was a trend towards benefit at 60 days with IVIG treatment.

There was a decrease in the number of new CAA using higher doses of IVIG; the meta-analysis of 400 mg/kg/day for five days compared with a single dose of 2 g/kg showed a significant reduction in the CAA at 30 days (RR 4.47; 95 percent CI 1.55 to 12.86). The duration of the fever was also significant lessened with the higher dose.

There was no difference between the different types of preparation of IVIG used and no differences in the incidences of adverse effects in any group.

The conclusion of this Cochrane review was that Kawasaki disease should be treated with 2g/kg single dose IVIG within 10 days of onset of disease, which is in accordance with the guideline. Similarly, the finding that there may be benefit up to 60 days means that even children with a delayed diagnosis may benefit from treatment.

Preterms and Immunoglobulins

Transport of immunoglobulin from the mother to the fetus across the placenta occurs after 32 weeks and significant endogenous synthesis does not occur until after 24 weeks after birth.³⁰ If the mother does not have antibody to specific pathogens, then pathogen specific antibodies are also deficient in the newborn.³¹ IVIG, being a broad-spectrum immunomodulating agent, may help to reduce the inflammatory response and limit organ damage. However, there is currently little evidence from controlled trials to support the hypothesis that IVIG limits neonatal inflammatory damage. In the Cochrane review of trials using IVIG for prophylaxis in preterm and/or low birth weight infants and for treatment of clinical or proven sepsis, there are no data on periventricular leukomalacia and very little on CLD or neurodevelopmental outcome.^{32,33} Furthermore the doses of IVIG used were lower than in adult studies, which typically start with 2 g/kg, followed by repeat doses of 400 mg/kg at one or two month intervals. An ideal randomized controlled trial to test the hypothesis that IVIG can reduce inflammatory damage should randomize neonates at high-risk of central nervous system or pulmonary injury to prophylactic, repeated high dose

IVIG or placebo. It should include short-term outcomes of serial cytokine response, T-cell activation, magnetic resonance imaging of the brain, oxygen dependency and long-term outcomes of neurodevelopmental and cognitive impairment.

INIS, the international neonatal immunotherapy study, is a large randomized placebo controlled trial of IVIG, in a cumulative dose of 1 g/kg, as an adjunct to antibiotic treatment in proven or suspected neonatal sepsis. It does not therefore fulfill the criteria for an ideal test of these hypotheses. However, it may provide preliminary insights, particularly in specific subgroups. These include infants born after chorioamnionitis, prolonged rupture of membranes or increased maternal C reactive protein, who are at high risk of cerebral inflammatory damage.³²⁻³⁸

IVIG in Hemolytic Disease of the Newborn (HDN)

When HDN is treated with IVIG in addition to phototherapy, there is a reduction in the degree of hemolysis and therefore the need for exchange transfusion. As the antibody has not been “washed out” (as would be the case during an exchange transfusion), there may be late hemolysis and anemia. When the effect of the IVIG has worn off, the Fc sites on the surface of the reticuloendothelial cells become free to bind antibody sensitized neonatal erythrocytes, thus causing hemolysis. This is postulated to be the reason for the excess late red cell transfusions required in the IVIG treated group. The incidence of late anemia may in fact be similar to that occurring in infants who had moderate hemolysis but did not require exchange transfusions.

The exact mechanism of action of IVIG in hemolytic disease of newborn is unknown. It is hypothesized that the anti-D sensitized neonatal erythrocytes are destroyed by antibody dependent cellular cytotoxic effects mediated by the Fc receptor on the cells of the reticuloendothelial system. IVIG would occupy the Fc receptor sites, thus competing with the anti-D sensitized neonatal erythrocytes and preventing hemolysis.² This mechanism explained the abrupt block in hemolysis and arrest in rising bilirubin levels with adjuvant phototherapy in these four cases but this observation needs to be validated by other studies as well.

Side effects of Intravenous Immunoglobulins

The side effects can be separated into undesirable effects of their active components, the IgG's and adverse effects due to the “impurity” of commercial preparation, soluble substances or viruses.

General Reactions

Occur in 1 to 15 percent of the patients. They usually start 15 to 30 min after the onset of the infusion; are often mild

and self-limited and include pyrogenic reactions, minor systemic symptoms such as myalgia, fever, chills, headache, low backache, vasomotor and cardiovascular manifestations marked by changes in blood pressure and tachycardia, shortness of breath and chest pain.³⁹ These reactions are generally attributed to activation of the complement system. These may also be due to antigen-antibody reactions, possible contaminants or to the stabilizer used.

Hypersensitivity and Anaphylaxis Reactions

Usually seen with patients with IgA deficiency and shock is seen in patients with anti-IgA formation.

Neurological Complications

Headache is the most common symptom. Acute aseptic meningitis has been reported beginning few hours to a few days after IVIG infusions. Has also been seen to have a greater frequency in children on drugs like INH, sulphamethoxazole or SLE patients receiving anti-inflammatory drugs. Incidents of stroke have also been seen.

Renal Complications

Acute renal failure has been seen in patients. These can be because of the immunoglobulins themselves or because of the sucrose used as a stabilizing agent. Glomerular injury in the form of proliferative glomerulopathy may be seen. In others, a functional mechanism is described - disturbances of glomerular perfusion especially when high doses were given at a faster rate.

Hematological Complications

Neutropenia has been reported, but the mechanism is unknown. Coombs positive hemolytic anemia has been reported. Decreased haptoglobin levels and mild reticulocytosis has been seen but without changes in hemoglobin levels.

Miscellaneous

- Alopecia
- Hypothermia
- Interference with vaccination: Antibody response to measles vaccination is inhibited for up to 5 months after IVIG infusion and responses to rubella vaccine for 2 months.

Viral Contamination

As these are biological products, the chances of viral contamination with hepatitis causing viruses- like HCV, HBV, HGV and HIV are always present.

Production of Immunoglobulins

Most of the IVIGs are produced from the plasma of “unselected” donors. “Unselected” donor is the term used to designate plasma donors obtained at random. These contain a wide range of antibodies that represent the cumulative exposure of these donors to the environment. IVIGs produced from “selected” donors are preparations in which plasma is segregate on the basis of antibody content. These products are known as specific immunoglobulins (SIG) and contain elevated levels of clinically relevant antibodies. SIGs are also known as hyperimmunes. Lower doses of SIG need to be used.

Virus Removal During IVIG Preparation

Virus elimination processes fall into two main categories- partitioning and inactivation (Table 3). Virus removal by partitioning may occur when virus particles are precipitated along proteins into discard fragments or when they are adsorbed during clarification filtration processes that use a finely divided solid as a filter aid. Virus inactivation may occur during heating, freeze-drying, pH modifications, incubations with organic solvents, treatment with detergents, chemical modification, enzymatic digestion, oxidation reactions, or exposure to ionizing radiation. Antibodies that bind to the virus and prevent them from being infective (virus neutralization) may also be considered as inactivating.⁴⁰

Virus inactivation was originally done by chemical modification of an intermediate IgG fraction with β propiolactone.¹⁸ This inactivated HBV, HIV and NANB hepatitis.

In 1988, Horowitz reported that the solvent/detergent process, originally developed to inactivate viruses in factor VIII concentrates, was an effective virucidal process for IVIG preparations.⁴¹ Subsequently, this has been shown to be a reliable virus inactivating process that does not alter the biological activities of these proteins.⁴² Few data is available on the elimination of nonenveloped viruses during IVIG manufacture. Encephalomyocarditis virus has been shown to be removed by cold ethanol fractionation and inactivated by heating for 10 hours at 60°C.

Table 3: Summary of viral inactivation methods*Antibody mediated virus neutralization*

- Present in all IVIG preparations but difficult to quantify for viruses that are neutralized by antibodies in the donor population
- Relevant for HBV, HAV, parvovirus B19
- Potentially expensive and difficult to control and validate on an industrial manufacturing scale

Treatment with pH4 or pH4.25

- Not generally considered as a viral inactivating procedure
- Includes pepsin at trace concentrations in some preparations
- Enveloped viruses (HCV, HIV) readily inactivated
- Acid resistant, nonenveloped viruses, e.g. poliovirus not inactivated
- Temperature and incubation time at pH4 may be important
- Usually combined with freeze dried final product formulation that may stabilize virus

B-propiolactone treatment (+UV irradiation)

- Used by one manufacturer
- Active against HCV and lipid enveloped model viruses (pseudorabies, vesicular stomatitis virus) and HAV
- Limited effect on SV40

Solvent-detergent process

- Inactivated lipid enveloped viruses (HIV, HBV, HCV)
- Mixture removed at the end by chromatography
- Excellent safety record for coagulation factor concentrates
- Not designed for inactivation of nonlipid enveloped viruses as HAV, B19

Pasteurization in the presence of stabilizers

- Used in one IVIG preparation
- Potential for increasing adverse reaction rate
- Excellent safety record for coagulation factor concentrates but isolated cases of viral transmission still occur (HBV, HCV, B19)
- Stabilizers for IgG may also stabilize viruses

Viral filtration

- Filters of different sizes are available that could remove the viruses while allowing the IgG molecule to pass through
- Currently under investigation for coagulation factors
- Initial results promising

UV Irradiation

- Experimental method under evaluation
- Capable of inactivating a wide range of viruses
- May be particularly relevant for viruses that are not inactivated by the treatment

Some IVIG Preparations in India ⁴³⁻⁴⁵

	<i>Sandoglobulin</i>	<i>Gammagard</i>	<i>Intraglobin</i>	<i>Verglob</i>	<i>IV gamma</i>	<i>Isiven V</i>
Preparation	Acid (pH4) with traces of pepsin	Chromatography	B propiolactone UV radiation Nanofiltration	PEG treated	PEG treated	pH4 treated
Additives	Sucrose	Glucose Glycine, Albumin	PEG, Albumin	0.45% Glucose saline	Glucose Albumin NaCl	Glucose Albumin NaCl
IgG subclass (%)						
G1	60.5	67	69	NA	NA	64
G2	30.2	25	29	NA	NA	28
G3	6.6	5	0	NA	NA	6
G4	2.6	3	1.8	NA	NA	2
IgA(g/L)	0.72	0.0009-0.0016	0.12	NA	NA	NA
Formulation	3-6% lyophilized	5% lyophilized	5% lyophilized	5% lyophilized	5% lyophilized	5% lyophilized

PEG=Polyethylene glycol, NA=Details not available

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Nutritional Anemia

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Anemia is the most prevalent problem in the world particularly in the developing countries.¹ The World Health Organization (WHO) has outlined the criteria for the diagnosis of anemia for various age and sex group by low hemoglobin (Hb) or hematocrit (Hct) (Table 1). Anemia is considered mild, when Hb concentrations are above 10 g/dl but below the cut-off value, moderate when the concentration is between 7 and 10 g/dl and severe when it is below 7 g/dl.² Epidemiological criteria for assessing the severity and magnitude of anemia in population have been defined by FAO/WHO³ (Table 2).

PREVALENCE

National Family Health Survey (NFHS)-3 data shows that 7 out of every 10 children age 6 to 59 months in India are anemic. Three percent of children age 6 to 59 months are severely anemic (less than 7.0 g/dl), 40 percent are moderately anemic (7.0-9.9 g/dl), and 26 percent are mildly anemic (10.0-10.9 g/dl).⁴ Anemia among children is widespread throughout India. The prevalence of anemia varies from 38 percent in Goa to 78 percent in Bihar. More than half of young children in 24 states have anemia, including 11 states where more than two-thirds of children are anemic.⁴ A prevalence rate of over 65 percent in preschool children has been reported in various studies undertaken in rural and urban India.⁵ In the adolescent period (10-19 yr), in a multicentric study, it was found that the incidence of anemia is about 50 percent and increases from 10 years onwards and continues to remain high till 18 years of age.⁶ By all accounts India falls in the category of high magnitude prevalence for anemia.

Prevalence survey and surveillance data usually do not distinguish between different causative factors of anemia. As nutritional deficiencies account for most of the anemic cases, it is often referred to as nutritional anemia from

public health view point. Iron deficiency (ID) is usually the most common cause of anemia. If in a population anemia prevalence exceeds 40 percent, all children <5 years of age and all women of child bearing age will be iron deficient.⁷ Iron deficiency affects nearly 2170 million persons worldwide, and 1200 million of them are anemic, of which 90 percent are in the developing countries.⁸ Besides iron deficiency anemia (IDA), the importance of other micronutrients in causation of anemia is being increasingly realized. In a recent study in an urban slum of Delhi, nearly half of the anemic young children had other nutritional deficiencies notably Vitamin B₁₂ and folic acid as the direct or associated cause.⁹ The nutrients which cause

Table 1: Hemoglobin and hematocrit cut-offs to define anemia

Age or sex group	Hb below g/dl	Hct below (%)
Children 6 months to 5 years	11.0	33
Children 6 to 14 years	12.0	36
Non-pregnant women	12.0	36
Pregnant women	11.0	33
Men	13.0	39

Table 2: Parameters for defining the magnitude of prevalence of anemia as a public health problem

Parameters	Magnitude		
	High	Moderate	Low
Percentage of population with less than defined cut-off	>40	10-39	1-9
Percentage of population with Hb <7 g/dl, especially women and children	>10	1-9	<1

Table 3: Normal requirement of some vitamins that may cause anemia

<i>Nutrients</i>	<i>Infants</i>		<i>Preschool</i>	<i>School</i>	<i>Adolescents</i>
	<i>0-6</i>	<i>6-12 months</i>	<i>1-5 years</i>	<i>7-12 years</i>	<i>13-18 years</i>
Vitamin A (µg/l)		350	400	600	600
Vitamin B ₆ (mg)	0.3	0.4	0.9	1.6	2.0
Thiamine (mg/1000 cal)			-----0.5-----		
Riboflavin(mg/1000cal)			-----0.6-----		
Vitamin C (mg)		25		40	
Vitamin E			-----0.8 mg/gm essential FFA-----		
Folate (µ)		25	40-50	60-70	100
Vitamin B ₁₂ (µ)		0.2		0.2-1.0	

Adapted from ICMR report¹⁰

anemia and their normal daily requirements are shown in (Table 3).¹⁰

IRON DEFICIENCY ANEMIA

Etiology

A thorough understanding of iron requirements, intakes and bioavailability is essential to explain why some individuals — infants, young children, women in reproductive age group (particularly pregnant women)—are at a greater risk of developing IDA than others. The iron requirements for various age/sex groups are given in (Table 4).¹⁰ The balance between requirements and the amount of iron absorbed can be disturbed by several factors working in concert or individually.

- *Inadequate iron supply:* Low overall dietary intake is one of the most important factors responsible for low iron intake. Low intake of iron rich foods further aggravates the situation.
- *Bioavailability of dietary iron:* Factors enhancing or inhibiting iron absorption play a significant role in determining the bioavailability of dietary iron. During first 6 months of life, breast fed infants are usually not iron deficient, as bioavailability of iron from breast milk is very high. Infants receiving predominantly cereal based weaning foods thereafter are however prone to anemia as iron absorption from this cereal based diet is very low. It is estimated that in the wheat millet based diet, iron absorption is around 2 percent and in rice-based diet, iron absorption is around 5 to 8 percent.
- *Decreased absorption of the iron:* High infection rates, Giardiasis and gastrointestinal problems interfere with food intake and the absorption. This may result in the development of anemia, particularly in young children when iron balance is precarious.
- *Chronic blood loss:* Hookworm infestations and various gastrointestinal pathologies may cause iron losses.

Table 4: Recommended dietary (iron) allowances for Indians

<i>Group</i>	<i>Particulars</i>	<i>Body weight (kg)</i>	<i>Iron (mg/d)</i>
Children	1-3 yrs	12.2	12
	4-6 yrs	19.0	18
	7-9 yrs	26.9	26
Boys	10-12 yrs	35.4	34
	13-15 yrs	47.8	41
	16-18 yrs	57.1	50
Girls	10-12 yrs	31.5	19
	13-15 yrs	46.7	28
	16-18 yrs	49.9	30
Men		60	28
Women		50	30
	Pregnant women	50	38
	Lactation (0-6 months)	50	30

However, chronic blood losses leading to IDA generally do not constitute a public health problem.

Pathogenesis

IDA is the end stage of a relatively long drawn process of deterioration in the iron status of an individual. It is only seen in the severe iron deficiency state, which may be divided into three functionally distinct stages of severity.

Stage I

Iron depletion with decrease in iron stores, reduction in ferritin levels and stainable iron in the bone marrow. Hemoglobin, serum iron, transferrin concentration and saturation are within normal limits.

Stage II

Iron deficient erythropoiesis leading to low serum ferritin, serum iron, and raised TIBC and free erythrocyte protoporphyrin; Hemoglobin may still be normal.

Stage III

Iron deficiency anemia (IDA) with significantly reduced Hemoglobin production resulting in microcytosis and hypochromia.⁶

IRON METABOLISM

There are 2 major sources of food iron: heme and non-heme iron. Heme iron is highly bioavailable, since it is absorbed intact within the porphyrin ring and is not influenced by most inhibitory factors in the diet. It is present in meat, fish and poultry as well as in blood products. In the developing countries esp. India, heme iron intake is lower or even negligible. The second type of dietary iron—non-heme iron is a more important source and is found to varying degrees in all foods of plant origin. This non-heme iron enters an exchangeable pool, which is markedly affected by promotive and inhibitory iron binding ligands. Some forms of non-heme iron, notably ferritin and hemosiderin only partially enter the exchangeable pool and are poorly absorbed. Besides this, the diet may also contain exogenous iron originating from the soil, water, and dust or cooking vessels. This is more frequently the case in developing countries where the amount of such contamination iron in a meal may be several times greater than the amount of food iron. The cooking of foods in iron pots may increase the iron content of a meal several fold.

About 1 mg of iron a day is shed from the body in urine, feces, sweat, and cells shed from the skin and gastrointestinal tract. Menstrual losses of an additional 20 mg a month and the increased requirements of pregnancy (500-1000 mg) contribute to the higher incidence of iron deficiency in women of reproductive age.

Iron is not absorbed from the stomach. Maximum absorption of iron occurs from the duodenum and it decreases as the food passes down the small intestine. The exact mechanism of iron absorption and its regulation are not clear. Two steps are involved in the absorption of iron: entry of iron from the intestinal lumen into the mucosal cell and its passage from the mucosal cell into the plasma. Only a fraction of the iron that enters the mucosal cell finds its way into the plasma the remainder being held in the cell as ferritin, which is lost from the body as the mucosal cell is desquamated into the lumen at the end of its life of 3 to 4 days. Iron status of the body at the time of the formation of the mucosal lining cells determines the amount of iron that is absorbed through these cells. With increased iron stores there is increased transferrin saturation and increased 'messenger' iron in the mucosal cell. This 'messenger' iron stimulates the production of

apoferritin. Thus, whenever there is increased transferrin saturation, a larger fraction of the iron entering the mucosal cell is held back as ferritin and discarded, as the cell is desquamated. Excessive accumulation of iron by absorption is thus prevented. Iron absorption is increased with decreased iron stores, increased erythropoietic activity and during pregnancy.

Iron metabolism is also affected by hepcidin. Hepcidin is a small peptide with a central position in the regulation of iron recycling and balance. Hepcidin is primarily expressed by the liver in response to acute-phase reactions, any further expression depends on the degree of hepatic iron storage, and hypoxia and/or anemia strongly down-regulate hepatic hepcidin release.¹¹ Movement of iron from the enterocyte into the bloodstream is mediated by the iron exporter ferroportin (iron-regulated transporter-1). Ferroportin (FPN) is located along the entire basolateral membrane of enterocytes, in tissue macrophages, in the liver (Kupffer cells), spleen and bone marrow, predominantly in the intracellular vesicular compartment. This protein also serves as an iron exporter in circulating phagocytic cells that recycle iron from senescent erythrocytes. Greater than 60 percent of total iron is present in erythrocytes. Thus, efficient heme iron recycling is critical in iron homeostasis. Hepcidin inhibits cellular iron export through binding directly to the iron exporter ferroportin and inducing its internalization and degradation in HEK-293 cells. The direct hepcidin-FPN interaction allows an adaptive response from the body in situations that alter normal iron homeostasis (hypoxia, anemia, iron deficiency, iron overload, and inflammation). Hepcidin (i) inhibits intestinal iron absorption, (ii) blocks iron transport across the placenta, and (iii) induces iron sequestration in macrophages. When body iron requirements are high (decreased iron stores or increased rate of erythropoiesis), the expression of hepcidin is decreased; a decline in the iron requirements leads to a reverse process.¹²

CLINICAL FEATURES OF IDA

Clinical features of iron deficiency anemia are similar to those due to anemia of any type. As the fall of hemoglobin is very gradual the onset of symptoms is very insidious. Symptoms depend on the rate of fall of hemoglobin and homeostatic adjustment of various systems in the body. Initially, pallor, anorexia and irritability may be noticed. Hyperdynamic circulation may lead to palpitation, fatigue, and shortness of breath, decreased exercise intolerance and congestive heart failure. Koilonychia, platynychia, glossitis, stomatitis, angular chelosis are the other common features. Formation of mucosal webs at the pharyngo-esophageal junction causes dysphagia, which is much more for solids than liquids. The triad of dysphasia due to esophageal webs, koilonychia and splenomegaly

Table 5: Benefits of effective IDA control program

Population group	Benefits
Children	Improved behavioral and cognitive development, where severe anemia is common, improved child survival
Adolescence	Improve cognitive development. In girls, better iron stores for later pregnancy
Pregnant women and their infants	Decreased low birth weight and perinatal mortality, where severe anemia is common, decreased maternal mortality and obstetrical complications
All individuals	Improved fitness and work capacity improved recognition

in a patient with IDD is known as the Plummer-Vinson or Patterson-Kelly syndrome. Gastritis is common in IDA but usually is asymptomatic. Mild degree of hepatosplenomegaly is also not uncommon. Pica is a well-documented feature of anemia in children. Craving to eat unusual substances such as dirt, clay, ice, laundry starch, salt, cardboard, etc. are seen in almost 70 to 80 percent of patients and usually are cured by prompt iron therapy. Pedal edema in IDA may be due to congestive heart failure, impaired renal function or associated protein deficiency. Rarely increased intracranial tension with papilledema may occur. Skull changes similar to those seen in congenital hemolytic anemia may be seen in children with iron deficiency since early life. These skeletal changes do not reverse with iron therapy.

There is increasing evidence that iron deficiency *per se* even in the absence of obvious anemia leads to many deleterious effects on various systems. Several morphological and biochemical changes at the tissue level have been shown to be the result of iron deficiency *per se*, independent of the hemoglobin level. Functional impairment of various tissues such as the myocardium, peripheral nerves, jejunum, cerebral cortex, kidney and liver have been demonstrated in patients of iron deficiency, which have been corrected by iron therapy before a significant rise in the hemoglobin level.

Consequences of Iron Deficiency

It has been shown that iron deficiency *per se* even in the absence of anemia leads to several morphological and biochemical changes at the tissue level with deleterious effect on various systems.

There are studies to suggest that children with iron deficiency are at high-risk of long-term impairment in mental and motor development. They also suffer from lower scores in IQ test, lack of concentration, short attention span and easy distractibility. Such deficits in cognitive functions may eventually result in school dropouts. What is worrying is that developmental deficits that occur due

Table 6: Laboratory screening for iron deficiency

Single measures
<ul style="list-style-type: none"> • Hemoglobin • Serum ferritin • Erythrocyte protoporphyrin • Serum transferrin receptor
Dual measures
<ul style="list-style-type: none"> • Serum ferritin + Hemoglobin • Erythrocyte protoporphyrin + Hemoglobin • Serum transferrin receptor + Hemoglobin • Serum ferritin + Serum transferrin receptor

to iron deficiency in infancy have been shown to be irreversible.¹³ Thus prevention of IDA in infants and growing children is an urgent need as it may lead to a permanent deficit in IQ (Table 5). Iron deficiency also adversely affects immune system thus increasing the susceptibility to infection. Another area of special significance is poor endurance and physical fitness even with mild anemia, which may be an obstacle to children for self-fulfillment and overall development.¹⁴ Other associations of IDA are thrombosis, febrile seizures, pica, temper tantrums, breath holding spells and possibly restless leg syndrome.

Assessment of Iron Status and Screening for Anemia

When negative iron balance ensues in a setting of normal body iron stores, the ultimate development of iron deficiency anemia is preceded by a number of different phases. The individuals begin to suffer from the adverse effects of iron deficiency well before they become frankly anemic. Initially iron is drawn from the stores to meet the needs of erythropoiesis. Exhaustion of body iron reserves is associated with decrease in stainable iron in the bone marrow, fall in serum ferritin to levels below normal and increase in iron absorption and iron binding capacity. These measurements are useful in evaluation of iron stores. Changes in hemoglobin concentration (Hb), serum iron, transferrin saturation (TS), free erythrocyte protoporphyrin (FEP) and marrow sideroblasts occur after the iron reserves are depleted. These tests are useful measures of functional iron (Table 6).²

Laboratory Evaluation of Iron Status

- *Hemoglobin concentration (Hb):* Both Hemoglobin and hematocrit (Hct) are equally useful tests and are interpreted similarly. On average hematocrit values are roughly equivalent to three times the Hemoglobin concentration. A fall in Hb or Hct represents anemia without any indication to its etiology. Hemoglobin (Hb) estimation, by cyanmethemoglobin method is considered sensitive, rapid and inexpensive investigation

for routine practice and field level. Hb estimation by Hemocue hemoglobin photometer has also been found simple and reliable, though it may be costly. The major limitation of Hb measurement is its low specificity. The Hb concentration alone does not distinguish between iron deficiency anemia and anemia due to other causes.

- *Erythrocyte morphology and red cell indices:* In a mild iron deficiency, red cell morphology and other red cell indices, e.g. MCV, MCH and MCHC are not altered. However, in iron deficiency anemia, RBC's become microcytic hypochromic and red cell indices are low, i.e. $MCV < 80$ fl, $MCH < 27$ pg and $MCHC < 33$ percent. MCV is more sensitive than MCH, but up to 30 percent cases of IDA could be misdiagnosed if only these indices are relied upon.
- *Red cell size distribution:* Electronic counters can provide red cell size distribution. The variability in red cell sizes is reported as red cell distribution width (RDW). An elevated red cells distribution width (RDW) more than 14.5 percent is strongly suggestive of iron deficiency. In thalassemia trait and anemia of chronic disease the RDW is normal. Some of the discriminant functions to differentiate iron deficiency anemia and thalassemia trait are given below:

Discriminant Function

Calculation	Iron deficiency	β -thalassemia trait	
$MCV - (5 \times Hb) - RBC - 3.4$	> 0	< 0	(England and Fraser)
$\frac{MCV}{RBC}$	> 13	< 13	(Mentzer)
$\frac{MCH}{RBC}$	> 3.8	< 3.8	(Srivastava)
RBC count	< 5.0	> 5.0	(Klee et al)
$MCH \times \frac{(MCV)^2}{100}$	> 1530	< 1530	(Shine and Lal)

- *Serum ferritin:* The serum ferritin is a sensitive laboratory index of iron status. It is estimated that each ng/ml of serum ferritin is equivalent to 8 to 10 mg of storage iron. A serum ferritin value of < 12 ng/ml is highly specific for iron deficiency but gives no information about its magnitude. Another major limitation of serum ferritin is that its level is increased in chronic disorders, e.g. chronic infection and thus coexisting iron deficiency anemia can be missed.
- *Serum iron, total iron binding capacity (TIBC) and transferrin saturation (TS):* A normal serum iron level varies considerably as it has a diurnal variation and peaks in the morning and decreases in the evening. Serum iron concentration may also be affected by chronic

infection, malignancy and chemotherapy. Serum iron value of < 40 μ g/dl (< 12 mcg/dl in young children) is considered diagnostic of iron deficiency uncomplicated by infection or other disorders which affect iron metabolism.

Total iron binding capacity (TIBC) is the measure of transferrin circulating in the blood. Usually there is enough transferrin present in 100 ml of serum to bind about 250 to 450 μ g of iron. Since normal serum iron concentration is 100 μ g/dl transferrin may be found to be one-third saturated with iron. In iron deficiency states, TIBC is increased and transferrin saturation level is less than 16 percent ($< 14\%$ for children). TIBC < 200 μ g/dl is characteristic of inflammatory disease.

Transferrin saturation = $\frac{\text{Serum iron}}{\text{TIBC}} \times 100$

- *Free erythrocyte protoporphyrin (FEP) and protoporphyrin:heme (P:H) ratio:* Erythrocyte protoporphyrin, the precursor of heme accumulates in red blood cells when it has insufficient iron to combine with to form heme. The FEP can be measured by a simple fluorescence assay performed directly on the thin film of blood. Therefore, both FEP and P:H ratio is elevated in iron deficiency. Normal values of FEP are 30 to 40 μ g/dl RBC and P:H ratio 16 (± 5.3). FEP values above 70 μ g/dl RBC and of P:H ratio above 32 is thought to represent iron deficiency.
- *Serum transferrin receptor (sTFR):* The serum transferrin receptor increases with enhanced red cell production but iron deficiency is the only disorder in which there is increased serum receptor combined with a low level of red cell production. Unlike the serum ferritin, which only identifies iron deficiency, the serum transferrin receptor measures its severity. Values above 9 mg/L are considered abnormal, mean levels in healthy male and female subjects are 5.6 mg/L. Unlike many other iron measurements, the level remains normal in patients with anemia of chronic inflammation or infection and therefore assists in identifying iron deficiency in population where chronic infection is common. The serum receptor is measured by the same ELISA system as the ferritin and requires only a few μ l of plasma or serum.
- *Stainable iron in the bone marrow:* Bone marrow aspirates can be stained for hemosiderin by Perl's reaction and iron content is graded from 0 to 4. Although it is the most accurate technique to evaluate iron status, it is an invasive procedure and therefore impractical.
- *Response to therapy:* In uncomplicated IDA, administration of iron shows a predictable reticulocytosis and a rise in Hb. Hb concentration remains the most dominant predictor of response to therapy in uncomplicated iron deficiency. A positive response to therapy can be defined as a daily increase in Hb concentration of 0.1 g/dl (0.3 or 1% rise in Hct) from the fourth day onwards.

Multiple Indices

Hemoglobin remains a key screening measurement, but it has a low sensitivity and specificity. Its utility can be enhanced combining it with a more specific index of iron status. A very useful combination of measurements is the hemoglobin and serum ferritin. If both measurements are normal, iron deficiency is excluded; if both are low, iron deficiency anemia is unequivocally identified. If the serum ferritin is low but the hemoglobin is normal, the individual is at risk of iron deficiency, while if the hemoglobin is low but the serum ferritin is normal further hematological assessment is required to identify the cause of anemia.

Treatment

Treatment of anemia depends upon the severity and associated complications. Cases with Hb level <5 g/dl may require hospitalization as some of the patients may already be in congestive cardiac failure. Blood transfusion is required only in most severe cases with Hb concentration <3 g/dl. Young children may have to be transfused at Hb level less than 4 to 5 g/dl due to higher risk of congestive cardiac failure or when superimposed infection may interfere with the response. Rapid correction of anemia by transfusion may be dangerous due to the risk of hypervolemia and cardiac dilatation. Packed or sedimented red cells should be slowly administered, preferably 2 to 3 ml/kg at one time.¹⁵

Medicinal Iron Therapy

For infants and children, the recommended therapeutic dose is 3 mg of iron per kg per day.¹ For women (15 years +) with severe anemia (Hb <7 g/dl) National Nutritional Anemia Control Program (NNACP) recommends three tablets of iron-folate per day (each tablet containing 100 mg of elemental iron and 500 µg of folic acid) for a minimum of 100 days in the adults.¹⁶ Although the desired Hb level is usually reached in 2 months, iron therapy should continue for another 2 months to build up iron stores to 250 to 300 mg or the serum ferritin level to 30 µg/L.

Preparations of Iron Tablets

Practically all-medicinal preparations now contain ferrous compounds, which are better absorbed than ferric iron. Ferrous sulfate, gluconate and fumarate are the compounds mostly used. Other ferrous compounds previously or still in use include ferrous succinate, lactate, glycine sulfate, glutamate, citrate, tartrate and pyrophosphate. Although ferrous succinate is probably more completely absorbed, these compounds, in addition to being more expensive, offer no advantages over ferrous fumarate, gluconate or sulfate. Iron absorption is comparatively poor from carbonate, citrate, choline-citrate, calcium citrate and pyrophosphate salts and combinations. Table 7 shows the iron content of some preparations.

Table 7: Elemental iron content of various iron tablets

<i>Preparation</i>	<i>Approximate iron content (%)</i>
Ferrous sulfate exsiccated	30
Ferrous sulfate (7H ₂ O)	20
Ferrous sulfate, anhydrous	37
Ferrous fumarate	33
Ferrous gluconate	12
Ferrous carbonate	16
Ferrous glycine sulfate	23
Ferrous succinate	35
Iron choline citrate	12
Ferric chloride	44
Ferric sulfate	27
Ferric hydroxide	50
Ferric ammonium citrate	18
Ferric saccharate	10
Ferric pyrophosphate	25
Ferric orthophosphate	28
NaFeEDTA	14
Hemoglobin	0.34
Elemental iron powders	
Hydrogen-reduced iron	97
Electrolytically reduced iron	98
Carbonyl-reduced iron	98

Combination with Other Nutrients

Folic acid can be combined with iron at negligible extra cost. Tablets with combination of folate and ferrous sulfate, are usually available and particularly useful for pregnant women. Addition of vitamin C (200 mg) increases the absorption of iron by about 30 percent, but addition of vitamin C may add to the cost significantly. Vitamin B₁₂ may need to be given in non-responders or those with evidence of megaloblastic anemia.

Side Effects

Side effects are seen in about 14 percent cases and not related to any particular iron compounds. Intolerance to oral iron is basically related to the dose of iron. Usual side effects are nausea, vomiting, constipation, diarrhea, and abdominal discomfort.¹⁵ Non-compliance is stated to be more often due to poor counseling and lack of motivation. Patients discontinue therapy as soon as they feel better and/or experience discomfort with the medications. Difficulty of sustaining motivation for two to three months in subjects who do not perceive them to be ill has posed a great challenge to health educators. It is essential to continue the therapy, if necessary, at a lower dose or the

tablets may be given with meals if that improves compliance. Iron taken with a meal is better tolerated, though absorption is reduced. The required amount may also be given in two divided doses, which will reduce side effects.

Parenteral Iron Therapy

Parenteral route should usually be avoided and is indicated in cases having severe side effects on oral therapy, noncompliance or gastrointestinal bleeding, which is aggravated by oral iron therapy. Complete iron requirement can be given in a single dose, known as total dose infusion. However, infusions can be given only in a hospital as anaphylactic reactions may occur. Iron dextran complex is the most commonly used preparation. The desired level of Hb to be increased can be precisely calculated. Keeping in account 50 percent or more iron for replenishing body store, the iron requirement can be determined from the equation:

$$\text{Iron (mg)} = \text{Weight (kg)} \times \text{Hb deficit (g/dl)} \times 80/100 \times 3.4 \times 1.5 \text{ or } \text{Weight (kg)} \times \text{Hb deficit (g/dl)}$$

Adverse reactions of parenteral iron therapy include anaphylaxis, skin rash, myalgia, arthralgia, etc.

Response to Therapy

Rapid hematologic response can be confidently predicted in iron deficiency. There is no evidence that the rate of Hb response is different in oral or parenteral therapy. Whether iron is given orally or parenterally the response to therapy should be carefully followed. Iron absorption, is maximum during the initial phase of therapy and declines from 14 percent in the 1st week to 7 percent in the 4th week to 2 percent after 4 months. A positive response to therapy can be defined as a daily increase in hemoglobin concentration of 0.1 g/dl (0.3 or 1% rise in hematocrit) from the fourth day onwards. Approximately 2 months are required to achieve a normal Hb level. Reticulocytes increase within 3 to 5 days and reach a maximum at 5 to 10 days, reticulocyte counts being 8 to 10 percent in severe anemia. The maximum rate of recovery from severe anemia in a child may be 0.25 to 0.4 g/dl per day increase in Hb or a 1 percent per day rise in hematocrit, which is more rapid than is anticipated in the adult. The expected clinical and hematological response to iron therapy are described in Table 8.

Nonresponders to Iron Therapy

This is evidenced by absence of rise in Hb or reticulocyte response, after 2 weeks of adequate therapy and needs to be investigated. Associated chronic infection may interfere with proper utilization of iron. Nutritional megaloblastic anemia is often associated and is seen in 2 to 13 percent preschool children in countries where malnutrition is common. Addition of folic acid as low as 100 to 200 μg per day will show fast response to treatment and reticulocytosis in

Table 8: Response to iron therapy in iron deficiency anemia

12-24 hrs	Replacement of iron enzymes; subjective improvement; decreased irritability; increased appetite
36-48 hrs	Initial bone marrow response; erythroid hyperplasia
48-72 hrs	Reticulocytosis, peaking at 5-7 days
4-30 days	Increase in Hb level
1-3 months	Repletion of stores

Table 9: Poor response to oral iron

Noncompliance
Ongoing blood loss
Insufficient duration of therapy
High gastric pH
Antacids
Histamine-2 blockers
Gastric acid pump inhibitors
Inhibitors of iron absorption/ utilization
Lead
Aluminum intoxication (hemodialysis patients)
Chronic inflammation
Neoplasia
Incorrect diagnosis
Thalassemia
Sideroblastic anemia

2 to 4 days in majority of cases. However, excess folate has no deleterious effect and hence recommended dose is 1 to 5 mg per day. Vitamin B₁₂ deficiency may be present in children, particularly infants and needs to be added if there is no response to iron-folate therapy. Nonresponse to therapy should also arouse suspicion for possibilities like thalassemia, pure red cell aplasia, renal failure and chronic blood loss, e.g. hereditary hemorrhagic telangiectasia (Table 9).

Other causes of microcytic anemias should be ruled out in case of nonresponse to iron supplementation therapy (Table 10).

Prevention of Nutritional Anemia

The three basic approaches to the prevention of IDA are:

- Supplementation with medicinal iron
- Dietary modification
- Fortification of food with iron

For the control of nutritional anemia the effective convergence of all the three approaches is recommended.

Supplementation with Medicinal Iron

Iron store present at birth and the highly bioavailable iron in breast milk protects an infant from IDA up to 6

Table 10: Characteristics of microcytic anemia associated with other disorders

<i>Iron</i>	<i>Chronic</i>	<i>Thalassaemia</i>	<i>Sideroblastic</i>	
Deficiency	Disorders	Trait	Anemia	
Degree of Anemia	Any	Seldom	Mild	Any
MCV	< 9.0 g/dl			
	Low	Normal/ low	Low	Low/high/normal
Serum ferritin	Low	Normal/ high	Normal	High
Soluble transferrin receptor assay	Increased	Normal	Increased	Normal
Marrow iron	Absent	Present	Present	Present

months. Supplementation with medicinal iron has been recommended by WHO for all children beyond 6 months of age till 12 months of age and low birth weight babies from 2 months onwards till 24 months of age.¹⁷ According to ESPGHAN guidelines, prophylactic enteral iron supplementation in newborn less than 1800 grams, should be started at 2 to 6 weeks of age (2–4 weeks in extremely-low-birth weight infants) at the dose of 2 to 3 mg/kg/day. Iron supplementation should be continued at least until 6 to 12 months of age.¹⁸

Daily Versus Weekly Supplementation

In humans, intestinal mucosal turnover time is five to six days and is used as the basis for the weekly preventive supplemental regimen. This could be a community based long-term and targeted regimen aiming at prevention of iron deficiency and at increasing iron reserves among adolescents and women. Recent results from a one-month supplementation study show that iron deficient and anemic women can absorb as much as 30 to 40 mg of iron per week from a single 60 or 120 mg dose of iron ingested on an empty stomach, demonstrating that if there is a high demand for iron as much as the equivalent of 4.3 to 5.7 mg of iron daily (30 to 40 mg/week divided by 7) can be absorbed from the supplement provided. This, plus the dietary iron absorption could supply increased iron demands. Indeed, weekly dosing preserves the absorption of 3 mg of iron ascorbate at higher levels than daily dosing suggesting that food iron absorption is better maintained, adding to the total amount of iron absorbed. (supplemental plus food iron).¹⁹ A recent meta-analysis on utility of weekly iron supplementation concludes that this modality provides therapeutic and prophylactic benefits. The effect on hemoglobin is only marginally lower than daily supplementation.²⁰ In the public health scenario, weekly supplementation has the advantage of being offered under supervised conditions. On the basis of a recent multi-centric study in India National consultation has now recommended that adolescent girls on attaining menarche should consume weekly dosage of one IFA tablet containing 100 mg elemental iron and 500 µg folic acid once a

week accompanied by appropriate dietary consultation. Thus a pack of 25 tablets would provide requirement for 6 months. Weekly dose is considered as cost effective, with fewer side effects and better compliance.²¹ Amongst 1 to 5 years old children, daily versus weekly supplementation in a dosing of 3 to 4 mg/kg showed similar results at the end of a 60-day trial.²²

Dietary Modification

Food based approach, though not suitable for treatment purposes, constitutes the most desirable and sustainable methods of preventing iron deficiency. Once the child has been weaned, dietary modification can help to increase iron intake through iron rich foods. On the basis of currently recommended dietary allowances it seems that the overall intake of iron is adequate (Table 11). However, the major limiting factor has been the poor bioavailability of iron due to presence of inhibitors like phytates in cereal-based diet. Phenolic compounds including tannin present in tea and coffee are also strong absorption inhibitors. Absorption promoter of iron like vitamin C plays a crucial role to prevent iron deficiency. Indian diet has been shown to be deficient in vitamin C as well. Just inclusion of guava fruits with lunch and dinner meals for one month have shown to raise Hb level by 2.2 g/dl.⁵ Absorption promoters and inhibitors (Table 12) can make a significant difference in the availability of iron from the food in an individual. Fermentation and germination can enhance iron absorption by increasing vitamin C content and lowering phytic acid content. Heme iron present in meat is not only better absorbed, but increases absorption of non-heme iron of vegetable foods. In India vegetarianism is practiced widely and as such iron and vitamin C rich food items like green leafy vegetables and fruits probably hold the key for successful prevention of iron deficiency.

Fortification of Foods

Fortification of foods with iron is a cost effective, long-term measure for improving the iron status of the entire population. India does not have any iron fortification program currently. A formula for double fortified salt, i.e. salt

Table 11: Iron content of food articles

<i>Class of food</i>	<i>Iron content mg/100 g</i>	<i>Articles rich in iron >10 mg/100 g</i>
Cereals	2.5-14.0	Bajra, barley, kangri, ragi, rice flakes, whole wheat flour
Pulses and legumes	2.7-11.0	Bengal gram, soyabean
Leafy vegetables	0.9-40.0	Amaranth, beet greens, bengal gram leaves, coriander, potato leaves, pudina, neem, radish top, turnip greens, spinach, methi, lettuce.
Roots and tubers	0.4-13.9	
Nuts and oil seeds	2.5-100	Gingely, mustard, pistachio
Fruits	0.1-10.0	Dates, raisins
Seafood	1.0-115	Fish, crab
Meat	2.0-18.8	
Milk	0.2-0.8	
Miscellaneous		Jaggery, yeast

Table 12: Factors influencing dietary iron absorption

<i>Heme iron absorption</i>	
Amount of heme iron especially as meat	
Content of calcium in meal	
Food preparation (time, temperature)	
<i>Non-heme iron absorption</i>	
Iron status of subjects	
Amount of potentially available non-heme iron (adjustments for fortification iron and contamination iron)	
Balance between positive and negative factors	
<i>Positive factors</i>	<i>Negative factors</i>
Ascorbic acid	Phytate
Meat, poultry, fish	Iron binding polyphenols
Germination	Including tannin
Fermentation	Calcium
	Soy protein

fortified with iodine and iron has been developed and is being field-tested. It could be a very cost effective measure if found effective.

Macrocytic-Megaloblastic Anemia

Macrocytosis is a rise in the mean cell volume of the red cells above the normal range (in adults 80-95 fl (femto-liters)). A simple mnemonic to calculate the upper limit

of MCV for age group 2 to 10 years is $84 + (\text{age in yrs} \times 0.6)$ fl.

Megaloblastic bone marrow is exemplified by developing red blood cells that are larger than normal, with nuclei more immature than their cytoplasm. The underlying mechanism is defective DNA synthesis.

After iron, vitamin B₁₂ and folate deficiency are the most important cause of nutritional anemia and lead to megaloblastic anemia. Newborns and infants are prone to deficiency if their mother is deficient in these micro-nutrients.²³

Vitamin B₁₂ (cobalamin) is found in animal tissues but not in vegetable matter. Microorganisms like bacteria and fungi synthesize it. The daily requirement of vitamin B₁₂ is 1.0 µg. Milk, vegetables, cereals, pulses, etc. are poor sources of B₁₂ so that a vegetarian diet is deficient in it. Liver, kidney, meat, fish, salmon, crabs, oysters, egg-yolk, etc. are rich sources. The steps of cobalamin absorption in the gastrointestinal tract are discussed below. Cobalamin is released by enzymatic digestion from protein complexes in food in the acid pH of the stomach, where it binds to R binder present in saliva and gastric juice. This binder is closely related to transcobalamin (TC) I present in plasma, and is similar to a binder in milk and other fluids. After release from R binder in the duodenum by pancreatic proteases, cobalamin binds to intrinsic factor (IF), which is synthesized by gastric parietal cells. Cobalamin in bile is also attached to R binder and complexes with IF in the duodenum. The IF-cobalamin complex attaches to its receptor cubulin on the ileal brush border. Within the enterocyte, the IF-cobalamin complex is digested, probably within lysosomes, and the cobalamin appears in portal blood attached to TCII. In the plasma, cobalamin can bind to either TCI or TCII. The cobalamin bound to TCII is transported into various tissues where it is available for its metabolic function. Cobalamin is stored by hepatocytes and is lost from the body with a half-life of about 400 days. Depletion thus requires a prolonged period of poor intake or absorption.

The daily requirement of folic acid in humans as per WHO recommendations is 3 µg/kg/day of food folate for adults²⁴ with supplements for pregnant and lactating women and infants. Folate is widely distributed in foods and is selectively concentrated in a few tissues like liver, kidney and spinach. Egg, milk and meat are poor sources. Folic acid is absorbed from the whole length of small intestine. Natural folates are largely in the polyglutamate form, and these are absorbed through the upper small intestine after deconjugation and conversion to the monoglutamate 5-methyl tetrahydrofolate. In the body, folate is stored in the liver but the major route of utilization of hepatic folate appears to be by secretion into the bile and reabsorption from the gut. The normal total body folate stores are 5 to 10 mg and one-third of this is in the liver. With the

deficient intake, folate stores get exhausted within a few weeks.

Vitamin B₁₂ deficiency usually manifests in children over 2 years as body store is 3 to 5 mg and the daily loss is just 2 to 4 µg per day. In contrast folate deficiency manifest as early as 4 months despite store of 5 to 20 mg as the daily loss is 100 mcg per day.

As far as blood tests are concerned it is not possible to differentiate B₁₂ and folate deficiencies. Effects of deficiency of either of the two are conditioned by the status for the other.

Nutritional Deficiency Occurs (Table 13)

- In newborns and infants, born to deficient mothers.
- In older children and adolescents having poor intake of diet causing malnutrition or practicing vegetarianism diet which leads to B₁₂ deficiency. Folate being heat labile is also lost up to 80 percent in cooked food.
- Impaired absorption due to absence of intrinsic factor or diseases involving ileum or bypassing it also leads to malabsorption like tropical sprue, celiac disease, regional ileitis, idiopathic steatorrhea.
- Defective utilization in liver diseases due to reduction in the enzymes involved in folate metabolism. Anticonvulsants like hydantoin, phenobarbitone, antimalarials like pyrimethamine and antimetabolites like aminopterin block folic acid metabolism.
- Increased requirements particularly infants like pre-term babies due to rapid growth. The requirement also increases during increased bone marrow activity in conditions like hemolytic anemias, bleeding, leukemias and other myeloproliferative disorders.

Clinical Features of Megaloblastic Anemia

Megaloblastic anemia has a gradual onset but varied clinical presentation and at times may even mimic a hematological malignancy.^{23,25} There is a possible increase in the prevalence of megaloblastic anemia esp. in pubertal females. There is also an increased incidence of megaloblastic anemia due to vitamin B₁₂ deficiency. It needs to be reinforced that megaloblastic anemia is an important cause of pancytopenia. Hyperpigmentation of dorsum of hands and finger's is a characteristic feature. Vitamin B₁₂ deficiency may cause impaired maturation of cells of the mucosa of the mouth, tongue, and esophagus leading to gastrointestinal features like glossitis, nausea, constipation, diarrhea, loss of appetite and weight loss. Failure to thrive, growth retardation, poor cerebral development, infantile tremor syndrome, convulsions may be seen. A minority of patients with vitamin B₁₂ deficiency develop a neuropathy due to symmetrical damage to the peripheral nerves and posterior and lateral columns of the spinal cord, the legs being more affected than the arms. Psychiatric abnormalities and visual disturbance may also occur. Men are more commonly affected than women. The neuropathy may occur in the absence of anemia. Psychiatric changes and at most a mild peripheral neuropathy may be ascribed to folate deficiency. Neurological features as seen in sub acute combined degeneration of spinal cord are however, seen basically in pernicious anemia and not generally seen in nutritional B₁₂ deficiency. Folate deficiency may be associated with neurological features like depression, psychosis, peripheral neuropathy; cardiovascular disease associated with atherosclerosis and thrombosis. There is also evidence to suggest that mothers

Table 13: Causes of megaloblastic anemia

1. Diet
<ul style="list-style-type: none"> • Vitamin B₁₂ deficiency: Veganism, poor quality diet • Folate deficiency: Poor quality diet, old age, poverty, synthetic diet without added folic acid, goats' milk
2. Malabsorption
<ul style="list-style-type: none"> • Gastric causes of vitamin B₁₂ deficiency: Pernicious anemia, congenital intrinsic factor deficiency or abnormality gastrectomy • Intestinal causes of vitamin B₁₂ deficiency: Stagnant loop, congenital selective malabsorption, ileal resection, Crohn's disease • Intestinal causes of folate deficiency: Gluten-induced enteropathy, tropical sprue, jejunal resection
3. Increased cell turnover
<ul style="list-style-type: none"> • Folate deficiency: Pregnancy, prematurity, chronic hemolytic anemia (such as sickle cell anemia), extensive inflammatory and malignant diseases
4. Drugs
<ul style="list-style-type: none"> • Folate deficiency: anticonvulsants, sulphasalazine
5. Defects of vitamin B ₁₂ metabolism—Transcobalamin II deficiency, nitrous oxide anesthesia—or of folate metabolism (such as methotrexate treatment)

deficient in folate may give birth to baby with neural tube defects (spina bifida, encephalocele, and anencephaly) and folate supplementation may also reduce the incidence of cleft palate and hare lip in the fetus.

Diagnosis of Megaloblastic Anemia

- *Peripheral blood smear:* Demonstrating multilobed neutrophils can make the diagnosis. The red cells show macro-ovalocytes. There may be leukopenia and thrombocytopenia. The reticulocyte count is normal or low in an untreated case. Occasionally, megaloblasts may be seen in the peripheral smear.
- *Bone marrow examination:* Bone marrow examination will show presence of megaloblasts, which are larger than the normoblasts of a corresponding developmental stage. The nucleus shows an open chromatin network with a normal cytoplasm and normal hemoglobinization. These cells are often called giant myelocytes and giant metamyelocytes.
- *Estimation of serum B₁₂ and folic acid:* A serum B₁₂ level of <100 pg/ml and a serum folate level of <3 ng/ml are diagnostic of their respective deficiencies. However, deficiency of one produces changes in the serum level of the other. In patients with severe deficiency of folate, the concentration of cobalamin in plasma may be subnormal. This will become normal over a period of days after folate treatment is begun. Reduced erythrocyte folate levels (<150 ng/ml) are diagnostic of folate deficiency. Red blood cell assays are less affected by recent changes in diet or medications.
- *FIGLU test:* In folate deficiency the conversion of formiminoglutamic acid (FIGLU) to glutamic acid is impaired. Thus when a loading dose of histidine which gets converted to FIGLU is given to a person with folate deficiency, he is not able to convert this FIGLU to glutamic acid resulting in excessive excretion of FIGLU in the urine which can be estimated.
- *Schilling test:* Absorption of B₁₂ can be tested by this test. 1000 µg of B₁₂ is given parenterally to saturate the stores. Now, Co-58 labeled B₁₂ is given orally and the amount of radio-activity in the urine is measured by a scintillation counter. Reduced excretion of Co-58 labeled B₁₂ in the urine is diagnostic of impaired B₁₂ absorption.
- Serum methylmalonic acid is elevated in cobalamin but not folate deficiency. It is also elevated in renal failure, thyroid disease, hemoconcentration, small bowel bacterial overgrowth and pregnancy. Serum homocysteine is elevated in both folate and cobalamin deficiency. Homocysteine levels are less specific and are elevated in renal dysfunction, hypothyroidism, vitamin B₆ deficiency and with certain medications such as cholestyramine, carbamazepine and valproic acid.

Hence, patients with suspected cobalamin or folate deficiency and normal serum levels should be investigated with plasma or serum methylmalonic acid and homocysteine levels.

However, the most practical, cheap and easily available test is a therapeutic trial. Here, 100 to 1000 µg of B₁₂, i.e. cyanocobalamin or hydroxycobalamin is given intramuscularly. Diagnosis of B₁₂ deficiency is made if:

- The megaloblastic changes in the erythroid series in bone marrow normalize in 48 hours.
- At least two of the following occur (i) serum iron decreases by 50 percent in 24 hours; (ii) reticulocyte count increases in 5 to 10 days; (iii) correction of thrombocytopenia in 2 weeks; (iv) correction of neutropenia in 2 weeks; (v) decrease in MCV by 5 fl in 2 weeks after reticulocytosis has subsided; (vi) decrease in plasma methylmalonic acid (MMA) and total homocysteine levels in two weeks; (vii) correction of anemia in 2 to 4 weeks; (viii) decrease in neutrophil lobe count in 4 weeks. To detect folate deficiency 0.5 mg/day of oral folate is given for 2 to 3 days. Within 2 weeks reticulocytosis and metabolic normalization is seen. High doses of vitamin B₁₂ in malnourished children may lead to tremors.

Correction of Vitamin B₁₂ and Folate Deficiency

The deficiency of both vitamin B₁₂ and folic acid can be corrected by either oral or parenteral supplementation of the respective vitamin. Injection of vitamin B₁₂ should be given by parenteral route if there is any doubt about the absorptive function. Vitamin B₁₂ injection of 100 µg may be given every 3 to 4 days for 3 to 4 weeks followed by oral route. Alternatively 1000 µg of vitamin B₁₂ is given weekly for 5 weeks. Oral dose of folic acid is 1.0 mg daily for 2 to 3 weeks. By parenteral route 5.0 mg of folic acid every week should be an adequate dose. In cases of megaloblastic anemia the response can be judged by the reticulocyte response seen between 5 and 10 days after starting the treatment. This is followed by a rise in hemoglobin.

In cases of combined deficiency vitamin B₁₂ should be supplemented before the folic acid for the fear of precipitation of neurological complications.

Megaloblastic anemia associated with antimetabolite (antifolate acid) therapy does not respond to folic acid but to folinic acid. Similarly folate deficiency in liver disease, which is due to reduction in the enzymes concerned with folate metabolism, will also respond to folinic acid. Treatment of the cause leading to deficiency like tapeworm infestation, malabsorption states, etc. should be treated simultaneously.

If folate deficiency is diagnosed, it is important to assess dietary folate intake and to exclude gluten induced enteropathy by tests for serum antigliadin and anti-endomysial antibodies, endoscopy and duodenal biopsy.

Table 14: Other causes of macrocytosis*

- Alcohol
- Myelodysplasia
- Liver disease
- Cytotoxic drugs
- Hypothyroidism
- Paraproteinemia (such as myeloma)
- Reticulocytosis
- Pregnancy
- Aplastic anemia
- Neonatal period
- Red cell aplasia

*These are usually associated with a normoblastic marrow

In cases of non-responsiveness to hematinics, other causes of macrocytosis besides nutritional deficiency should also be excluded (Table 14).

CONCLUSION

Nutritional anemias are a global cause for concern, especially in developing countries. Reduction of nutritional anemia should receive top priority for national health and wealth. This will require a multipronged approach with better utilization of health infrastructure through proper planning and full participation of communities.

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Disorders of Platelet Function

ATK Rau, K Shreedhara Avabratha

Platelets are small (1 to 4 μm in diameter) anucleate bodies with a volume of about 7 to 11fl and originate from the cytoplasm of bone marrow megakaryocytes. Platelets are critical component for the first phase of hemostasis ('the platelet plug') stopping the initial leak of blood from injured blood vessels (Figs 1 and 2).

A review of normal platelet function is essential to understand disorders of platelet function. There are four sequential steps of platelet function in hemostasis (Flow chart 1).¹

- *Platelet adhesion:* The initial event is the attachment or adhesion of platelets to the vessel wall and is initiated by the exposure of the vascular sub endothelium following injury to the endothelial surface. Circulating

platelets are recruited to the site of injury and bind to the exposed components of the sub endothelium, which includes collagen, fibronectin, von Willibrand factor (vWF), fibrinogen, and thrombospondin via various glycoprotein (GP) receptors on the platelet surface like GPIb/IX, GPIa/IIa, GPIIb/IIIa)²

- *Platelet activation:* Receptor-ligand binding leads to platelet activation, mediated through calcium-dependent cytoskeletal changes in the platelet. This is followed by the sequential release from platelet granules of substances which promote platelet aggregation. There are two important granules—alpha granules (containing vWF, platelet factor 4, thrombospondin, fibrinogen, β -thromboglobulin and platelet derived



Fig. 1: The resting platelet

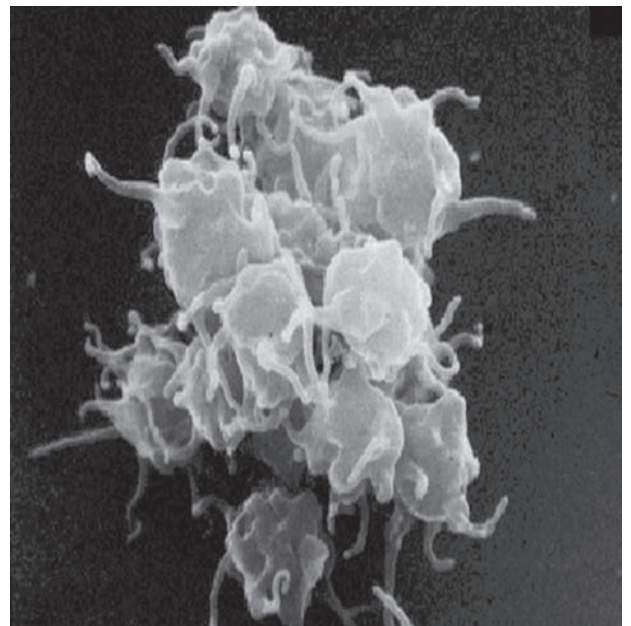
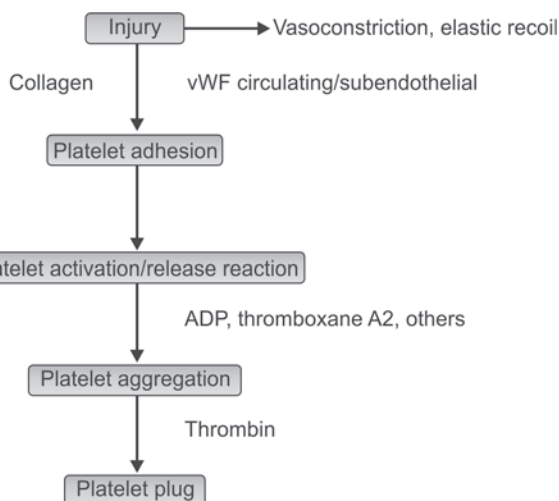


Fig. 2: The activated platelet

Flow chart 1: Schematic summary of role of platelets in hemostasis



growth factor) and dense granules (contain ADP and serotonin). ADP mediates the entire process of this second stage by 'inside out' signaling leading to a conformational change in GPIIb/IIIa on the platelet surface

- **Platelet aggregation:** Fibrinogen binds to the conformationally altered GPIIb/IIIa receptor on two or more adjacent platelets, resulting in serial platelet aggregation and accumulation at the site of vascular injury. Platelet agonists including thrombin, epinephrine and collagen enhance the aggregation phenomenon
- **Interaction with coagulation factors:** Aggregated platelets provide a binding surface to and interact with circulating coagulation factors. Activation of these platelets alters their phospholipid membranes allowing enhanced binding with coagulation factor complexes including the tenase and prothrombinase complexes, which then leads to the formation of the stable platelet plug.

CLINICAL FEATURES OF PLATELET FUNCTION DISORDERS (PFDs)

The clinical features of the platelet type of bleeding typically involve the skin or mucous membranes—petechiae, ecchymosis, epistaxis, menorrhagia, and gastrointestinal bleeding. Intracranial bleeding can occur, but rarely. Deep muscle hematomas and hemarthrosis typically seen in patients with coagulation defects infrequently occur in platelet disorders. In inherited platelet function disorders bleeding is usually present since early childhood but may be variable. In some instances bleeding may be severe and life threatening. In acquired hemorrhagic disorders the clinical picture is dominated by the underlying disease. In most cases a detailed history and physical examination will reveal the etiology of the platelet dysfunction (e.g. a

history of medication, diagnosis of myeloproliferative disorders, presence of cataract or hearing defects in MYH-9 disorders, oculocutaneous albinism in patients with Hermansky-Pudlak syndrome and hyper extensible joints in Ehlers-Danlos syndrome).

DISORDERS OF PLATELET FUNCTION

Disorders of platelet function include several rare congenital disorders as well as many common acquired conditions (e.g. effects of drugs). Although many inherited platelet disorders have been described, most are extremely rare, and even well-known disorders such as the Bernard-Soulier syndrome (BSS) and Glanzmann's thrombasthenia (GT) are uncommon, with a frequency of one in 10^5 to 10^6 in the general population and are usually seen in inbreeding populations or consanguineous relationships.³ By convention the inherited platelet function disorders are classified by their predominant features⁴ (Table 1).

LABORATORY EVALUATION OF PLATELET DYSFUNCTION

The initial evaluation of a patient suspected to have PFD should include a complete blood count, including a platelet count, and examination of the peripheral blood smear. The platelet count in these cases is either normal or mildly reduced. Large platelets are seen in BSS (mean platelet

Table 1: Classification of inherited disorders of platelet function

- Disorders of adhesion:
 - Bernard-Soulier syndrome (BSS)
 - von Willebrand disease (platelet type)
- Disorders of aggregation:
 - Glanzmann's thrombasthenia
 - Afibrinogenemia
- Disorders of secretion and abnormalities of granules:
 - α granule abnormality
 - Gray platelet syndrome
 - δ granule (dense granule) abnormality
 - storage pool defect
- Disorders of platelet secretion and signal transduction:
 - Defects in platelet agonist interaction
TX A₂, collagen, ADP, epinephrine
 - Defects in calcium mobilization
 - Defects in arachidonic acid pathways
- Disorders of platelet procoagulant activities
 - Scott syndrome
- Defects in cytoskeletal regulation
 - Wiskott-Aldrich syndrome
- Miscellaneous

volume >11 fl) and small platelets are characteristic of the Wiskott-Aldrich syndrome (MPL <5 fl). The so called “grey” platelets in the gray platelet syndrome appear pale and hypogranulated on the blood smear and indicate a congenital deficiency of alpha granules.

Screening Tests

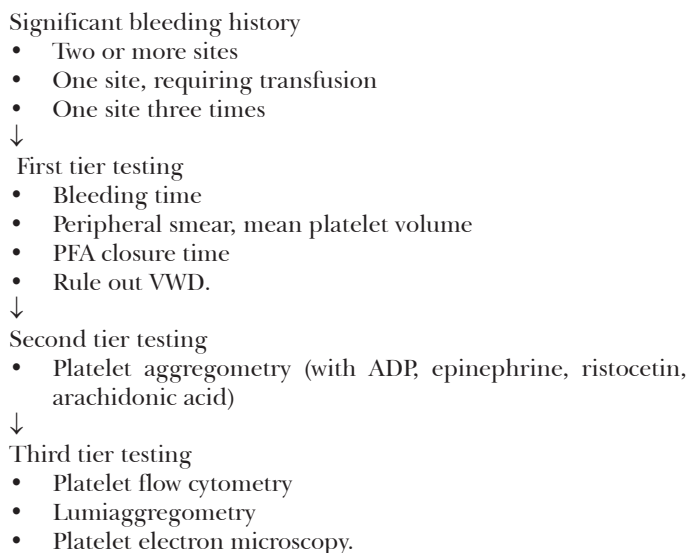
The primary screening tests in PFD are the bleeding time (BT) and platelet function analyzer-100 (PFA-100) assay techniques. However, the BT and the more specific clot retraction test are the only commonly available tests available in our setting. Unfortunately the BT is dependent on a number of other factors, including the skill of the technician and the cooperation of the patient⁵ and has largely been abandoned by most reference laboratories. The PFA-100 assay system requires small quantities of citrated venous blood (0.8 ml per cartridge) and is, therefore, useful for studying pediatric samples. However, the exorbitant cost of the device and of processing the samples, limits its use. It measures certain aspects of the platelet function by measuring the ability of the platelets in whole blood to occlude an aperture (closure time) in a membrane treated with either collagen and epinephrine or collagen and ADP under conditions of moderately high shear stress. Although the PFA-100 closure time is abnormal in some forms of platelet disorders, the test does not have sufficient sensitivity or specificity to be used as a screening tool for platelet disorders in general.⁶

PLATELET AGGREGATION STUDIES (FLOW CHART 2)

Specific platelet function tests may be performed using assessment of aggregation to a panel of agonists with platelet rich plasma or through whole blood aggregometers. The pattern obtained usually helps to diagnose and classify the defect. Common agonists employed include ADP, epinephrine, collagen, arachidonic acid, ristocetin and thrombin. von Willebrand disease (vWD) and BSS may be associated with defects in aggregation with ristocetin, while GT has a flat aggregation profile to all agonists except ristocetin. Lumiaggregometry measures the release or secretion of ATP by the dense granules upon stimulation by agonists and can help diagnose platelet granule related disorders.

Flowcytometry is the technique that measures protein expression on the cell using monoclonal antibodies. Its most common clinical use in PFD is in the diagnosis of inherited defects in platelet surface glycoproteins as in the detection of the decreased expression or absence of GPIb in BSS and GPIIb/IIIa in GT. Electron microscopy can be used to detect structural abnormalities, including a decreased number or abnormal morphology of alpha and dense granules in the platelet. Some families with severe platelet function may benefit from identification of

Flow chart 2: Approach to diagnosis of platelet function disorders



their molecular defect(s) to allow antenatal diagnosis to be offered. Flow chart 2 represents an approach to diagnose functional platelet disorders.⁷

SOME SPECIFIC PLATELET FUNCTION DISORDERS

Glanzmann's Thrombasthenia (GT)

Named after the famous Swiss pediatrician, this is a rare inherited autosomal recessive bleeding disorder, the hallmark of which is failure of platelet to bind fibrinogen and aggregate after activation. GT is the most common of the inherited platelet disorders.⁸ The underlying defect is an abnormality in the genes encoding either chain of integrin α IIb β_3 fibrinogen receptor (also known as GPIIb/IIIa complex or CD416). The fibrinogen molecule contains two GPIIb/ IIIa binding sites by which platelets are linked together into multicellular aggregates. The loss or dysfunction of the GPIIb/IIIa complex leads to failure of aggregation. Patients with GT have lifelong, repeated and often life threatening mucocutaneous bleeding beginning at an early age and may require platelet transfusions for severe episodes. The efficacy of long-term platelet transfusions is limited as patients often become allo-immunised and develop antibodies to platelets. Recent evidence suggests that recombinant activated factor VIII may be a useful supplement to platelet transfusions.⁹

Bernard-Soulier Syndrome (BSS)

The second most recognized inherited platelet disorder, caused by mutations in GPIb/IX complex, which is the principal receptor for vWF. In the absence of this receptor, platelets cannot adhere to vascular sub endothelium under high shear stress. Bleeding time is prolonged and the

associated lack of sialic acid may shorten platelet survival and lead to thrombocytopenia. Absence of ristocetin induced aggregation is the hallmark of this syndrome, which cannot be corrected by the addition of normal plasma. Flow cytometry analysis of platelet glycoproteins may also aid in the diagnosis. The bleeding manifestations of patients with BSS are similar to those of other patients with severe platelet dysfunction. Treatment is with platelet transfusions, desmopressin (DDAVP), aminocaproic acid (EACA) or tranexamic acid. Activated factor VIIa has also been reported to be useful in patients with BSS.

Platelet Type (Pseudo) von Willebrand Disease

Platelet-type vWD is an autosomal dominant bleeding disorder often associated with a prolonged BT, mild thrombocytopenia and decreased circulating levels of high molecular weight vWF multimers. Patient with this disorder have a mild to moderate bleeding diathesis. Unlike type 2B vWD, where mutations in vWF results in increased affinity of the abnormal vWF towards normal platelet GPIb/IX complex, pseudo vWD is primarily a platelet disorder caused by an alteration in the platelet GPIb/IX complex which leads to increased affinity for normal vWF multimers.¹⁰ In either case, the circulating levels of vWF in the blood is decreased, increasing the chances of bleeding. Platelet-type vWD can be distinguished from type 2B vWD by the addition of normal vWF to patient platelet-rich-plasma which results in spontaneous aggregation in the pseudo-vWD platelets but not in type 2B vWD platelets. Platelet-type pseudo vWD should be treated with platelet transfusions.

Hereditary Macrothrombocytopenias

These are a heterogeneous group of disorders characterized by an autosomal dominant inheritance of mild to moderate thrombocytopenia with large platelets and varying degrees of platelet dysfunction. Some of the syndromes have, in addition, leukocyte inclusions, interstitial nephritis, sensorineural hearing loss and cataracts. The four most common defects include the May-Hegglin anomaly, the Fechner syndrome, the Sebastian syndrome and Epstein syndrome—all of which are postulated to be variants of a single disorder arising from mutations in the heavy chain of a prominent non muscle myosin MYH9.¹¹

Platelet Storage Granule Defects

Patients with dense granule storage pool deficiency (SPD) exhibit a mild to moderate bleeding diathesis as well as abnormalities in platelet aggregation. The two most common SPDs are the Hermansky-Pudlak syndrome and the Chédiak-Higashi syndrome associated with albinism and immunodeficiency respectively. Patients with α granule deficiency also have a tendency to bleed. The platelets in peripheral smears on Wright stain appear gray, hence the

name 'gray platelet' syndrome. There is no specific treatment for platelet storage pool disorders. In the event of excessive bleeding, supportive blood component therapy should be instituted. EACA/tranexamic acid may be useful in a few. A number of other platelet function disorders exist but are uncommon, encountered mainly in case reports and clinically insignificant.

ACQUIRED PLATELET FUNCTION DISORDERS

Common causes include drugs, uremia, liver cirrhosis, myeloma, myeloproliferative disorders and after cardiopulmonary bypass. Many drugs alter platelet function. Aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), dipyridamole, clopidogrel and ticlopidine are some of the drugs used in clinical practice. Aspirin inhibits the cyclo-oxygenase system irreversibly whereas other NSAIDs reversibly inhibit cyclo-oxygenase. When an acquired platelet disorder is suspected, it is useful to examine platelet function by measuring the bleeding time, examining platelet dependent closure time in a PFA-100 and performing platelet aggregometry. When a specific acquired platelet disorder is diagnosed, many treatment options are available including most importantly controlling the underlying disease, giving platelet transfusion and administering a hemostatic drug.⁷

MANAGEMENT OF PLATELET FUNCTION DISORDERS

Most patients with platelet function defects have mild bleeds and may need only supportive care. Offending agents must be avoided. Aminocaproic acid (50-100 mg/kg intravenously or orally every 4 to 6 hours) and tranexamic acid (15 to 20 mg/kg orally every 6 to 8 hours or 10 mg/kg intravenously every 8 hours) are helpful to stabilize the clot. Estrogen/progesterone preparations are useful in the prophylaxis of vaginal bleeding. Desmopressin (DDAVP) has been used with variable success in platelet function disorders. The exact nature of the effect of DDAVP is unclear but is now believed to act by enhancing the liberation of vWF from both vascular endothelium and platelets.¹² It can be given as an intravenous infusion (0.3 μ g/kg) or subcutaneously 0.3 μ g/kg once daily or as intranasal spray 150 to 300 μ g once daily. Platelet transfusions may be restricted only for major bleeds, so as to reduce the development of alloantibodies. Recombinant factor VIIa (rFVIIa) appears to have a wide spectrum of clinical use in a variety of bleeding disorders due to both platelet dysfunction and coagulopathy.¹³ Bone marrow transplantation remains the only curative option available in some instances of inherited PFD.

INDIAN SCENARIO

Inherited disorders of platelet function are rare in the northern parts of the country where consanguinity is

uncommon. A large number of GT was found in South India as compared to other parts of the country possibly due to the higher degree of consanguinity prevalent in that part of the country.^{14,15} A study from AIIMS, New Delhi reported 144 cases of platelet function defects over a period of 21 years.¹⁶ In a similar study from PGIMER, Chandigarh, 16 out of 402(4%) patients investigated for a bleeding diathesis were found to have an inherited platelet function defect over a 3 years period.¹⁷ Besides being rare disorders, facilities for screening for platelet function defects are available in very few centers. The exorbitant cost of the reagents and equipment possibly contribute to under reporting of these disorders.

CONCLUSION

Platelet function disorders are an uncommon and often underreported cause of recurrent bleeding. They may occur as a result of inherited defects of the platelet or vascular endothelium or may occur as a result of an acquired underlying cause. It requires a reference laboratory to accurately diagnose these disorders and screening tests are often equivocal. Therapy includes platelet transfusions and fibrinolytic drugs as well as therapy of the underlying or precipitating cause. Repeated platelet transfusions can lead to the development of alloantibodies and as such must be used judiciously. Stem cell transplant is curative in some conditions. A high index of suspicion is essential to lead to the diagnosis.

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Recent Advances in the Treatment of Hemoglobinopathies

Mir Sadaqat Hassan Zafar, Anupam Sachdeva, SP Yadav

The hemoglobinopathies encompass all genetic diseases of hemoglobin. They fall into two main groups: thalassemia syndromes and structural hemoglobin variants (abnormal hemoglobins). α - and β -thalassemia are the main types of thalassemia. The main structural hemoglobin variants are HbS, HbE and HbC. There are many subtypes and combined types in each group. The highly variable clinical manifestations of the hemoglobinopathies range from mild hypochromic anemia to moderate hematological disease to severe, lifelong, transfusion dependent anemia with multiorgan involvement. A lot of work has been done in the last two decades on finding a complete cure for these diseases in terms of stem cell transplantation and gene therapy.

THALASSEMIA

Treatment of thalassemia depends on the type of disease. Subjects with β -thalassemia minor (β -thalassemia trait) are not symptomatic from this condition, may have only mild degrees of anemia, and require no specific therapy. Patients with β -thalassemia intermedia must be monitored closely for progression of their anemia, and/ or the development of worsening evidence of the complications of hemolysis or extramedullary erythropoiesis. Mainstays of therapy for β -thalassemia major are chronic hypertransfusion combined with iron chelation, and supportive measures directed at the complications of the expanded erythron and iron overload. Iron overload is the major cause of mortality and morbidity associated with thalassemia. Both transfused iron overload and excessive iron absorption from the gastrointestinal tract (GIT) are contributory for the iron overload in thalassemics. Emerging therapies include the wider use of allogeneic bone marrow transplantation, the only curative modality, pharmacologic

manipulation of fetal hemoglobin levels and eventually, it is to be hoped, gene therapy.¹

IRON CHELATION THERAPY

Every child who is maintained on a high-transfusion regimen ultimately develops iron overload and dies of siderosis of the myocardium. Therefore, such children must be started on a program of iron chelation within the first 2 to 3 years of life. Iron chelation should be started after the patient has received more than 10 to 15 units of blood or with serum ferritin level of over 1000 ng/ml. Apart from parenteral deferoxamine, two oral iron chelators deferiprone and deferasirox have been studied extensively and are in clinical use (Table 1).^{2,3} Deferitritin (GT56-252) is an oral iron chelator in development, presently in phase I clinical trial. Other iron chelators that have been found too toxic or not sufficiently effective for clinical use include desferriethion and HBED (hydroxybenzyl ethylene diamine).³

HEPCIDIN AGONISTS

As a result of hepcidin deficiency, patients with β -thalassemia intermedia develop iron overload in a manner similar to those with hereditary hemochromatosis. Accordingly abnormal iron absorption in these patients might be prevented by administration or upregulation of hepcidin. In β -thalassemia major, transfusions rather than dietary iron absorption are the predominant cause of iron overload. The studies undertaken to evaluate the effect of over-expressing hepcidin on iron overload and erythropoiesis have used genetic models and have not explored the feasibility of using hepcidin or its agonists as drugs. Further studies in mouse models of thalassemia followed by rigorous clinical trials are needed.⁴

Table 1: Iron chelators

Property	Deferoxamine	Deferipone	Deferasirox
Route	SC/IV	Oral	Oral
Dose	25-50 mg/kg/day	75 mg/kg/day	20-30 mg/kg/day
Schedule	Over 8-24 hours/day	3 times/day	Daily
Excretion	Urine/Feces	Urine	Feces
Plasma clearance $t_{1/2}$	20 minutes	53-166 minutes	1-16 hours
Adverse effects	Local skin reaction, ototoxicity, infections ophthalmic toxicity, skeletal impairment	Agranulocytosis, GIT disturbances, transaminase elevation, arthralgias	GIT disturbances, transaminase elevation, raised creatinine, rash, proteinuria
Advantage	Long-term data	May be superior in removing cardiac iron	Only oral chelator licensed for use in United States
Disadvantage	Compliance problems may be greater	Variable efficacy in removal of hepatic iron	Long-term data lacking. Efficacy at removal of cardiac iron not known
Monitoring	Long bone films in growing children, annual eye and ear check-up	Weekly CBC	Monthly KFT, LFT and urine analysis
Clinical experience	35 years	23 years	5-6 years

MANIPULATION OF HbF SWITCHING

Hydroxyurea

Hydroxyurea (HU), a cytotoxic drug commonly used in the treatment of myeloproliferative disorders, has been shown to increase fetal hemoglobin synthesis in patients with beta thalassemia and sickle cell disease. The use of HU has been helpful in some patients with beta-thalassemia intermedia, although its successful use in beta-thalassemia major has been less frequently noted.⁵

Histone Deacetylase Inhibitors

The disappointing results obtained with hydroxyurea in thalassemia have led to a search for other agents capable of increasing the production of HbF. The histone deacetylase inhibitors butyrate and trichostatin A activate gamma globin expression via a *p38* mitogen-activating protein kinase (MAPK)-dependent mechanism.⁶

Butyric Acid Analogs

The most promising histone deacetylase inhibitors presently under study are derivatives of butyric acid, including arginine butyrate, sodium phenylbutyrate and related substances. Used alone, these agents are inadequately potent in most patients, except at doses that are potentially toxic or poorly tolerated because of the requirement for prolonged intravenous infusions. Promising results have been obtained with the use of combination therapy with hydroxyurea and intermittent pulses of butyric acid compounds. For poorly understood reasons, intermittent pulse therapy appears to increase the potency and

sustainability of the hemoglobin switching effect obtained with butyric acid compounds. Whether this or other combination regimens will eventually prove to be therapeutically efficacious remains to be seen.⁷

Kit Ligand

In one study, addition of kit ligand, with or without dexamethasone, to cell cultures from patients with beta thalassemia intermedia or beta thalassemia major increased cell proliferation, reduced the percent of apoptotic and dyserythropoietic cells and induced a marked increase of gamma-globulin synthesis required for the production of HbF. Confirmatory *in vivo* studies in experimental animal models of thalassemia will be required before such treatment can be considered in human subjects, especially since infusions of kit ligand (stem cell factor, Stemgen) have been associated with potentially severe allergic side effects.⁸

GENE THERAPY

Even though globin gene expression can be readily manipulated in experimental animals, including murine models of beta thalassemia, the search for a safe, efficient, and specific targeting vector in humans has been difficult, with limited success to date. The challenges are considerable. The donor globin gene must be inserted into the pluripotent hematopoietic stem cell, in a fashion that allows its tightly regulated but high level expression only in the red cell lineage and only during the period of terminal erythroblast maturation. Many of the sequences flanking the globin genes that are necessary for this regulation have

been identified and utilized effectively in animal models. Experiments in animal models suggest that a significant therapeutic benefit could be achieved if the transferred globin gene is expressed at about 15 percent of the level of the alpha-globin mRNA, with about 20 percent of the erythroid precursors expressing the vector genome.⁹⁻¹¹

HEMATOPOIETIC STEM CELL TRANSPLANT

Allogeneic hematopoietic stem cell transplant (HSCT) still remains the only definitively curative option for patients with thalassemia. Advances in transplantation biology have made it possible to perform haploidentical stem cell transplantation in patients with thalassemia who lack a related or unrelated HLA- matched donor.

SICKLE CELL DISEASE

A definitive cure is not currently available for most patients with sickle cell disease (SCD). Gene therapy for SCD is especially formidable, due to the difficulty in transducing hematopoietic stem cells and the necessity for erythroid-specific, high level, and balanced globin gene expression. As a result, increasing attention has been focused on the use of hematopoietic cell transplantation. Ideally, these more aggressive therapies should be reserved for patients at high-risk, since the mean survival in SCD is currently 42 years in men and 48 years in women.¹²

Less aggressive therapies for SCD are aimed largely at symptom control during painful vaso-occlusive episodes (previously called sickle cell crises) and at the prevention of symptoms by prophylactic blood transfusion to lower the HbS concentration.¹³

However, at present, hydroxyurea is the only major medical modality with proven efficacy in patients with frequent symptoms related to SCD and many of the agents described below, with the exception of hydroxyurea and hematopoietic cell transplantation, are mainly of historic interest.

INDUCTION OF HbF SYNTHESIS

Enhanced concentrations of hemoglobin F have, in most studies, a marked inhibitory effect on sickling and improve the clinical course of SCD. There are at least two ways in which this might be achieved:

- Direct activation of the respective promoter genes appears to be the mechanism by which 5-azacytidine and butyric acid and its derivatives increase HbF.
- Erythropoietin and hydroxyurea seem to work by recruitment into proliferation and differentiation of population of erythroid precursors which retain the gamma-chain synthesis program but remain dormant in the bone marrow of the adult unless called up in cases of acute erythroid expansion.

While several of these agents can increase the level of hemoglobin F, only hydroxyurea has shown significant clinical effects in terms of reduction of pain crises, chest syndrome, and transfusions in patients with SCD.¹⁴

Hydroxyurea

It is generally assumed that the beneficial effects of hydroxyurea in patients with SCD are due to the induction of hemoglobin F, most likely related to an effect on genes regulating transcription and translation. Other factors also may play a role, such as the generation of nitric oxide (NO) by hydroxyurea, which may, in part, reverse the depletion of this potent pulmonary vasodilator caused by red cell hemolysis. The benefit of hydroxyurea therapy also may be due in part to a reduction in reticulocytes and young, low density HbSS red cells, since these cells are particularly likely to adhere to vascular endothelium. It is relatively nontoxic, its myelosuppressive effects are readily reversible, and it is not known to induce tumors, although it appears to increase the incidence of acute myeloid leukemia when used in patients with the malignant myeloproliferative neoplasms like polycythemia vera and essential thrombocythemia. Accordingly, long-term follow-up for the development of malignancy in patients with SCD treated with this agent is a major priority.^{15,16}

The use of hydroxyurea is indicated in patients with SCD with one or more of the following problems:

- Frequent painful episodes
- History of acute chest syndrome
- History of other severe vaso-occlusive events
- Severe symptomatic anemia
- Very young children

The suggested initial dose is 15 mg/kg per day in a single oral dose. For patients with a creatinine clearance <60 ml/min, the starting dose should be 7.5 mg/kg per day. Peripheral blood counts should be obtained every 2 weeks, serum chemistries every 2 to 4 weeks, and hemoglobin F every 6 to 8 weeks. The drug should be temporarily stopped if the absolute neutrophil count is <2000 μ l, the platelet count is <80,000/ μ l, the hemoglobin <4.5 g/dl, or the absolute reticulocyte count <80,000/ μ l. If there is no major toxicity, the dose should be increased every 6 to 12 weeks by 5 mg/kg per day until the desired endpoint is reached (i.e. a maximum dose of 30 to 35 mg/kg per day or unacceptable degrees of cytopenia). After a stable dose of hydroxyurea has been achieved, blood counts and serum chemistries should be obtained every 4 to 8 weeks to follow hepatic and renal function. Hemoglobin F levels should be obtained every 3 to 4 months to assess treatment efficacy.¹⁶

5-Azacytidine

In erythroid cells, with the developmental switch from gamma globin (HbF) to beta globin (HbA) production in

the newborn period, the inactive gamma gene becomes methylated and the actively expressed beta globin gene becomes hypomethylated. Since 5-azacytidine is an anti-neoplastic drug that inhibits maintenance methylation of DNA, it was hoped that use of this agent would hypomethylate the gamma globin gene and reactivate HbF production.¹⁷

5-Aza Deoxycytidine

The related drug, 5-aza-2'-deoxycytidine (decitabine; given at a dose of 0.2 mg/kg subcutaneously 1 to 3 times per week in two cycles of 6-weeks duration) has shown efficacy in short and long-term trials in increasing HbF levels and total hemoglobin levels in patients failing to respond to hydroxyurea. HbF levels as high as 20 percent have been noted after such treatment. Other than mild neutropenia, no untoward effects were noted. Long-term effects of such treatment are not yet known.¹⁸

SHORT CHAIN FATTY ACIDS

Butyrate inhibits histone deacetylase (HDAC) and promotes elevated levels of core histone acetylation affecting chromatin structure and transcription rates of gamma-globin gene. However, there are conflicting reports regarding the efficacy of butyrate therapy in patients with beta-thalassemia and SCD. Analogs of butyrate (e.g. arginine butyrate) as well as acetate and other short chain fatty acid derivatives also appear to induce HbF. More studies are needed to assess the efficacy and safety of these potentially nonteratogenic and nonmutagenic means of inducing HbF production.¹⁹

REDUCING INTRACELLULAR Hb CONCENTRATION

The rate of polymerization of deoxygenated HbS is dependent upon the HbS concentration. Polymerization-induced membrane damage, leading to enhanced dehydration, results in the presence of a substantial population of very dense cells. These dense cells are much more prone to sickle and contribute disproportionately to the vaso-occlusive aspects of the disease.

Mechanism of Erythrocyte Dehydration

Dehydration in sickle erythrocytes is due to the loss of potassium, chloride, and water from the erythrocyte. Two ion transport pathways, K Cl co-transport and a calcium activated potassium channel, play a prominent role in this process.

- In normal red cells, the K Cl co-transporter is activated only in reticulocytes. Transport rates are much higher in sickle red cells due in part to chronic hemolysis, an increase in the population of young cells, and induction of the co-transporter by acidification or urea, particularly at sites of stagnant circulation.

- The second pathway for cellular dehydration is sickling-induced loss of potassium and water through the calcium-dependent (Gardos) potassium channel. Although sickle red cells have increased calcium content, the steady state cytosolic calcium concentration is normal because of compartmentalization of the increased calcium within intracellular vesicles. However, when the cell membrane is distorted by sickling, cytosolic calcium transiently increases and activates the potassium channel with consequent loss of potassium and water from the cell.^{20,21}

Inhibiting the Transport Channels

For the reasons enumerated above, inhibition of the Gardos channel might have a beneficial effect on SCD by improving the hydration state of red cells, thereby reducing HbS polymer formation. Two agents that inhibit this channel are described below.

Clotrimazole

The Gardos channel is specifically inhibited by the antifungal drug clotrimazole. The efficacy of this drug has been demonstrated by *in vitro* incubation experiments, studies in transgenic mice with SCD, and observations in patients with SCD. One report evaluated five patients who were treated with clotrimazole (20 mg/kg per day); the red cell Gardos channel was inhibited, cell potassium content increased, and the red cells became less dehydrated. At the end of this short-term study, there was a modest increase in hemoglobin levels and a significant reduction in serum indirect bilirubin concentrations.²²

Senicapoc

Senicapoc (ICA-17043) is a highly potent Gardos channel blocking agent that has specifically inhibited the efflux of potassium from red cells of transgenic HbSS mice as well as red cells from human subjects with SCD. In a randomized placebo-controlled phase II study, a dose of 10 mg/day of senicapoc raised hemoglobin levels (the primary study endpoint) in patients with HbSS by an average of 0.6 g/dl. Significant improvements in hematocrit and reticulocyte count, and significant reductions in percent dense red cells, indirect bilirubin, and lactate dehydrogenase were also seen.²³

MAGNESIUM

Cytosolic magnesium modulates calcium and potassium channels in a variety of tissues. Intracellular divalent cations, particularly magnesium, effectively retard potassium and water loss from HbSS red cells *in vitro*. The potential clinical utility of this approach was assessed in patients with SCD who were treated with oral magnesium supplementation (0.6 mEq/kg per day of magnesium pidolate)

and studied after 4 weeks and 6 months. Erythrocyte K Cl co-transport was reduced significantly, sickle erythrocyte magnesium and potassium content rose, and the number of dense sickle erythrocytes was reduced; the last effect may have been due to an increase in cell volume. Similar beneficial effects of magnesium supplementation have been noted in patients with β -thalassemia intermedia. Whether these changes would result in a significant increase in circulating levels of hemoglobin and/ or have important clinical effects with long-term therapy have yet to be determined. In a preliminary report, the cellular changes induced by oral magnesium supplements were associated with a significant reduction in the number of painful crises.^{24,25}

HEMATOPOIETIC STEM CELL TRANSPLANT

Hematopoietic cell transplantation (HCT) currently offers the only hope for cure of SCD, although the reported experience is limited. HCT for SCD is still under careful evaluation in the United States. Many physicians taking care of patients with SCD have adopted a wait-and-see approach to HCT because of the uncertainties concerning patient selection, the risks associated with the procedure, the variable clinical course with medical therapy, and the promise for better medical therapies as described above.

GENE THERAPY

Although still experimental, gene therapy has the potential to cure SCD. Expression of the human sickle gene in transgenic mice and creation of plasmids with the human beta globin locus are examples of the possible feasibility of this approach.

Increasing Expression of HbF

As noted above, higher levels of HbF are associated with reduced disease severity in patients with SCD. The SAD mouse model of SCD produces polymerized hemoglobin and exhibits many of the features of SCD seen in patients. To test the efficacy of increasing levels of HbF, SAD mice were mated with transgenic mice that overexpress different levels of the human A gamma globin gene. Expression of 9 to 16 percent HbF was sufficient to produce a significant therapeutic effect, with improvements in all hematologic parameters and survival.

RNA Repair

An alternative genetic approach is to use ribozymes, which are small RNA molecules that can specifically bind to complementary RNA sequences and catalyze the cleavage of the target RNA, to increase the expression of HbF and/ or reduce that of HbS via RNA repair.

In one *in vitro* model, e.g. a trans-splicing group I ribozyme was used to alter mutant beta globin constructs in

erythrocyte precursors derived from the peripheral blood of patients with SCD. Sickle beta globin transcripts were converted into messenger RNAs encoding gamma-globin. In another model, ribozymes were used to decrease the concentration of sickle beta globin chains and mRNA.

The efficacy of this approach will depend upon the ability to develop suitable vectors and optimization of constructs to permit a clinically relevant increase in protein expression. Efficiency does not have to be 100 percent as evidenced by the observation that sickle cell trait, in which the concentration of HbS is approximately 50 percent of total hemoglobin, is a benign condition.^{26,27}

NICOSAN

Only one herbal agent tested to date, nicosan (Niprisan®, Hemoxin, Nix-0699), has proved to have an efficacy/toxicity ratio sufficiently high to merit testing in clinical trials. Nicosan is a plant extract that has been successfully used in Nigeria to prevent painful crises associated with SCD. Although its exact mechanism of action, active ingredient(s), and long-term side effects are unknown, nicosan inhibits sickling *in vitro*, as well as *in vivo* in a transgenic mouse model of SCD.²⁸

NITRIC OXIDE

Studies are underway on the role of nitric oxide (NO) in the management of acute pain episodes and acute chest syndrome. *In vivo* administration of gaseous nitric oxide increases the whole blood oxygen affinity of sickle erythrocytes with no effect on blood containing only normal hemoglobin. This approach is problematic since it is likely that any compound that increases oxygen affinity will stimulate red cell production. There is good clinical evidence that an increase in red cell mass has a negative impact upon the clinical course of SCD. Thus ongoing trials will appropriately find the answer.²⁹

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Thrombophilia in Children: Approach to Diagnosis and Management

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With advances in pediatric and neonatal care, particularly in the intensive care setting, pediatric thromboembolism is an increasingly diagnosed entity. Confirmation of this has been done by improvement in imaging modalities. However few clinical trials have been performed in this area in children and management is largely extrapolated from adult practice. However direct extrapolation is fraught with certain difficulties. The epidemiology and etiology for pediatric thrombosis varies from that of adults. The pharmacokinetics and pharmacodynamics of anticoagulants are known to be different in children, compared to adults and there may be some practical considerations precluding the use of long term anticoagulation in children. There is also limited data available on the safety and efficacy of anticoagulants to manage specific indications in pediatric practice. The long-term consequences of both the thrombotic event and therapy for the same are highly significant in young children. This chapter summarises the epidemiology, etiology, approach and therapy guidelines for pediatric thrombosis.

EPIDEMIOLOGY

The annual incidence of venous thrombo-embolism (VTE) in children has been estimated at 0.7 to 1.0 per 100 000 population with a prevalence of 5.3 per 10 000 hospital admissions based on the Canadian registry. Neonates and adolescents comprise the age groups where thrombosis is more common. Better imaging facilities have also resulted in a larger number of cortical venous thrombosis to be detected. Thrombosis in children is often secondary to some primary disease state or intervention and is often associated with multiple triggers unlike in adults. Over 90 percent of pediatric events are related to underlying medical or surgical risk factors of which central venous lines (CVL) are the most important. There is also a higher incidence of upper limb thrombosis in children. Thrombosis

is associated with significant morbidity and mortality. In the Canadian registry, mortality directly attributable to VTE occurred in 2.2 percent, with recurrent thrombosis in 8.1 percent and post-thrombotic syndrome (PTS) in 12.4 percent with an average follow-up period of 2.86 years.

Pediatric and neonatal thrombosis can be classified in various ways: arterial and venous, acute and chronic, small, medium and large vessel, based on site of thrombosis, symptomatic and asymptomatic, idiopathic or secondary to an underlying condition, first or recurrent thrombosis. All these aspects play a role in the ultimate management of the child. The commonest scenario of thrombosis is venous thrombosis secondary to a central catheter. The other important sites of thrombosis are cortical venous thrombosis (CVT), renal vein thrombosis (RVT) and arterial ischemic stroke (AIS). The majority of pediatric and neonatal thrombosis is secondary to certain triggers which predispose the occurrence of a thrombosis. The common triggers include:

- Central venous/arterial catheters
- Factors predisposing to endothelial damage and DIC, e.g. sepsis, birth asphyxia
- Factors predisposing to high viscosity of blood, e.g. polycythemia (neonates, cyanotic CHD, dehydration)
- Factors causing vascular stasis, e.g. postsurgery, sickle cell disease
- Factors causing loss of anticoagulants, e.g. nephrotic syndrome, hematological malignancies (hyperleucocytosis, asparaginase use)
- Factors causing vascular inflammation, e.g. systemic vasculitis, SLE, APLA syndrome.

If there are no secondary causes for thrombosis, the possibility of inherited thrombophilia must be considered. We will first discuss hereditary thrombophilia and approach to testing for these rare entities. This is followed by an approach to arterial ischemic stroke.

Hereditary Thrombophilia

Thrombophilia refers to the propensity to develop thrombosis and can be applied clinically to patients who develop spontaneous venous thromboembolism (VTE), VTE with severity out of proportion to the stimulus, recurrent thrombosis, or VTE at a young age.

Familial predisposition to thrombosis was described by Jordan and Nadorff in 1956 where multiple young members of various generations of a family were diagnosed with venous thrombosis. Antithrombin III deficiency was the first described inherited thrombophilia in 1965. Protein C and S deficiency was described 20 years later. Neonatal purpura fulminans was described in 1983. Most reports initially measured the levels of these anticoagulants in blood and later evaluated the genetic defects by PCR. In 1990 factor V Leiden defect was described which showed abnormal increased tendency to clot rather than a lack of anticoagulant. The prothrombin 20210 mutation defect was described in 1996. Testing for inherited thrombophilias has increased significantly over the last 15 years. The utility of such testing in childhood varies greatly depending on the clinical situation.

Individuals that demonstrate clinical “thrombophilia” do not necessarily have laboratory evidence of “thrombophilia,” and vice versa.

The most common laboratory thrombophilias and the tests used to establish the diagnosis are listed in Table 1. The inherited defects in which the pathogenic link to thrombosis is well understood include deficiencies of protein C, protein S and antithrombin, the factor V Leiden mutation, and the prothrombin gene mutation. Other

thrombophilias, which are less well characterized and not necessarily genetically determined, include elevated homocysteine, elevated lipoprotein(a), dysfibrinogenemias, and increased levels of factors VIII, IX and XI. Level 1 testing (Table 1) includes the thrombophilia tests that are most prevalent in pediatric studies. If the results of these tests are normal and thrombophilia is strongly suspected, level 2 tests can be performed.

There are numerous other proposed causes of thrombophilia. Some of these have been tested in only a small number of patients and none have gained widespread acceptance as risk factors for thrombosis. Though most of the prothrombotic alterations listed above may be inherited, several can also be acquired. Table 2 lists several clinical settings associated with acquired abnormal thrombophilia test results. Antiphospholipid antibodies (lupus anticoagulant, anti- β_2 glycoprotein antibody and anticardiolipin antibody) are well-established acquired thrombophilic risk factors, although there are reports of familial cases.

Interpreting report of coagulation and anticoagulation factor levels is particularly challenging in children. Neonates are known to physiologically have lower levels of both pro and anticoagulant levels and these vary as the child grows. This is known as developmental hemostasis. Hence levels assessed at the time of an acute thrombotic event in young infants needs to be checked again as the child grows if clinically indicated.

There are usually multiple coexisting factors predisposes to thrombosis in a child with a symptomatic thrombosis. Inherited thrombophilias may or may not be one of

Table 1: Most common thrombophilias and diagnostic laboratory studies

	<i>Thrombophilia</i>	<i>Laboratory Tests</i>
Level I Testing	Factor V Leiden mutation	Polymerase chain reaction or screening with clotting assay
	Prothrombin 20210 mutation	Polymerase chain reaction
	Antithrombin deficiency	Chromogenic or clotting assay
	Protein C deficiency	Chromogenic or clotting assay
	Protein S deficiency	Clotting assay or immunologic assay of free and total protein S antigen
	Hyperhomocystenemia	Fasting homocysteine
	Elevated lipoprotein (a)	ELISA
Level II Testing*	Antiphospholipid antibodies	Phospholipid-based clotting assays, (PTT, DRVVT or Staclot LA) with confirmatory assay using exogenous phospholipid, ELISA assays for IgG and IgM antibodies directed against cardiolipin and β_2 glycoprotein
	Elevated factor VIII	One-stage clotting assay, chromogenic assay
	Dysfibrinogenemia	Clotting assay (Clauss method), immunologic assay, thrombin time
	Elevated factor IX, XI	One-stage clotting assay

*If thrombophilic defect strongly suspected and level I testing is normal

Table 2: Conditions associated with acquired thrombophilic laboratory abnormalities**Acute thrombosis**

Low protein S
Low protein C
Low antithrombin

Infection

Antiphospholipid antibodies

Inflammation

Elevated factor VIII
Low free protein S
Elevated Lp(a)

Nephrotic syndrome

Low protein S
Low protein C
Elevated Lp(a)

Complex congenital heart disease (single ventricle)

Low protein S
Low protein C
Low antithrombin

Asparaginase (acute lymphoblastic leukemia)

Low antithrombin

Liver disease

Low protein S
Low protein C
Low antithrombin

Warfar therapy

Low protein S
Low protein C

Heparin therapy

Low antithrombin

Nutritional deficiency

Elevated homocysteine

Pregnancy

Low protein S

by the presence of an inherited thrombophilia. Pediatric thrombosis registries from both Canada and the Netherlands have reported that patients with catheter-related thrombosis do not have an increased prevalence of underlying thrombophilia.

Pediatric Stroke and Inherited Thrombophilias

Currently, thrombophilia testing of neonates and older children who have had a stroke is common, but as with venous thrombosis, the contribution of testing for a thrombophilic risk factor to improved clinical outcomes has not been demonstrated. The reported prevalence of prothrombotic conditions in pediatric stroke varies from 20 to 50 percent, for reasons that are similar to the variance reported in pediatric VTE. Inherited thrombophilias (protein C deficiency, elevated lipoprotein (a), factor V Leiden mutation and prothrombin mutation) have been associated with an increased risk of recurrent stroke in older children, suggesting that testing in this setting may be useful.

Role of Testing for Hereditary Thrombophilia: Various Clinical Scenarios*Acute Management*

Identification of a thrombophilic marker will almost never influence the acute management of a patient with venous thrombosis, in which the mainstay of therapy is therapeutic anticoagulation. The exception would be a neonate or older child with severe (homozygous or compound heterozygous) deficiency of protein C or S or antithrombin deficiency who presents with purpura fulminans, extensive large vessel thrombosis or disseminated intravascular coagulation, which can be life-threatening. Early identification of one of these rare conditions is likely to influence treatment because replacement therapy with plasma-derived concentrate (protein C or antithrombin) or fresh frozen plasma is effective in the management of such a patient.

Duration of Therapy

Current guidelines regarding the duration of anticoagulant therapy for pediatric VTE are extrapolated from adult studies, and most recommendations are for 3 to 6 months of therapy for older children. The paucity of data in neonates is reflected in the guidelines for neonatal VTE, where recommendations range from observation to anticoagulation from 2 weeks up to 3 months. Given that optimal duration of therapy in children is not established, whether or not the presence of an underlying thrombophilia should influence the duration of therapy in children is not known. Recently, a risk-based strategy for treatment of pediatric VTE has been recommended, tailoring the duration of therapy based upon the risk for poor outcome (recurrent thrombosis or post-thrombotic syndrome). In

them. The reported prevalence of thrombophilia in children with venous and arterial thrombotic events varies greatly, from as low as 13 percent to as high as 79 percent, and it is likely that this discrepancy has caused confusion regarding the role of testing. This tremendous variation is likely due to differences in study design, definition of congenital prothrombotic disorders, small sample sizes and different patient populations. Among older children with spontaneous VTE in the Canadian cohort, inherited thrombophilia was identified in 60 percent, confirming that this group has the highest likelihood of having an abnormal result within the larger studied population and therefore has the potential to benefit most from testing. There are divergent views on whether a child with a catheter related thrombosis should have testing for hereditary thrombophilias. Several studies suggest that the risk of symptomatic catheter related thrombosis is not increased

this strategy, risk assessment is determined using a number of patient characteristics (provoking condition, factor VIII activity, D-dimer, inherited and acquired thrombophilias) as well as characteristics of the thrombus itself (extent, location, and resolution). Heterozygous mutations confer a very low risk of recurrent thrombosis and hence does not warrant long term anticoagulation. However, patients who have a “high-risk” defect, such as antithrombin deficiency, homozygous factor V Leiden mutation, or more than one congenital risk factor, may benefit from long-term anticoagulation. Therefore, one rationale for thrombophilia testing may be to identify the rare patient with a high recurrence risk genotype who may benefit from long-term anticoagulation. Exactly which defects warrant long-term anticoagulation and the risk-benefit ratio of such an approach are not yet known, and long-term follow-up on sufficient numbers of patients is needed to more clearly define this risk so that patients can be appropriately counseled.

Patients who meet the criteria for antiphospholipid antibody syndrome are candidates for long-term anticoagulation, and so testing for antiphospholipid antibodies is warranted, particularly in patients with spontaneous thrombosis. Many pediatric patients with thrombosis have transient elevations of these antibodies particularly induced by infections, and the contribution of these transient antibodies to thrombosis is not known.

Thromboprophylaxis in High-risk Situations

Identification of an inherited thrombophilia in a child with VTE may lead to the increased use of thromboprophylaxis in future high-risk situations (e.g. surgery, pregnancy)

Identification of Other Family Members

Discovery of an inherited thrombophilia in an individual with VTE may lead to the identification of other family members who can be counseled regarding their risk. These asymptomatic individuals may be more likely to receive primary prophylaxis in the presence of transient risk factors. Young women who are identified in this way can make informed decisions regarding estrogen-containing contraception. It is also possible that knowledge of an inherited thrombophilia may lead to healthy lifestyle choices. At present, there are no studies that demonstrate the benefit of such familial testing and counseling.

Deciding Which Patient Should be Tested

In 2002 the subcommittee for perinatal and pediatric thrombosis of the scientific and standardization committee (SSC) of the international society of thrombosis and hemostasis (ISTH) recommended that all pediatric patients with venous or arterial thrombosis be tested for a full panel of genetic prothrombotic states. The rationale for this recommendation was that pediatric patients often

have several risk factors for thrombosis, and that even if several acquired risk factors were present an evaluation for inherited risk factors should also be conducted. However as knowledge of pediatric thrombosis grows it is clear that a single recommendation regarding thrombophilia testing that applies to all neonates and children with thrombosis may not be optimal. Recommendations for thrombophilia testing based on current understanding regarding the contribution of prothrombotic risk factors to pediatric thrombosis and the potential for benefit are outlined in Table 3.

When Should Testing be Performed and Possible Fallacies

Thrombophilia testing in the acute setting may result in an incorrect diagnosis of inherited conditions. When interpreting the results of thrombophilia testing, it is important to remember that levels of antithrombin, protein C and protein S may transiently decrease during acute thrombosis. Similarly, factor VIII and lipoprotein(a) can be elevated in inflammatory conditions. Therefore, any test that is abnormal during the acute setting should be repeated later, ideally off anticoagulation. Levels of antithrombin may be decreased in patients who are on heparin, and vitamin K antagonists result in low levels of protein C and protein S. For these diagnostic assays, low levels must be confirmed when the infant or child is well, and testing both parents should also be considered before committing to a diagnosis of an inherited deficiency. The diagnostic accuracy of molecular mutation testing will not be affected, and so these tests can be sent even during an acute episode.

Arterial Ischemic Stroke

Childhood-onset arterial ischemic stroke (AIS) is characterized by findings of arterial-distribution ischemia in a child. Patients typically present with sudden-onset neurological deficits, but are often not diagnosed until over 24 hours thereafter. The frequent delay in diagnosis may in large part be explained by the rarity of this disease, which occurs in 2 per 100 000 children per year. Although underlying cardiac or sickle cell disease (SCD) account for many cases of childhood AIS, there remains a large group of patients without major medical illness. In these cases the identified risk factors are distinct from those of both perinatal AIS (in whom AIS occurs before 29 days of life) and adult AIS. In approximately 80 percent of previously healthy cases, neurovascular imaging reveals cervical/ cerebral arteriopathy, characterized by dissection, occlusion, or stenosis in the cerebral vasculature. In addition, in all subtypes of childhood AIS and irrespective of previous medical history, genetic and acquired thrombophilias are common. These thrombophilias likely interact along with other identified risk factors to initiate and/ or propagate thromboembolism in childhood AIS patients.

Table 3: Recommendations regarding thrombophilia testing in children

<i>Who</i>	<i>Recommendation</i>	<i>Why</i>	<i>Comments</i>
Adolescents with spontaneous thrombosis	Testing should be strongly considered	Identify combined defects Counsel regarding risk of recurrence Counsel/test other family members	This group has the highest prevalence of inherited thrombophilia
Neonates/children with non-catheter related venous thrombosis or stroke	Testing should be considered	Identify combined defects Counsel regarding risk of recurrence Counsel/test other family members	—
Neonates/children with symptomatic catheter related thrombosis	Not enough data to make a recommendation	Reports vary regarding the role of thrombosis in catheter-related thrombosis	—
Neonates/children with asymptomatic catheter related thrombosis	Testing is not recommended	Thrombosis in the setting of catheter-related thrombosis is extremely common No data to suggest thrombophilia is increased	Consider testing if there are recurrent events
Asymptomatic children with a positive family history	Decision to test should be made on an individual basis only after counseling	Counsel adolescent females on risk of estrogen Thromboprophylaxis in high-risk situations	Be careful about false reassurance Test parent first, if possible Encourage waiting until child is older
Asymptomatic children—routine screening (prior to catheter placement, leukemia therapy or oral contraceptives)	Testing is not recommended	Not cost effective Many patients with risk factor will not have an event Catheter-related thrombosis not necessarily increased with inherited thrombophilia and there is no effective prophylaxis	—
Neonates/children participating in thrombosis research	Testing is recommended	More data on long term outcomes are needed to definitively determine the role of genetic risk factors and optimal therapies	—

Despite recent advances in understanding childhood AIS risk factors, the efficacy of antithrombotic, anti-inflammatory and other therapies remains largely unknown. Unlike in sickle cell disease—where chronic transfusion is used as primary prevention in selected cases, the utility of preventative or therapeutic interventions in other subtypes of childhood AIS remains understudied.

Effective treatments for childhood AIS are urgently needed as 70 percent of patients suffer life-long neurological morbidity which is both costly and adversely impacts quality of life. In addition, there is a high rate of recurrence (7–20% at 5 years).

Antithrombotic therapies (whether antiplatelet or anti-coagulant) are often employed as secondary prevention

strategies. Presently, however, the current standard of care is highly variable world-wide, largely due to a paucity of evidence regarding the types and durations of therapy that appear most beneficial, and in which groups of childhood AIS patients.

ANATOMICAL FACTORS IN AIS

In some cases of childhood-onset AIS, the site of thrombus generation is identifiable. Several possible scenarios are observed. Deep venous thrombosis of the limbs or central vasculature (e.g. vena cavae) may result in paradoxical embolism through a patent foramen ovale (PFO) or other right-to-left shunting intracardiac lesion. Left-sided cardiac thrombi can directly embolize to the cerebral arterial circulation.

In situ arterial thrombosis may also arise from dissection of extracranial vessels, causing a local and/or embolized thrombus. Lastly, *in situ* thrombosis may also develop in children with cerebral arteritis (e.g. in the setting of systemic lupus erythematosus) and in those with cerebral arteriopathy.

With regard to extracranial sources for cerebrovascular thromboembolism, it is likely that in many cases of complex congenital heart disease, impaired cardiac function and/or turbulent blood flow may provide sufficient circumstance for thrombus generation. Multiple studies demonstrate that patent foramen ovale (PFO) is associated with as much as a 4 to 6-fold increase in risk of AIS. A recent single center prospective cohort of children with SCD and stroke demonstrated a higher prevalence of PFO in this group (25%) as compared to children with stroke without SCD (12%), suggesting that paradoxical embolism may also contribute to risk of AIS in SCD (where elevated cerebrovascular flow velocity on transcranial Doppler and moyamoya syndrome already serve as important risk factors). Several centers have reported that congenital heart defects and/or cardioembolic sources of thrombus account for approximately 12 to 15 percent of childhood-onset AIS patients. Local small vessel vasculitis can also cause stroke in children with systemic rheumatologic conditions, as well as in primary inflammatory diseases of the cerebral vasculature. In many instances, cerebral angiitis (whether small vessel or large arterial) in the setting of rheumatologic conditions is superimposed upon a background of systemic inflammation, that may act together with antiphospholipid antibodies, other acquired thrombophilias and anatomic considerations of arterial stenosis to promote *in situ* thrombus formation.

THROMBOPHILIA AND AIS

Genetic thrombophilias have been associated with both incident and recurrent AIS. Several studies have demonstrated the increased frequency of heterozygous factor V Leiden (FVL) polymorphism in childhood-onset AIS case as compared to healthy controls. The prothrombin G20210A polymorphism was found in 6 percent of patients as compared to 1 percent of controls. Protein S deficiency has been reported in multiple case reports of childhood-onset AIS, as well as in association with an antibody mediated response to varicella. Protein C deficiency has been demonstrated as a risk factor for incident AIS in multiple case-control studies with a relative risk of recurrent childhood-onset AIS of 3.5. Lipoprotein(a) elevation has also been associated with cardioembolic subtype of childhood-onset AIS.

APPROACH TO DIAGNOSIS

The approach to diagnostic evaluation of childhood-onset AIS remains controversial and diverse. It is crucial to

identify anatomic causes of clot formation through imaging modalities. Conventional angiography provides gold standard vascular imaging of the head and neck, but carries a small chance of transient global amnesia, secondary vascular injury and/or stroke. Computed tomography with angiography (CTA) exposes the child to increased radiation burden, but contains less artifacts than magnetic resonance angiography (MRA). American heart association (AHA) pediatric stroke guidelines suggest that “the least invasive study that will provide an adequate assessment is usually the test to perform, but whether to do a test and the order in which a study is performed will vary with the clinical situation”. Repeat imaging at 3 to 12 months is essential, as 19 percent of unilateral vascular anomalies will transiently worsen, 6 percent can progress, and only 23 percent of non-progressive disease will completely normalize. One approach to thrombophilia testing outlined by the subcommittee for perinatal and pediatric thrombosis of the scientific and standardization committee of the international society of thrombosis and haemostasis (ISTH), suggests an initial evaluation of: complete blood count, antithrombin, protein C activity, free and total protein S antigen, FVL and/ or functional activated protein C resistance assay, prothrombin G20210A, homocysteine level +/- MTHFR, lipoprotein (a), lupus anticoagulant, anticardiolipin antibodies, and hemoglobin electrophoresis (for sickle cell disease screening). Typically, abnormal potentially-acquired thrombophilia findings should be retested at about 12 weeks from initial testing. In specific clinical settings rheumatologic disease (such as lupus), metabolic disease (such as fabry disease) and mitochondrial disease (such as MELAS) need to be evaluated for antithrombotic treatment for AIS.

Therapy currently is largely based on extrapolation from adult guidelines. Three consensus-based guidelines have been developed to assist in clinical care: the American heart association (AHA) scientific statement on management of stroke in infants and children, the American college of chest physicians (ACCP) guidelines on antithrombotic therapy in neonates and children, and the Royal College of Physicians (RCP) clinical guidelines for diagnosis, management and rehabilitation in pediatric stroke. Prospective studies and cooperative trials investigating the safety and efficacy of antithrombotic therapeutic modalities (both antiplatelet and anticoagulant) are urgently needed to better inform clinical care for children.

There is currently not enough evidence to support the use of IV or intra-arterial thrombolytics in children or neonates. There are a few case series of its use in the hyperacute setting of stroke in children with the major complication of bleeding.

Antithrombotic therapies (whether antiplatelet or anticoagulant) are often employed as secondary prevention strategies, initiated in the acute phase of childhood-onset AIS. Presently, however, the current standard of care

is highly-variable world-wide. Both aspirin and LMWH have been used without any major bleeding complications. However, the influences of stroke subtype, stroke size and comorbidities upon safety and efficacy of anticoagulation and antiplatelet therapy remain insufficiently studied. While all three guidelines suggest extended anticoagulation in dissection and cardioembolic subtypes of childhood-onset AIS, optimal duration of anticoagulation is also unclear and insufficiently studied. For sickle cell disease exchange transfusion to maintain HbS <30 per cent is advised in the setting of AIS.

Certain guidelines for the diagnosis and management of pediatric thrombosis in various settings have been put forward by the Haemostasis and Thrombosis Task Force of the British Committee for Standards in Haematology (BCSH). These are summarized below:

Lab Evaluation of Venous Thromboembolism

Acute VTE

VTE can occur as a complication of various systemic disorders which should be excluded by appropriate investigations. Laboratory investigations should also establish the safety of initiating anticoagulation and should include a full blood count and baseline coagulation screen. Whereas the negative predictive value of measurement of D-Dimer for VTE diagnosis has been validated in adults its use in children has not been validated. D-Dimer levels may vary with age in children and results may therefore be difficult to interpret.

Evaluation of Thrombophilic States

The reported prevalence of thrombophilic defects in children with VTE varies between 10 and 78 percent. This probably reflects differences in patient populations, definitions of thrombosis, investigations undertaken and study size. Deficiencies of antithrombin, protein C or protein S, the presence of the F5 R506Q (factor V Leiden) and the F2 G20210A gene mutations have been reported in these cohorts, as have hyperhomocysteinaemia, increased lipoprotein (a) levels and elevated plasma levels of factor VIII. The contribution of such abnormalities to the aetiology of childhood thrombosis remains uncertain, though they are widely believed to be contributory. Duration of anticoagulant therapy has been shown in some studies to be influenced by the results of testing for inherited thrombophilia. Some other studies have shown the predictive value of factor VIII and D dimer as markers of recurrent thrombosis. However, there are no definitive recommendations to decide the duration of anticoagulation based on these factors. Certain general guidelines for evaluation are as follows and are discussed in detail below:

- Routine testing for heritable thrombophilia in unselected children presenting with a first episode of VTE

is not indicated particularly if there are other systemic causes for the same.

- Initiation and intensity of anticoagulant therapy following a diagnosis of acute VTE should be the same in children with and without heritable thrombophilia.
- Testing for heritable thrombophilia after a first episode of VTE has uncertain predictive value for recurrence. Decisions regarding duration of anticoagulant therapy in relation to the results of testing for heritable thrombophilia, factor VIII levels and D-dimer are not evidence-based and are not recommended as sole determining factors for the duration of anticoagulation in children.
- Children presenting with an unprovoked VTE should be tested for the presence of anti-phospholipid antibodies and those with persistently positive results should remain on long-term anticoagulation.

Diagnosis of VTE in Specific Situations

- Diagnosis of Central Venous Line (CVL) and non-CVL related VTE in the upper limb (UL)
 - US is recommended for the initial assessment of the peripheral upper limb, axillary, subclavian and internal jugular veins but may be relatively insensitive for the detection of central intrathoracic VTE.
 - Contrast MRV is recommended for assessing the central veins for VTE.
 - Multi-detector computerized tomography (CT) venography (MDCT venography) may be considered for the assessment of the central veins if MRV is unavailable. Magnetic resonance imaging (MRI) should always be preferred to CT due to radiation dose considerations in children.
- Diagnosis of CVL and Non-CVL related VTE in the lower extremity (LL)
 - Doppler US is recommended to assess the LL venous system for VTE.
 - If the US is normal and the clinical suspicion of VTE remains high this should be repeated after a week to assess for proximal progression of any calf vein thrombus.
 - MRV should be considered in children with suspected proximal extension of femoral VTE.
- Investigation of a blocked CVL
 - A chest X-ray is recommended to visualize the CVL position.
 - A contrast linogram is recommended to determine potential occlusion at the tip of the CVL and presence of retrograde flow.
 - Surveillance for asymptomatic VTE is not recommended.
 - Doppler US, conventional venography or contrast enhanced MRV may be required to exclude large vessel thrombosis.

- Diagnosis of pulmonary embolism (PE)
 - If available, isotope lung scanning may be considered as the initial imaging investigation, providing the chest X-ray is normal and there is no significant concurrent cardiopulmonary disease. Otherwise CT pulmonary angiography (CTPA) is recommended as the initial imaging modality for suspected PE.
 - Non-diagnostic isotope lung scanning should be followed by further imaging.
 - Patients with a good quality negative CTPA do not require further investigation or treatment.
 - Pulmonary magnetic resonance angiography (MRA) should be considered as an alternative to CTPA when iodinated contrast injection or radiation is a significant consideration.
- Diagnosis of Cortical Vein Thrombosis
 - Children in whom CVT is suspected should have an urgent brain MRI including T2* imaging and MRV to detect both intraparenchymal hemorrhage and sinus thrombosis
 - If urgent MRI is unavailable, a pre- and post-contrast CT scan with CT venography (CTV) should be performed as a first line investigation to detect both intraparenchymal hemorrhage and sinus thrombosis (1B).
 - Imaging should include the petrous temporal bones and air filled sinuses to establish sinusitis/mastoiditis as a potential cause for CVT.
 - Children in whom CVT is suspected on CT could have confirmatory MRI replaced by CTV if MRI/MRV is not available.
 - Conventional cerebral angiography could be considered for those children with suspected cortical vein thrombosis not confirmed on MRI/MRV.

Management of Venous Thromboembolism

The aims of antithrombotic therapy in children with VTE are to reduce the risk of death due to thrombus extension or embolization; to reduce the incidence of recurrent thrombosis; to reduce the incidence of PTS by limiting vascular damage and fourthly, to maintain vessel patency in those with ongoing requirements for vascular access.

The management of childhood VTE is often complex, which partly reflects the frequent co-existence of other medical and surgical problems in these children. The agents most frequently used are unfractionated heparin (UFH), low molecular weight heparin (LMWH) and the oral vitamin K antagonists (VKA). Many aspects of the hemostatic system are age-dependent and this has implications for the use of anticoagulants in this age group. Despite this there is only limited data available on the efficacy and safety of these drugs for the management of specific indications in pediatric practice. Although either UFH or LMWH may be

used for initial therapy, LMWH is the more frequently used agent in clinical practice. UFH has disadvantages in terms of venous access, frequent monitoring and poor bioavailability; however, particularly in postoperative or critical care settings, the short half-life and easy reversibility may have advantages. For ongoing management, while VKA therapy may be appropriate for some children, for others, particularly those with complex co-existing problems, the use of LMWH may have significant practical advantages. VKA control is particularly problematic in very young children and may also be difficult in those receiving multiple concomitant medications or in those with frequent requirements for surgical and other interventions and a where there is a high-risk of bleeding.

TREATMENT INTENSITY

Only limited data are available on the optimal intensity of warfarin therapy in the management of childhood VTE. The target International Normalized Ratio (INR) continues to be based on adult data. A target INR of 2.5 is therefore generally accepted as being appropriate for the management of childhood VTE. Anticoagulation should be initiated with LMWH followed by warfarin (INR 2.5) or continuing LMWH. UFH may be used for initial therapy where rapid reversal of anticoagulation may be required. Ongoing therapy with LMWH may be preferable in infants under 1 year of age. Duration of anticoagulation should be up to 3 months in secondary VTE and 6 months in idiopathic VTE. Recurrent idiopathic VTE and children with antiphospholipid syndrome: duration life-long.

THROMBOLYTIC THERAPY

Thrombolytic therapy offers the possibility of achieving more rapid relief of vessel occlusion than is likely to be achieved with conventional anticoagulant therapy but is associated with an increased risk of bleeding. Both urokinase (UK) and tissue plasminogen activator (t-PA) have been used successfully in children, however, indications for treatment and optimal dosing regimens have not been established.

The most commonly used regimen is t-PA 0.1–0.6 mg/kg/h, with re-evaluation after 6 hours. Although variable outcomes have been reported, recent data have suggested a reduced risk of PTS in children with high-risk lower limb DVT. Children, particularly those with CVL-related VTE, are at risk for major central venous occlusion involving the pelvic veins, superior vena cava (SVC) and inferior vena cava (IVC) and may also develop intracardiac involvement. In these circumstances thrombolytic therapy may have advantages over conventional anticoagulation in the early stages of treatment but the risks and benefits of treatment require individual consideration. Massive pulmonary embolism is uncommon in children but thrombolytic

therapy may be appropriate in selected cases with hemodynamic compromise although it may be associated with a significant risk of bleeding.

Thus the use of thrombolytic therapy is not indicated for the majority of children with VTE but should be considered in the presence of extensive thrombosis, particularly those involving the pelvic veins, SVC, IVC or intracardiac sites. Thrombolytic therapy should also be considered for selected children with massive PE.

If clinically feasible a CVL associated with either occlusive or non-occlusive VTE should be removed following 2 to 4 days of therapeutic anticoagulation.

Children with CVT with no associated intra-cranial hemorrhage should be anticoagulated with LMWH or UFH. In the presence of hemorrhage resulting in a local mass effect or intraventricular hemorrhage, it is reasonable to withhold anticoagulation. The presence of less significant intracranial hemorrhage or parenchymal infarction are not contraindications to anticoagulation.

In the event that anticoagulation is not given, reimaging with MRV or CTV is recommended to look for thrombus extension. Anticoagulation should be continued with warfarin (target INR 2.5) in children over 1 year of age. LMWH may be preferable in infants under 1 year of age. Anticoagulation should be continued for

- Three months if there was a clear and treated precipitating factor, e.g. infection.
- Six months if there is no identified precipitant.
- Anticoagulation may need to be continued for longer in patients where there is an ongoing risk factor (e.g. continuing treatment with asparaginase), in those with recurrent idiopathic CVT and in those with ongoing symptoms or signs attributable to venous hypertension; duration should be considered on an individual basis.

Reimaging should be undertaken prior to stopping anticoagulation in patients with ongoing symptoms attributable to venous hypertension (e.g. headache, vomiting, papilledema, visual obscurations, visual field deficit) or with progressive neurological signs. Reimaging is not required in patients with stable neurological signs, unless consideration is being given to extending anticoagulant therapy, in which case it may be helpful to establish whether or not recanalization has occurred. There is no evidence to support the routine use of thrombolysis in pediatric CVT.

THERAPEUTIC AGENTS AND DOSING RECOMMENDATIONS FOR THE TREATMENT OF VTE IN CHILDREN

Unfractionated Heparin

- Initial doses of UFH
- Loading dose 75 IU/kg over 10 minutes IV
- Starting dose

- Infants <1 year 28 IU/ kg/h
- Children >1 year 18 to 20 IU/kg/h

UFH acts via anithrombin and the efficacy of this agent may be reduced in infants with low circulating antithrombin levels.

LMWH

- Enoxaparin: 1 mg/kg twice per day or 2 mg/kg once per day SC
- Dalteparin: 100 U/kg twice per day or 200 U/kg once per day SC
- Tinzaparin: 175 U/kg once per day SC
- Infants <8 weeks of age and/or <5 kg require 50 per cent larger doses e.g. Dalteparin 150 U/kg twice per day and Enoxaparin 1.5 mg/kg twice per day, possibly due to a larger volume of distribution and/or reduced antithrombin levels.
- Recommended 'prophylaxis' doses are usually half treatment doses.
- Target anti-Xa activity taken 4 h following subcutaneous injection.
- Therapeutic 0.5–1.0 U/ml.
- Prophylactic 0.1–0.4 U/ml.

Warfarin

- Initial loading dose of 0.2 mg/ kg PO for 2 days.
- Subsequent dose adjustments should be based on the INR result.
- Reversal of warfarin with Vitamin K: Vitamin K can be given PO or IV.

THROMBOLYTIC AGENTS

t-PA

Recommended doses vary, the following is the most frequently used dose range: 0.1–0.5 mg/kg/h for 4 to 6 hours.

Lower doses of 0.015–0.06 mg/kg/h for 12 to 96 hours have also been used with success and potentially may reduce the risk of bleeding.

t-PA can be given systemically or locally via a catheter-directed approach which allows a lower dose to be administered. Infants have physiologically low levels of plasminogen which may affect the efficacy of t-PA and may be enhanced by administering fresh frozen plasma prior to the infusion.

In conclusion pediatric and neonatal thrombosis is an evolving field in clinical investigation and management. Though most thrombosis may be secondary to underlying factors, the group of inherited thrombophilic states are gaining in importance. There is currently little evidence based data to guide the management of pediatric thrombosis. However both diagnostic tests and therapy options are evolving and the coming years will elucidate better all aspects of pediatric thrombophilia.

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Section 4

Intensive Care

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Pediatric Intensive Care: Past, Present and Future

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During the last century western world has seen dramatic reduction in child mortality and overall improvement in child health. Overall economic development, better public health interventions, improved nutrition and maternal health and wider immunization coverage are some of the driving factors to achieve this. Developments in pediatric intensive care also have played a small but significant role in these remarkable outcomes. A well equipped pediatric intensive care unit (PICU) with its new age technology and trained manpower has given hope to many of the critically ill children.

Despite all these advances in developed world, 90% of world children living in developing countries have not shared this remarkable prosperity and progress. The World Health Organization estimates that every year >10 million children die all over the world and 99 percent of these deaths occur in developing countries.¹

In a country like India where provision of basic health care to the masses in itself is a challenge, access to tertiary level pediatric intensive care for the general population is almost nonexistent. In developing countries like India, most of care of seriously ill children is provided by nurses, paramedic workers, nonspecialist doctors in rural or remote hospitals or overburdened staff in overcrowded urban government hospitals. In most such hospitals resources are inadequate, access to information and technology is poor and ongoing professional development and staff training is minimal. These basic deficiencies affect lives of millions of children each year and form background to any consideration of appropriate role of intensive care. The long-standing argument that the resources needed for the intensive care setup can be better utilized for delivering basic health care to larger population is also losing its sheen with changing social dynamics. With family size getting smaller, the need for better and better pediatric intensive care is going to get bigger.

ORGANIZATION²⁻¹⁰

Pediatric critical care is ideally provided by a PICU that must provide multidisciplinary definitive care for a wide range of complex, progressive and rapidly changing medical, surgical and traumatic disorders occurring in pediatric patients of all ages.

The physical facilities for PICUs will vary as a result of differences in hospital architecture, size, space, and design. The PICU should be located in proximity to elevators for patient transport, to the physicians' on-call room, and to family waiting and sleep areas. Proximity to the emergency department, operating room, and recovery room is desirable. When designing a PICU, the psychological, spiritual, cultural, and social needs of the patient and family should be taken into consideration, and policies should reflect a patient- and family-centered approach.

Several distinct room types are required within the PICU, including rooms for patient isolation and separate rooms for clean and soiled linens and equipment. A separate room for family counseling is necessary for private discussions between the staff and the family. An area for storing patients' personal effects is also desirable. A conference area for staff personnel is highly desirable and should be located near the unit. Separate facilities for patient's families, including space for sleeping and bathing, are essential. Space will be allocated for a medication station (including a refrigerator and a narcotics locker), a nourishment station, counters, and cabinets. A laboratory area for rapid determination of blood gases and other essential studies is desirable. A computerized link to the laboratory or another rapid and reliable system should be available for reporting laboratory results.

Electrical power, oxygen, medical compressed air and vacuum outlets sufficient in number to supply all necessary equipment should meet local code and other accrediting requirements. In most cases, 12 or more electrical

outlets and a minimum of two compressed air outlets, two oxygen outlets and two vacuum outlets will be necessary per bed space. Reserve emergency power and gas supply (oxygen, compressed air) are essential.

Drugs for resuscitation and advanced life support must be present and immediately available for any patient in the PICU. These drugs should be available in accordance with advanced cardiac life support and PALS guidelines and should include all those necessary to support the patient population that the PICU serves.

Portable equipment will include an emergency (code or crash) cart, a procedure lamp, pediatric-sized blood pressure cuffs for systemic arterial pressure determination, a Doppler ultrasonography device, an electrocardiograph, a defibrillator or cardioverter with pediatric paddles and preferably with pacing capabilities, thermometers (with a range sufficient to identify extremes of hypothermia and hyperthermia), an automated blood pressure apparatus, transthoracic pacer with pediatric pads, infant warmers, heating and cooling devices, lights for phototherapy, temporary pacemakers, a blood warming apparatus, and a transport monitor. A suitable number of infusion pumps with microcapability (0.1 mL/hr) must be available. Oxygen tanks are needed for transport and backup of the central oxygen supply. Similarly, portable suction machines are needed for transport and backup.

Certain small equipment appropriately sized for pediatric patients must be immediately available at all times. Such equipment includes suction catheters, tracheal intubation equipment (laryngoscope handles, sizes and types of blades adequate to intubate patients of all ages, and Magill forceps), endotracheal tubes of all sizes (cuffed and uncuffed), oropharyngeal and nasopharyngeal airways, laryngeal mask airways, central catheters for vascular access, catheters for arterial access, thoracostomy tubes, transvenous pacing catheters, and surgical trays for vascular cutdowns, open-chest procedures, cricothyroidotomy, and tracheostomy.

Mechanical ventilators suitable for pediatric patients of all sizes must be available in the PICU. Equipment for chest physiotherapy and suctioning, spirometers, and oxygen analyzers must always be available for every patient. Oxygen monitors (pulse oximeters and transcutaneous oxygen monitors) and CO₂ monitors (transcutaneous and end-tidal) are required; portable (transport) ventilators are desired.

Bedside monitors in all PICUs must have the capability for continuously monitoring heart rate and rhythm, respiratory rate, temperature, hemodynamic pressure, oxygen saturation, end-tidal CO₂, and arrhythmia detection. Bedside monitoring in PICUs must be capable of simultaneously monitoring systemic arterial, central venous and intracranial pressures. All monitors must be maintained and tested routinely.

Mechanism of disposal of contaminated waste (segregation of garbage and contaminated medical waste) and adequate disposal of needles and sharp objects needs to be as per standard applicable pollution control guidelines.

The medical director/intensivist incharge should be a pediatrician trained and experienced in critical care of children with following responsibilities: (a) Establishing policies and protocols with the help of a group of experts including but not limited to Pediatric consultants and subspecialists, nursing director, administration, laboratory and blood bank representatives; (b) Smooth functioning of PICU with implementation of policies and protocols including admission and discharge criteria; (c) Quality assurance and improvement (membership of hospital audit/quality improvement committee); (d) Advise administration regarding equipment needs; (e) Establishing teaching and training system of medical, nursing and ancillary staff; (f) Maintaining PICU statistics for mortality and morbidity; and (g) Being member of infection control committee.

The medical staff should be round the clock post-graduate level pediatrician in PICU with good airway and pediatric advanced life support skills and active PALS certification.

A skilled and competent nursing staff forms an important component of PICU. A nurse head with substantial pediatric expertise should be designated for PICUs. In collaboration with the nursing leadership team, the nurse head is responsible for assuring a safe practice environment consisting of appropriate nurse staffing, skill level mix, and supplies and equipment. The nurse head shall participate in the development and review of written policies and procedures for the PICU; coordinate multidisciplinary staff education, quality assurance and nursing research.

Patient care should be carried out or supervised by a pediatric critical care nurse. All nurses should complete a clinical and didactic pediatric critical care orientation before assuming full responsibility for patient care. Pediatric advanced life support (PALS) or an equivalent course should be required. Nurse-to-patient ratios should be based on patient acuity, usually ranging from 2:1 to 1:3.

All PICU must be regularly staffed by physiotherapists, dieticians and respiratory technicians for enhancing patient care. In addition, technicians, radiographers, and biomedical engineers should be available on a 24 hours (in hospital) basis for emergencies/problems that require immediate attention. Secretarial/clerical staff is required to carry out communication as well as paper work necessary for smooth functioning of the unit. It is also essential to have cleaning staff that is efficient and sensitive to urgent patient care needs. Presence of social worker is desirable to help support families emotionally as well as financially in stressful circumstances.

Strong evidence from western world demonstrate that centralization of pediatric intensive care services result in lower mortality than do decentralized or fragmented services.⁹ However, several prerequisite accompany centralized services including transportation to a tertiary hospital from peripheral facilities and appropriate pre-transport management.¹⁰ Planning should take into account entire spectrum of services necessary for care of the critically ill, including pre-hospital resuscitation, transport and subspecialty support services.

INTERHOSPITAL TRANSIT¹¹⁻¹⁶

Interhospital transport of the patients in Indian scenario presents a challenge because of lack of specialized transport teams.

Presence of written policy documents or guidelines, dedicated equipment and trained personnel will be useful to units undertaking interhospital transports often. Patients may need to be transferred to another hospital for further care when deterioration in patients' clinical condition is expected and facilities for the same are not available at the admitting hospital, for diagnostic or interventional purposes or when the patient's family desires so. The indication for transport, risks and expected benefit must be clearly documented in the medical records. Informed consent should be taken in the standard format. If non-urgent, the transport should be planned for morning to avoid peak traffic. This will also enable investigations to be done at the receiving hospital. The referring consultant must confirm the availability of bed at receiving hospital.

Communication and coordination are important aspects of interhospital transport. The destination hospital or referral center must be informed of the time when the patient sets off from the hospital and expected time of arrival of the patient at the destination. The transport team must be in constant contact with the referring consultant and the destination hospital. The receiving hospital must ensure that on arrival, the patient is immediately taken up for the desired management.

Selecting the mode of transport will depend partly on clinical requirements, vehicle availability, road conditions and on conditions at the referring and receiving sites. In case of air transport, weather conditions and aviation restrictions for airborne transport aircraft landing facilities decide its feasibility.

Care should be taken while shifting patient from hospital bed to ambulance trolley, trolley into the ambulance, shifting trolley from ambulance and to the receiving hospital bed. During these maneuvers extra vigilance is needed to prevent disconnections, equipment malfunction and dislodgement of indwelling catheters. If the transport team does not belong to the referring hospital, ensure complete hand over of relevant clinical details.

This handover and patients clinical status should be documented in the patient's medical records. Ensure that the all relevant imaging films, copies of medical records and investigation reports are given with the patient before beginning transport.

If the patient is intubated and ventilated, patient's head must be secured to prevent movement with the movement of the vehicle. Patient should otherwise be securely strapped to the trolley. Check that the ETT is secured properly. All monitoring leads are attached properly and monitors are working. Make sure the alarms are set and are working. In ventilated patients, check that the ventilator is connected properly and is working. Ensure enough oxygen and battery backup for the duration of transport. The patient should be examined for hemodynamic stability before starting the vehicle. Ensure proper monitoring and maintain record of vitals. Make sure that the patient receives timely doses of all medications. Make sure that all infusions and drips are going and oral and endotracheal suction is carried out in timely manner. If transportation is through road driving should be slow and steady to avoid jerky movements.

Accompanying personnel along with the patient should ideally be a physician along with a nurse and a ward-boy. All unstable patients and ventilated patients should be accompanied by a trained person, competent to handle airway problems including the ability to intubate, cardiopulmonary resuscitation, initiate and titrate vasoactive drugs and to manage mechanical ventilation.

The patient's clinical status is assessed immediately and thoroughly on arrival, a relevant history and other details are obtained from the transport team and the hand over is documented. The personnel at the receiving end will exchange the equipments of the referring hospital or ambulance with that of the receiving hospital.

INTRAHOSPITAL TRANSPORT¹⁷⁻²²

Intrahospital transport requires development of protocols and proper documentation at each stage during transport. Preparation of patient for transport involves identification of high risk patients and their needs, essential infusions, fluid resuscitation, patent and secured airway, pharmacological and sedation requirements. Proper pretransport coordination between the receiving and departing location is important to avoid unnecessary delay and proper communication and documentation of the patients' condition at time of transfer is essential. The equipments should be regularly checked for proper working and charging for duration of transport, monitors and ventilators properly secured. The accompanying personnel should be trained enough to handle airway problems including the ability to intubate, cardiopulmonary resuscitation, initiate and titrate vasoactive drugs and manage mechanical ventilation during transport of critically ill patients.

Vitals should be monitored and recorded at fixed intervals with documentation. The transport staff must remain with the patient until the receiving team is fully ready to take over care. When taking the patient back, a handover takes place and again patient status should be documented.

Quality Control

All pediatric intensivists are committed to improve quality of care to their patients. A number of processes can contribute to the ultimate goal of improving outcomes for patients admitted to the PICU. These include:

- Defining the goals and standards to be achieved in conjunction with the resources available
- Addressing the issues associated with provision of safe care
- Responding appropriately to potential or actual adverse events
- Monitoring the standards, processes and outcome of pediatric intensive care
- Learning from available data, developing and implementing strategies to improve delivery of quality care
- Evaluating the initiatives and reiterating the process from beginning.

At the beginning of 21st century a number of landmark reports were published such as: “*to err is human; building a safer health system*” from Institute of medicine²³ and UK NHS—“*organization with memory*”.²⁴ These and other publications all around the world prompted escalation in patient safety initiatives throughout the world. The public at large developed unprecedented awareness of medical error and harm that might be experienced as a result of entering health care system. This has resulted in a greater emphasis being given to the process of safe medical practices. Let us understand few terms related to safe medical practices.

Patient safety is the avoidance, prevention and amelioration of adverse outcomes or injuries stemming from process of health care. Although other definitions may exist but simple words that have long been in the core of medical ethics, originated with Hippocrates—“First do no harm”. The Patient expect to receive health care without experiencing preventable harm.

Medical error is the failure of planned action to be completed as intended due to error in execution or error in planning.

Mistake is knowledge based failure: a plan was carried out correctly but planned action was wrong for the situation. Active error typically occurs in patient care area and effect is almost immediately appreciated. Latent errors are usually system related and difficult to recognize. Fully investigating and uncovering latent error is more likely to result in development of better system.

The process of improvement in health care is generally referred to as *continuous quality improvement (CQI)*, which is a continuous process of reviewing and improving the practices and procedures associated with improvement in services.²⁵ Many physicians and health care professionals lack formal training in CQI.

Medical Error—Human Error or System

Medical error results when the health care worker fails to perform perfectly (active error) and system does not have adequate redundancy or layers to prevent the error from reaching the patient. Component of active error will always be there because of limitations, inherent to humans, like emotions, perceptions, stress, fatigue, cognition, environment of performers and their decision-making abilities. Thus reduction and limitation of medical error in the PICU must take into account these elements as well as other principles of system analysis and event investigation.

Safety is not the responsibility of a single person, device or department within a system but rather the product of interaction of components of the system.²³ Leaders in PICU should strive to find ways to simplify and standardize care.

Pediatric Intensive Care Unit Environment

The physical and psychological environment of PICU contributes to the risk for medical error. Decision making in PICU is complex and involves interpreting multiple pieces of data in short amount of time in an environment that frequently requires multitasking. Patient care must be triaged as it is impossible to be at the bedside of more than one patient at a time. Intensivist must have a working knowledge of many types and brands of equipment. The environment is noisy, full of distraction and lack of standard and ergonomic design. It is rare for a task to progress to completion without interruption. All these characteristic correlate to the complexity of the PICU environment and have potential to negatively impact patient safety.

In the PICU the high acuity of illness, constant exposure to death, grieving parent, fatigue inappropriate staffing (number and skill sets) on ever changing body of knowledge, lack of equipment standardization, multiple simultaneous demand and use of many interventions associated with narrow therapeutic window all affect human performances.

A publication by the agency for health care research and quality in 2005 highlighted the impact of working condition (such as interruption and keeping pace with the changing need of patient) on clinical decision making abilities of nurses.²⁶ A study by Crayson found that error tends to occur within 30 minutes after sudden changes in patient need in an environment that is dominated by distraction and interruption.²⁷ Since patient status and

census are constantly changing and multitasking is normal in PICU, it is most error prone area in hospital.

It is clear from sleep literature that acute and chronic sleep deprivation negatively impact performance and place sleep deprived practitioners at risk for personal injury, mood disturbances and stress related illnesses.^{26,28} The extent to which fatigue related error actually contribute to patient harm is largely unknown. Although emerging data describes the benefit of decreasing sleep deprivation and fatigue, increased number of patient handover has become new source of error. Hence, new strategies for improving teamwork and access to patient information are necessary to minimize the occurrence of handover related error.

COMMUNICATION

Effective communication is another area that plays an extremely important role in improving safety better overall care. Communication between all members of health-care team is crucial to develop safe medical practices. The Joint Commission on Accreditation of Healthcare Organization (JCAHO) has noted that poor communication is a factor in majority of sentinel events. The 2006 JCAHO national patient safety goals include several requirements for improving communication throughout the hospital.

Patients in the PICU move through various departments of the hospital to have specialized procedures and diagnostic testing and at the same time health care providers from multiple disciplines enter PICU for patient management. In ideal system information should flow easily between all team members and patient data should be timely available, be legible and be comprehensive. A specific structure for sharing patient information, particularly at the time of patient handover, facilitates good communication as has been demonstrated by the use of daily goals.

The ideal communication system is difficult to achieve in health care for several reasons including authority gradients, time and physical restraints, technology limitation and perception that teamwork is not essential to good patient care outcomes.

A traditional hierarchical approach to patient care in medicine hinders effective and timely communication between attending physician and trainees, physician and nurses and administration and staff. A technique called situation, background, assessment and recommendation (SBAR) has been introduced to the health care field as a method to improve communication between team members and overcome perceived and real restriction related to hierarchy. This technique provides health care worker with framework for communicating a concern about patient or situation and empowers the worker to move up

the authority gradient if concern is not addressed in professional and timely manner.

Pediatric Intensive Care: A Framework for the Future

Pediatric Intensive Care

- Delivers care to the most critically ill children, most of whom will be artificially ventilated
- It is a low volume, high cost service
- Cannot be provided in every locality
- Requires highly trained specialist staff
- Should be available to all children who need it regardless of where they live.

Key Limitation of the Current Service

- It has developed in an ad hoc unplanned way during the past twenty years
- It is currently provided in a wide range of different settings, in designated pediatric intensive care beds, general children's wards, adult intensive care units, single specialty hospitals, and special care baby units
- Until very recently, there has been relatively little evidence on the standards which provide the best outcomes for critically ill children, and no such standards have as yet been laid down
- The number of designated pediatric intensive care unit is small
- Specialist retrieval services, needed to transport critically ill children to the nearest specialized center, are still relatively few and are often not provided on a continuous 24-hour basis
- There are too few clinicians and nurses with pediatric intensive care skills.

RECOMMENDATIONS

Audits of the Current Service

Health authorities and hospitals in each area need to carry out a study to assess how many children in their area are likely to need intensive care each year, and where they are receiving care now. The study should establish:

- The numbers of children per 1000 in the population who need intensive care each year
- The profile of demand throughout the year
- The current configuration of the service
- The average length of stay in each hospital providing the service
- The percentage of intensive care which can be predicted in advance (e.g. as a result of major elective surgery)
- The numbers of children needing long-term ventilation

- The extent of need for high dependency care to relieve pressure on intensive care beds.

Organization of the Service

In future the pediatric intensive care service should be delivered in four types of hospitals:

- District general hospitals admitting children, which must be able to initiate intensive care;
- Lead centers, providing most of the intensive care needed in the area and supporting the whole service for the area through the provision of advice and training;
- Major acute general hospitals with large adult intensive care units, which already provide a considerable amount of pediatric intensive care;
- Specialist hospitals providing some intensive care in support of the specialty, e.g. cardiac, neurosurgery, burns.

Standards

Each of these types of hospital should in future comply with certain standards in each of the following categories:

- Training and education of personnel;
- Competencies and equipment for specific forms of treatment;
- Access to specialist services on site or access to advice on particular specialties;
- Facilities for families and an environment for the successful care of children;
- Support services on site or on call.

Action Plan

The health authorities and hospitals should follow a timetable for introducing the necessary changes to the pediatric intensive care service:

- As an immediate first step, provision of extra single, isolated beds should cease;
- All areas should now carry out a prospective study to establish the extent of need for pediatric intensive care and where it is currently provided;
- Children needing intensive care should no longer be looked after in the inappropriate location of general children's wards;
- A lead center should be designated in each area;
- Steps should be taken to stop caring for children in centers which do not meet the standards set out
- A retrieval service should be funded and staffed on a 24 hour basis in each geographical area;
- Protocols should be developed describing how the service is to be organized and managed across the whole area to provide the best possible outcomes for critically ill children.

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Update on Cardiopulmonary Resuscitation Guidelines

Soonu Udani

INTRODUCTION

Adequate and well performed “cardiopulmonary resuscitation (CPR) and emergency cardiovascular care (ECC)” saves lives and is a skill that should be inculcated at the basic level in the lay public, especially those in contact with children in schools and playgrounds, and at the advanced level in all health care providers.

Cardiac arrest in infants and children rarely results from a primary cardiac cause. It is often the end result of progressive respiratory failure or shock, and termed as “asphyxial arrest”. A period of systemic hypoxemia, hypercapnea and acidosis, progresses to bradycardia and hypotension, and cardiac arrest is the end result.

Another mechanism of cardiac arrest, although only in approximately 5 to 15 percent of arrests, is ventricular fibrillation (VF) or pulseless ventricular tachycardia (VT). Although rare as the initial cardiac rhythm, during an arrest, it may be seen in about 27 percent of children.¹ Increasing evidence suggests that sudden unexpected death in young people can be associated with genetic abnormalities in myocyte ion channels termed “channelopathies”. These cause fatal arrhythmias and VF/VT is often the presenting rhythm.²

Basic life support is usually described as a sequence of actions, and this continues to be true for the lone rescuer. Most Health care providers, however, work in teams, and team members typically perform basic life support (BLS) actions simultaneously. Health care providers are again encouraged to *tailor rescue actions to the most likely cause of arrest*. This discussion is for the trained health care provider, namely, the pediatrician who will encounter a situation in the office, hospital or intensive care unit. The challenge is to organize the rescuers into an efficient team, use basic skills, very little medication and *provide high quality CPR*.

With this aim, the 2010 guidelines^{2,3} have been modified from the 2005 document and here some highlights of the changes plus some critical points that are germane to high quality CPR are discussed. The neonate is not discussed (Table 1).

Change in the BLS sequence of steps from A-B-C (airway, breathing, chest compressions) to C-A-B (chest compressions, airway, breathing) for adults, children, and infants (excluding the newly born). This fundamental change in CPR sequence will require re-education of everyone who has ever learned CPR, but the consensus of the authors and experts involved in the creation of the 2010 AHA and also the PALS³ Guidelines for CPR and ECC is that the benefit will justify the effort. To also have multiple guidelines for subgroups is confusing and does not lend to high quality CPR. (Class I, LOE C)^{2,3} summarized in Table 1.²

Chest compressions can be started almost immediately, whereas positioning the head and achieving a seal for mouth-to-mouth or bag-mask rescue breathing all take time. Chest compressions provide vital blood flow to the heart and brain, and studies of out-of-hospital adult cardiac arrest showed that survival was higher when bystanders made some rather than no attempt to provide compressions. Animal data demonstrated that delays and interruptions in chest compressions reduced survival, so any maneuver/s that can result in delays or interruptions should be minimized throughout resuscitation. Since we presume that there would be more than one person present, as chest compressions are started, ventilation should be undertaken by the second person. *As skill sets may be uneven between the two providers, the one with the lesser airway skills should manage the chest compressions as the rate and depth can be instructed during the process. Whether one or more people are present chest compressions MUST be initiated first—this assures that the victim gets this important intervention FIRST.*

Table 1 : Summary of key BLS components for adults, children and infants*

		Recommendations	
Component	Adults	Children	Infants
Recognition	Unresponsive (for all ages)		
	No breathing or no normal breathing (i.e. only gasping)		No breathing or only gasping
	No pulse palpated within 10 seconds for all ages (HCP only)		
CPR sequence	C –A–B		
Compression rate	At least 100/min		
Compression depth	At least 2 inches (5 cm)	At least ¼ AP diameter About 2 inches (5 cm)	At least ¼ AP diameter About 1½ inches (4 cm)
Chest wall recoil	Allow complete recoil between compressions HCPs rotate compressors every 2 minutes		
Compression interruptions	Minimize interruptions in chest compressions Attempt to limit interruptions to <10 seconds		
Airway	Head fit - chin fit (HCP suspected trauma: jaw thrust)		
Compression-to-ventilation ratio (until advanced airway placed)	30:2 1 or 2 rescuers	30:2 Single rescuer 15:2 2 HCP rescuers	
Ventilations: when rescuer untrained or trained and not proficient	Compressions only		
Ventilations with advanced airway (HCP)	1 breath every 6-8 seconds (8-10) breaths/min) Asynchronous with chest compressions About 1 second per breath Visible chest rise		
Defibrillation	Attach and use AED as soon as available. Minimize interruptions in chest compressions before and after shock: resume CPR beginning with compressions immediately after each shock		

Abbreviations: AED, automated external defibrillator; AP, anterior-posterior; CPR, cardio-pulmonary resuscitation; HCP, health care provider

*Excluding the newly born, in whom the etiology of an arrest is newly always asphyxial

From: Executive Summary: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Circulation 2010;122:S639.

- “Look, listen, and feel” is *removed* from the CPR sequence.
- *After delivery of 30 compressions*, the lone rescuer opens the victim’s airway and delivers 2 breaths→ The second rescuer, if present, can open the airway simultaneously.
- If 2 rescuers are present, a *15 chest compressions to 2 breath cycle may then be started.*² *This differs from adults where the cycle remains 30:2,² hence it may be reasonable to add that in adolescents and witnessed cardiovascular collapse, the 30:2 ratio could or should be used. (authors note)* The provider should check only briefly for no breathing or only gasping after determining unresponsiveness. *No more than 10 seconds should be spent in a pulse check and calling for help.*

NB: As most newborn arrest is ashyxial in nature, the ABC sequence with warming and judicious oxygen use is still the recommendation. (see NRP guidelines)

CHEST COMPRESSION RATE

At least 100 per minute and it provides high quality CPR and is an important determinant of return of spontaneous circulation (ROSC) and survival with good neurologic function.

Key Features

- Reduce the number and length of any interruptions
- Each cycle of 30 compressions and 2 breaths completed in 18 secs (not 23)

- Allow complete chest recoil after each compression to assist cardiac filling
- Avoid excessive ventilation (8-10 breaths per minute) Overzealous ventilation prevents cardiac filling, hampers venous return to the heart, hampers coronary filling and constricts cerebral blood vessels reducing blood flow.

CHEST COMPRESSION DEPTH

Deeper is better and does no harm. Uniformity is better than having too many different values.

Adult — 2 inches 5 cm or 1/3 AP diameter

Children — 2 inches 5 cm or 1/2 AP diameter

Infants — 1.5 inches 4 cm or 1/2 AP diameter.

VENTILATION

The use of a definitive airway by tracheal intubation is important and should be undertaken as soon as possible. After initial bag and mask ventilation with 100 percent oxygen the most skilled member of the team should undertake the task. Bag-mask ventilation requires training and periodic retraining in selecting a correct mask size, maintaining an open airway, providing a tight seal between mask and face, providing ventilation, and assessing effectiveness of ventilation. Two people often provide more effective ventilation with better sealing and chest rise in difficult situations of low compliance or obstructive airways.⁴

When bag-mask ventilation is unsuccessful and when endotracheal intubation is not possible, the LMA is acceptable but some basic skill and a little experience is needed. (Class IIa, LOE C) as its insertion is associated with a higher incidence of complications.

Size of ET tube

If an uncuffed endotracheal tube is used for emergency intubation,

→ select a 3.5 mm ID tube for infants

>1 and <2 years of age—4.0 mm ID tube

>2y, formula: Uncuffed endotracheal tube ID (mm) 4+ (age/4)

RSI or rapid sequence intubation using sedatives, neuromuscular blocking agents, and other medications to rapidly sedate and neuromuscularly block the child is the best way but a back-up plan should be in place if intubation fails. Cricoid pressure during intubation is now removed as a MUST as it may interfere with both intubation and ventilation in less than the most skilled hands (Class III, LOE C).

Overzealous bagging with high peak pressures and rates during cardiac arrest increases intrathoracic pressure → impedes venous return → decreases cardiac output → decreases cerebral and coronary blood flow. These effects will reduce the likelihood of ROSC or quality CPR.⁵

CHECK FOR PLACEMENT⁶

The following are methods for confirming correct position:

- Look for bilateral chest movement and listen for equal breath sounds—lung fields—axillae.
- Listen for gastric insufflation sounds
- Check for exhaled CO₂ by ET CO₂
- If there is a perfusing rhythm, check saturation with a pulse oximeter
- If you are still uncertain, perform direct laryngoscopy and visualize the tube beyond vocal cords
- Chest X-ray to verify position.

Once an advanced airway is in place, asynchronous ventilation at the rate of 8-10 in a child and continuous chest compressions at the rate of AT LEAST 100/min continues.

Only if an advanced airway is not in place 15:2 ventilation-to-co press-ion ratio is practiced (Class IIb, LOE C) with 2 rescuers.

Capnography Stressed

Whenever available, and a perfusing rhythm is present, capnography must be performed to check the ETT. All other clinical methods have their fallacies. Colorimetric methods are useful but do not help trend the CO₂ and medications like epinephrine and acid from the stomach interfere with the readings giving false-negative values.⁷ During cardiac arrest, if exhaled CO₂ is not detected, confirm tube position with direct laryngoscopy (Class IIa, LOE C) because the absence of CO₂ may reflect very low pulmonary blood flow rather than tube misplacement.⁸

Capnometry and graphy is extremely useful to monitor success of CPR as with ROSC and improved pulmonary blood flow, the ET CO₂ starts rising with gas exchange. An ET CO₂ reading of >20 mm Hg during CPR is an indicator of good quality CPR.

Gastric Tube

This is a common and hasty procedure by many health care workers during CPR. If chest rise or oxygenation are compromised, pass the tube *after intubation* because a gastric tube interferes with gastroesophageal sphincter function, allowing regurgitation during intubation.⁹

Oxygen Use

Until additional information becomes available, it is reasonable to use 100 percent oxygen during resuscitation. Once circulation is restored, monitor systemic oxygen saturation. It may be reasonable, when appropriate equipment is available, to titrate oxygen to saturation >94 percent. Provided appropriate equipment is available, once ROSC is achieved, adjust the FiO₂ to the minimum concentration needed to achieve oxygen saturation of at least 94 percent with the goal of avoiding hyperoxia while ensuring adequate oxygen delivery. Since oxygen saturation of 100

percent may correspond to a PaO_2 anywhere between 80 and 500 mm Hg (Class IIb, LOE C). Whenever possible, humidify oxygen to prevent mucosal drying and thickening of pulmonary secretions.

Medication and IV Access

IV access should be procured ASAP. If there is a delay, intraosseous access should be immediately obtained. The intratracheal route should be discouraged as its use may further delay the search for an IV access. Lipid-soluble drugs, such as lidocaine, epinephrine, atropine, and naloxone (mnemonic “LEAN”) can be administered via an endotracheal tube. However, the effects may not be uniform.¹⁰ Although in neonates and infants the results may be better.

If CPR is in progress, stop chest compressions briefly, administer the medications, and follow with a flush of at least 5 mL of normal saline and 5 consecutive positive-pressure ventilations. 10 times the dose is probably needed.^{3,11}

This interrupts both, compressions and ventilation and puts unnecessary fluid into the trachea. The IO route is quicker, safe and more effective. It is an ABSOLUTE SKILL for a pediatrician. (authors note)

In-Hospital Use of AEDs: (automated external defibrillator) Despite limited evidence, AEDs may be considered for the hospital setting as a way to facilitate early defibrillation (a goal of shock delivery ≤ 3 minutes from collapse), especially in areas where staff have no rhythm recognition skills or defibrillators are used infrequently. *This is common in India where there is often not an expert to guide rhythm recognition. Instead of investing in a routine defibrillator, the pediatrician practicing alone and relying on staff could invest in an AED.* For defibrillation of children 1 to 8 years of age with an AED, a pediatric dose-attenuator system is preferred if available. For infants (<1 year of age), a manual defibrillator is preferred. The upper and lower limits for safe or effective defibrillation are not clearly known, but doses >4 J/kg (as high as 9 J/kg) have effectively defibrillated children with no significant adverse effects. 18 to 50 percent of VF cases terminate with initial doses of 2 J/kg with monophasic waveforms. Newer defibrillators have biphasic wave forms.¹² While biphasic currents may be better, monophasic will do as well.

Shock First vs CPR First

CPR should be started while the AED/defibrillator is being called for or being readied.

When VF is present for more than a few minutes, the myocardium is depleted of oxygen and energy. A brief period of chest compressions can deliver oxygen and energy to the heart, increasing the likelihood that a shock will likely stop VF and be followed by ROSC.

One Shock Protocol vs 3-Shock Sequence

Evidence suggested significant survival benefit with asingle-shock defibrillation protocol compared with a 3-stacked shock protocol. If one shock fails to eliminate VF, the incremental benefit of another shock is low. Resumption of CPR is likely to be of greater benefit than another immediate shock followed by immediate CPR rather than stacked shocks and will limit interruptions; which is a main goal for high quality CPR. Synchronized cardioversion must not be used for treatment of VF because the device is unlikely to sense a QRS wave and thus, a shock may not be delivered. Synchronized cardioversion should also not be used for pulseless VT or polymorphic VT (irregular VT). These rhythms require delivery of high-energy *unsynchronized* shocks (i.e. defibrillation doses). Although there is a likelihood of response, using synchronised cardioversion may delay conversion as higher doses may be required and more shocks may be required.

The precordial thump may be considered for patients with witnessed, monitored, unstable VT (including pulseless VT) if a defibrillator is not immediately ready for use, but it should not delay CPR and shock delivery.

Paddle placement and size: Use the largest paddles or self-adhering electrodes (both are equally effective) that will fit on the child's chest without touching (about 3 cm between the paddles or electrodes). Make sure the gel is not smeared all over the chest but only put for paddle placement. This will dissipate the current.

- “Adult” size (8 to 10 cm) for children >10 kg (approximately = >1 year)
- “Infant” size for infants <10 kg¹³ Place over the right side of the upper chest and the apex of the heart (to the left of the nipple over the left lower ribs) so the heart is between the two paddles. Apply firm pressure. There is no advantage to the anteroposterior position but it can be used if needed.¹⁴

Implanted pacemakers and IEDs do not interfere with paddle placement. If the site is known, the paddles should be placed away from the device.

Integration of Defibrillation with Resuscitation Sequence

Algorithm for shockable rhythm: VF, wide complex tachycardia with shock or hemodynamic instability, VT:

- Provide CPR until the defibrillator is ready to deliver a shock;
→ after shock delivery, resume CPR
- If a “shockable” rhythm is still present, continue chest compressions after a rhythm check (when possible) while the defibrillator is charging (so chest compressions are delivered until shock delivery)

- Give 1 shock (2 J/kg) as quickly as possible → immediately resume CPR
- Continue CPR for about 2 minutes
- Obtain vascular (IO or IV) access simultaneously. **VERY IMP STEP**
- After 2 minutes of CPR, (includes chest compressions + EPI—see below) check the rhythm; recharge the defibrillator to a higher dose (4 J/kg)
- If a “shockable” rhythm persists, give another shock (4 J/kg). *If rhythm is “nonshockable”, continue with the asystole/PEA algorithm*
- Immediately resume chest compressions
- Continue CPR for approximately 2 minutes
- While continuing CPR, give amiodarone (Class IIb, LOE C) or lidocaine if amiodarone is not available¹⁵
- If defibrillation is successful but VF recurs, resume CPR and give another bolus of amiodarone before trying to defibrillate with the previously successful shock dose. Search for and treat reversible causes.

During CPR give epinephrine 0.01 mg/kg (0.1 ml/kg of 1:10,000 concentration), maximum of 1 mg (Class I, LOE B) every 3 to 5 minutes.

It is helpful if a third person prepares the drug doses before the rhythm is checked so it can be administered as soon as possible. Timing is less important and chest compressions should not be interrupted. Just prior to the rhythm check, the rescuer operating the defibrillator should prepare to recharge the defibrillator (4 J/kg or more with a maximum dose not to exceed 10 J/kg or the adult dose, whichever is lower).

Non-shockable rhythm or pulseless electrical activity (PEA) or asystole:

PEA is an organized electric activity—most commonly slow, wide QRS complexes—without palpable pulses. Sometimes, there is a sudden impairment of cardiac output with an initially normal rhythm but without pulses and with poor perfusion. This subcategory, formerly known as electromechanical dissociation (EMD), may be more reversible than asystole.

For asystole and PEA follow this algorithm:

- CPR with at least 100/min and 8 to 10 breaths/min and a definite airway → continue and give epinephrine in a dose of 0.01 mg/kg (0.1 ml/kg of 1:10,000 solution) maximum of 1 mg (10 ml), every 3 to 5 minutes. (Class I, LOE B). *There is no survival benefit from high to dose epinephrine, and it may be harmful, particularly in asphyxia (Class III, LOE B). High dose epinephrine may be considered in exceptional circumstances, such as beta blocker overdose (Class IIb, LOE C).*
- Continue cycles until ROSC or until the rhythm becomes shockable → go to shockable algorithm.

SPECIAL SITUATIONS

Pediatric Bradycardia

- Support a patent airway, breathing, and circulation

- Administer 100 percent oxygen, attach an ECG monitor/defibrillator, and obtain vascular access IV/IO
- Reassess the patient to determine if bradycardia persists and is still causing cardiorespiratory symptoms despite adequate oxygenation and ventilation.
- If pulses, perfusion, and respirations are adequate → no emergency treatment is necessary → Monitor and proceed with evaluation.
- If heart rate is <60 beats per minute with poor perfusion despite effective ventilation with oxygen, start CPR.
- After 2 minutes re-evaluate patient
- Check airway, oxygen source, and effectiveness of ventilation
- Next step → Medications and pacing:
- Continue to support airway, ventilation, oxygenation, and chest compressions (Class I, LOE C) → If bradycardia persists or responds only transiently, give epinephrine IV/IO (Class I, LOE B).
- Primary AV conduction block (i.e. not secondary to factors such as hypoxia), give IV/IO atropine 0.02 mg/kg ET dose of 0.04 to 0.06 mg/kg (Class I, LOE C).
 - Emergency transcutaneous pacing may be lifesaving if the bradycardia is due to complete heart block or sinus node dysfunction unresponsive to previous treatment especially if it is associated with congenital or acquired heart disease (Class IIb, LOE C).
 - Pacing is not useful for asystole or bradycardia due to postarrest hypoxic/ischemic myocardial insult or respiratory failure.¹⁶

Wide-complex (>0.09 second) NOT 0.08 secs. Tachycardia wide-complex tachycardia often originates in the ventricles (ventricular tachycardia) but may be supraventricular in origin, consultation with an expert in pediatric arrhythmias is strongly recommended before treating children who are hemodynamically stable.

The following are important considerations in treating wide complex tachycardia in hemodynamically stable patients:

- Adenosine may be useful in differentiating SVT from VT and converting wide-complex tachycardia of supraventricular origin. Adenosine should be considered only if the rhythm is regular and the QRS is monomorphic. Do not use adenosine in patients with known Wolff-Parkinson-White syndrome and wide-complex tachycardia.
- Consider electric cardioversion after sedation using a starting energy dose of 0.5 to 1 J/kg. If that fails, increase the dose to 2 J/kg (Class IIb, LOE C)
- Consider pharmacologic conversion with either intravenous amiodarone (5 mg/kg over 20 to 60 minutes) or procainamide (15 mg/kg given over 30 to 60 minutes). Stop or slow the infusion if there is a decline in blood pressure or the QRS widens.

In hemodynamically unstable patients:

Electric cardioversion is recommended using a starting energy dose of 0.5 to 1 J/kg. If that fails, increase the dose to 2 J/kg (Class 1, LOE C).

Torsades de Pointes

This polymorphic VT is associated with a long QT interval, which may be congenital or may result from toxicity with type IA antiarrhythmics (e.g. procainamide, quinidine,) or type III antiarrhythmics (e.g. sotalol and amiodarone), tricyclic antidepressants, digitalis.

Treatment

Torsades de pointes VT typically deteriorates rapidly to VF or pulseless VT, so providers should initiate CPR and proceed with defibrillation when pulseless arrest develops. Regardless of the cause, treat torsades de pointes with a rapid (over several minutes) IV infusion of magnesium sulfate (25 to 50 mg/kg; maximum single dose 2 g).

Shock—hypovolemic/septic: This is not an uncommon cause for cardiovascular collapse and fluid resuscitation with 10 to 20 ml/kg NS must be given, repeatedly if need be, to fill an empty heart for successful CPR. Fluid during CPR is always helpful in augmenting cardiac output whatever the cause may be.

Medications

This is re-emphasized in the new guidelines.

Calcium: Not recommended in arrest in the absence of documented hypocalcemia, calcium channel blocker overdose, hypermagnesemia, or hyperkalemia (Class III, LOE B). Routine calcium administration in cardiac arrest provides no benefit and may be harmful.^{17,18}

NaHCO₃: There is no mention of the use of this drug except in tricyclic antidepressant poisoning. (Class III, LOE B). Reversing shock with fluids and appropriate inotropes is more rewarding and both calcium and NaHCO₃ can be detrimental to hypoxic cells. Excessive sodium bicarbonate may impair tissue oxygen delivery; cause hypokalemia, hypocalcemia, hypernatremia, hyperosmolality; decrease the VF threshold.^{2,3}

Atropine: Atropine sulfate is a parasympatholytic drug that accelerates sinus or atrial pacemakers and increases the speed of AV conduction.^{2,3}

Precautions: Small doses of atropine (<0.1 mg) may produce paradoxical bradycardia because of its central effect. Larger than recommended doses may be required in special circumstances such as organophosphate poisoning. It has no place in PEA or asystole (see bradycardia algorithm).

Vasopressin: While there may be insufficient evidence in the pediatric literature for its routine inclusion, in refractory shock post CPR it is certainly a rescue medication.¹⁹ Although trials did suggest a lower rate of ROSC and survival. Adult trial also did not demonstrate great benefits.²⁰

Postarrest care: There is an evolution of cardiac dysfunction after an arrest. The initial hyperdynamic phase soon settles into a low output state of cardiac exhaustion and drugs are needed to maintain cardiac output.²¹ No one drug has been proven to be of greater value than another in children and the pros and cons of each must be balanced according to each child's need and cardiovascular and hemodynamic status. Epinephrine is the most commonly used post CPR drug. Dobutamine or Milrinone may also help with diastolic dysfunction that has been often reported.²² See Table 2 for drugs.

Potential adverse effects of catecholamines:

- Local ischemia
- Ulceration
- Tachycardia
- Atrial and ventricular tachyarrhythmias
- Hypertension
- Metabolic changes (hyperglycemia, increased lactate and hypokalemia).

Glucose: Appropriate to monitor blood glucose levels as children may be hypoglycemic. Avoid hypoglycemia as well as sustained hyperglycemia following cardiac arrest. Although there is no firm evidence for insulin use, extrapolated from critical care practice, if hyperglycemia persists above 180 to 200 with spillage and osmotic diuresis, it would seem reasonable to control it to levels below 150-180 with intravenous insulin at 0.05-0.1 u/kg/hr.

Neurologic System: A primary goal of resuscitation is to preserve brain function.

- Do not routinely provide excessive hyperventilation. Cerebral ischemia may worsen as will cardiac output. It may be used as short rescue therapy for signs of impending cerebral herniation
- Therapeutic hypothermia (32°C to 34°C) may be considered for children who remain comatose after resuscitation from cardiac arrest (Class IIb, LOE C).²³ Avoid rewarming from 32 to 34°C faster than 0.5°C per 2 hours unless the patient requires rapid rewarming for clinical reasons. Hypothermia is reasonable for adolescents resuscitated from sudden, witnessed, out-of-hospital VF cardiac arrest (Class IIa, LOE C), as there are adult and neonatal studies for this modality of support. Know the complications and methods well before embarking on this.²⁴
 - Monitor temperature continuously, if possible, and treat fever (>38°C) aggressively with antipyretics and cooling devices because fever adversely influences recovery from ischemic brain injury (Class IIa, LOE C).²⁵
- Treat postischemic seizures aggressively; search for a correctable metabolic cause such as hypoglycemia or electrolyte imbalance.

Table 2: Drugs used post CPR for cardiovascular support

<i>Medication</i>	<i>Dose</i>	<i>Comment</i>
Epinephrine	0.01 mg/kg (0.1 ml/kg 1:10,000) IV/IO 0.1 mg/kg (0.1 ml/kg 1:1000) ET* Maximum dose 1 mg IV/IO; 2.5 mg ET	Continued infusion if hypotension persists (don't mix with NaHCO ₃)
Amrinone	0.75–1 mg/kg IV/IO over 5 minutes; may repeat × 2 then: 5–10 mcg/kg/min	Inodilator
Dobutamine	3–20 mcg/kg per minute IV/IO	Inotrope; vasodilator
Dopamine	2–20 mcg/kg per minute IV/IO (don't mix with NaHCO ₃)	Inotrope; chronotrope; renal and splanchnic vasodilator in low doses; pressor in high doses
Epinephrine	0.1–1 mcg/kg per minute IV/IO	Inotrope; chronotrope; vasodilator in low doses (not in CPR) pressor in higher doses
Milrinone	Loading dose: 50 mcg/kg IV/IO over 10–60 min then 0.25–0.75 mcg/kg per minute	Inodilator
Lidocaine	Bolus: 1 mg/kg IV/IO Infusion: 20–50 mcg/kg/minute	Antiarrhythmic post-VT/VF if Amiodarone doesn't work
Sodium nitroprusside	Initial: 0.5–1 mcg/kg per minute; titrate to effect up to 8 mcg/kg per minute	Vasodilator Prepare only in D5W
Norepinephrine	0.1–2 mcg/kg per minute	Vasopressor

- Sodium balance: Cerebral edema is expected 24 to 48 hours later and may last up to 7 days. Rapid shifts in Na are deleterious to neurons and initially it is best to use 0.9NS without Dextrose and then titrate to keep the Na between 140 to 145 mEq/L or higher. As the edema is cytotoxic, mannitol has very little role.

Family member's presence is a recommendation by the AHA 2010 committee.^{2,3} It may be best that this be left to the various regions to decide this within their cultural and ethical boundaries. It is extremely important to make this decision within the zone of comfort of the entire team as well as family members and not extrapolate Western values on our system. Whatever the decision, the lines of communication with the closest family members, allowing them contact with the child and giving them access to perform religious and cultural rites within reason, are compassionate and important measures that all caregivers are duty bound to provide. Termination of resuscitative efforts.

There are no reliable predictors of outcome to guide when to terminate resuscitative efforts in children.

Clinical variables associated with survival include:

- Length of CPR; the shorter the better.
- Number of doses of epinephrine, more than 3 is associated with poor outcome
- Age: Neonates and infants have better outcome²⁵ witnessed versus unwitnessed cardiac arrest, where bystander help improves chances of survival
- First and subsequent rhythm: Shockable rhythms treated rapidly have good outcomes^{26–28}

Intact survival has been documented after unusually prolonged in-hospital resuscitation

None of these associations, however, predict outcome.

KEY POINTS AND MESSAGES

- Check the patient for responsiveness and presence/absence of breathing or gasping.
- Call for help, activate emergency response system, get AED/defibrillator.
- Check the pulse for no more than 10 seconds.
- Give 30 compressions.
- Open the airway and give 2 breaths.
- Resume compressions.
- Compressions should be initiated within 10 seconds of recognition of the arrest.
- At a rate of at least 100/min. Each set of 30 compressions should take approximately 18 seconds or less.
- Cricoid pressure deemphasized
- Bag and mask not recommended for lone rescuer. Mouth to mouth with protective device
- Do not hyperventilate 8 to 10/min older and 12 to 20/min in infants
- Look, listen, and feel for breathing removed
- After delivery of 30 compressions, lone rescuers open the victim's airway and deliver 2 breaths
- Cardiac compressions without of good depth without interruptions emphasized for good quality CPR
- Epinephrine every 2 to 5 mins
- Follow algorithms for shockable vs nonshockable rhythms
- Defibrillation use an initial dose of 2 to 4 J/kg

- For refractory VF 4 J/kg, and higher energy levels, not to exceed 9 J/kg or the adult dose
- Wide QRS definition 0.09 not 0.08 secs
- Drugs: Calcium NaHCO_3 very very limited indications
- Oxygen 100 percent at first then titrate with pulse oximeter to 95 percent
- Use of EtCO_2 for ETT placement and ROSC check emphasized
- Postarrest care important.

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Rapid Response System: Acute Care and PICU in 21st Century

Arvind Dahiya, Heather Duncan

Abstract

Children show sign of deterioration before cardiorespiratory arrest and unplanned pediatric intensive care unit (PICU) admission from wards.

Systematic and structured approach with a rapid response system (RRS) to early recognition and intervention has shown to reduce cardiac arrest by 65 percent and hospital mortality by 37 percent (adults). RRS will be more effective where the incidence of adverse events is high.

100000 lives campaign (USA) has recommended rapid response team (RRT) as one of the 6 key recommendations to avoid preventable deaths in hospitals.

Rapid response system is now an integral part of health care systems in developed countries.

INTRODUCTION

In developed countries, the incidence of unexpected cardiopulmonary arrest in children is around 1 to 3 per 1000 admissions, of those who had cardiopulmonary arrest only 1 in 4 patients was discharged from hospital, and of those discharged 1 in 3 had poor neurological outcome.

Cardiac arrest in adult and children can happen suddenly but up to 80 percent of these patients showed clinical deterioration in the 24 to 28 hours preceding cardiopulmonary arrest or unplanned emergency PICU admission. Research in adult and pediatric patients has highlighted failures to recognize deterioration early and also highlighted that up to 50 percent patient received suboptimal care.

Review of 30121 patients in New York showed that adverse events occurred in 3.7 percent of the hospitalizations and 27.6 percent of the adverse events were due to negligence, out of these 13.6 percent led to death. Another report from USA estimated that almost 100000 patients are dying every year because of medical errors. Reliable and robust data from India is not available but compared to USA the situation may be the same or worse. Further studies also suggested that incidence of serious adverse events in hospitalized patients can be up to 17 percent.

Survival of sick patients also depends on the place of admission as one study from Michigan highlighted that

as compared to emergency department admissions PICU mortality was almost 3 times higher than for unplanned ward admissions from pediatric wards.

This prompted health care leaders to find the solutions to recognize early deterioration and ensuring early intervention by experienced team, mainly from intensive care. Significant efforts were invested to educate ward staff to recognize signs of early deterioration and staff members were empowered to call for experienced help at early stage. In addition outcomes were continuously monitored and feedback given to staff. All these led to the development of Rapid Response Systems (RRS). A RRS includes identification with an early warning score/trigger (Afferent limb) and rapid response team (RRT) (Efferent limb).

Establishing a RRS is a key recommendation of “Saving 100000 Lives” campaign in the USA. This initiative was launched in 2004 in the USA and is now widely accepted all over the USA and either replicated or implementation is in progress in many other countries such as Australia, Scandinavia, South Africa and Brazil. RRS was initially implemented in adult wards. Recently various single and multi center studies have validated pediatric EWS and also documented the importance of RRT in preventing cardiopulmonary arrests in pediatric wards. Most pediatric wards in the UK now have some form of EWS in place.

So far no study has been done to develop or validate use of RRS/ RRT for sick in-patient children in India.

What is a Rapid Response System?

A rapid response system is a patient centered, hospital wide concept, which aims to reduce hospital mortality and morbidity. RRS is essentially a dedicated, multidisciplinary team of doctors, nurses, resuscitation officers or respiratory therapists, usually from the intensive care unit. The aim is to ensure early identification of clinical deterioration and invite expert intervention at an early stage.

RRS redefines the traditional concept of intensive care. Now ICU does not work in isolation and is not seen as ivory tower of high-tech medical technology for supporting organs for critically ill patients. ICU's are not confined within walls anymore and now function in partnership with primary medical/surgical teams all over the hospital. RRS ensures early intervention by experts and continuity of care.

There are four components of rapid response system

- Trigger mechanism (Afferent limb): Trigger score or early warning score (EWS)
- Response mechanism (Efferent Limb): Rapid response team (RRT) or medical emergency team (MET)
- Governance and administrative structure
- Quality improvement arm.

Trigger Mechanism (Afferent Limb)

Trigger mechanisms vary and are based on physiological parameters and diagnostic criteria or combination of both. Selected parameters have age specific threshold (for children) and a call for help can be initiated when threshold is crossed. Two types of trigger mechanisms are in use.

- *Trigger Score*: Call is initiated if there is change in any predefined single criteria or multiple criteria.
- *Early Warning Score*: Early warning score is based on aggregate score of predefined criteria and deviation of score beyond a threshold is used as a trigger to call for help.

There is not much comparative data to make evidence based decision regarding reliability of either system. In general single parameter trigger score may be simple to use and would be helpful to screen larger population. Multiparameter early warning score would be helpful to monitor the trend. Call for help can even be initiated in absence of change in parameter or score beyond threshold if nursing staff is worried about condition of patient.

Any member of staff can initiate call and there is no need to go through traditional nursing or medical hierarchy. No one is criticized for making a call, even if call does not lead to any intervention.

Response Mechanism (Efferent Limb)

Response mechanism can be different in different countries and can have different name and structure.

- Rapid response team (RRT)—USA
- Medical emergency team (MET)—Australia
- Critical care outreach team (CCOT)—UK
- Critical care response team (CCRT)—Canada.

These can be broadly divided into two categories:

Single Tier Approach

In this structure RRT/MET once called review the patient and either admits the patient to intensive care or only gives advice. So, there is no separate team for advice. These types of teams are led by doctors and experienced nurses from intensive care. For example, in Australia MET's are single tier structures.

Two-tier Approach

Teams in the UK are good example of the two-tier approach. Experienced critical care nurses first monitor ward patients with the help of a centralized system. Physiological parameter based early scoring system is used and team reviews patients who score above trigger score. Nurses provide support and advice if required or call critical care physicians if the patient needs intervention. Irrespective of score any ward staff can also call CCOR team if they are worried (Table 1).

EVIDENCE FOR RRS

Dr Ross Kerridge in Royal Liverpool Hospital, Sydney, Australia first implemented rapid response systems with MET's in adult wards in 1990. Since, then many studies have been published from western countries. Not many studies have been documented from developing countries. RRS has been well adopted in adult wards but in pediatrics, it is still a relatively new concept.

Adult Studies

One of the best study outcomes came from Austin Hospital in Australia. MET in Austin hospital achieved 65 percent decline in adult cardiac arrest. More over in cardiac arrest population 80 percent reduction in bed day and 22 percent decline in hospital mortality was observed.

Evidence from various studies has been summarized in Table 2.

Only RCT so far failed to demonstrate any significant reduction in cardiac arrest, unplanned ICU admissions and hospital mortality. Though results are disappointing and puzzling but can be explained by few but very critical shortcomings in this study. Study period was small (6 months) and it is widely expected that RRS take time to mature and show result over longer period. Reduction in unexpected cardiac arrest and death was observed in both groups during study period (education effect). Further analysis also showed that there was MET, significantly variable in study hospitals.

Table 1: Characteristics of RRS

Afferent component	Triggering criteria Monitoring system - Human and technologic monitoring with alarm limits Mechanism for triggering response
Efferent component	Resources arrive quickly - first response 15 minutes Personnel with defined set of competencies - generally from ICU RRT carries all necessary equipment for resuscitation and intervention Systematic assessment (A-G method)
Quality improvement component	Rigorous, systematic and methodical evaluation of events Regular feedback of RRS call related knowledge: <ul style="list-style-type: none"> • To primary team • To care system designers • To patient/family Application of process improvement strategies to prevent adverse events
Governance and administrative structure	Implement and sustain the service: <ul style="list-style-type: none"> • Education/training of all hospital staff • Interpret response team effectiveness data to manage resources • Ensure ongoing training/education

Table modified from Findings of the First Consensus Conference on Medical Emergency Teams, Michael A DeVita et al

Table 2: Rapid response system and evidence from adult studies

Bellomo et al 2003	RRR in adult cardiac arrest - 65%, $p < 0.001$ Decrease in bed days in cardiac arrest survivors - RRR - 80%, $p < 0.001$ Reduction in Hospital mortality RRR - 26%, $p < 0.004$
Bellomo et al 2004	Reduction in serious adverse events - 57%, $p < 0.001$ Reduction in emergency ICU admission - 44%, $p < 0.001$ Reduction in postoperative deaths - 36% $p = 0.0178$ Duration of Hospital stay after major surgery - 23.8 to 19.8 days, $p = 0.0092$
Buist et al	Reduction in cardiac arrest from 3.77 to 2.05/1000 admissions
Kenward et al	Reduction in cardiac arrest from 2.6 to 2.4/1000 admissions
Jones et al 2005	Decreased cardiac arrest rate from 4.4 to 1.9/1000 admissions Inverse relationship between increase in RRS call rate and cardiac arrest rate - $p = 0.01$
Jones et al 2007	Reduce deaths in surgical patients - $p = 0.0174$ Increased deaths in medical patients - $p = 0.0001$
Jones et al 2007	Patient admitted during study period over (4.1 years) had survival rate of 71.6 % as compared to 65.8 % during control period, $p = 0.005$
MERIT 2005	Increased call rate during study period but no significant drop in cardiac arrest and hospital mortality
Chan et al	Reduction in cardiac arrest calls from 11.2 to 7.5/1000 admissions, $p = 0.06$ No significant decrease in hospital wide deaths
Buist et al	Increased use of RRS reduced cardiac arrest by 24% every year from 2.4 -0.66/1000 admission

Pediatric Studies

In 2005, a survey showed that only 21 percent units in the UK had some form of RRS. But now most of the pediatric hospitals have some form of RRS and result from a repeat survey are still awaited. Compared to adult numbers of studies are significantly less but as shown in table significant

reduction has been noticed either cardiac arrest and hospital mortality (Table 3).

Chan and et al performed a systemic review for both adult and pediatric RRS studies and pooled data is shown in Tables 4 and 5.

Table 3: Rapid response system and evidence from pediatric studies

Sharek et al	Mean monthly mortality rate decreased by 18% (1.01 to 0.83 deaths per 100 discharges; P=0.007 Mean monthly code rate per 1000 admissions decreased by 71.7%, 2.45 to 0.69 codes per 1000 admissions Mean monthly code rate per 1000 patient-days decreased by 71.2%
Brilli et al ³³	After implementation of RRS cardiopulmonary arrests rate reduced from 0.27 to 0.11 per 1,000 patient days after compared with baseline of 0.27, p = 0.03 Cardiopulmonary arrests rate reduced from 1.54 per 1,000 admissions decreased to 0.62, p = 0.02
Tibballs et al ³⁴	Total hospital deaths decreased from 4.38 to 2.87/1000 admissions, p <0.0001 Unexpected ward death decreased from 13 (0.12/1000) to 6 (0.04/1000) p = 0.03 Survival from cardiac arrest increased from 7 of 20 patients to 17 of 23, p =0.01
Hunt et al ³⁵	73% decrease in the incidence of respiratory arrest, P = .03 No significant reduction in cardiac arrest

Table 4: Pooled data from various studies showed significant decline in hospital cardiac arrest (outside intensive care) after implementation of RRS in both adult and pediatric population. CI indicates confidence interval. (Modified from systemic review of RRT by Chan et al)

	Control group		Intervention group		Weight,%	RR (96% CI)	Lower after RRT	Higher after RRT
	Patients, No.	Deaths, No.	Patients, No.	Deaths, No.				
Adults studies								
Bristow et al (hospital 1 vs 2) ²⁰	13059	66	18338	69	7.29	0.88 (0.62-1.23)		
Bristow et al (hospital 1 vs 3) ²⁰	19545	99	18338	69	7.64	0.88 (0.62-1.23)		
Bristow et al ²³	19317	73	22847	47	6.97	0.50 (0.35-0.73)		
Bellomo et al ²⁷	21090	63	20921	22	5.71	0.35 (0.22-0.57)		
Kenward et al ³³	53500	139	53500	128	9.71	0.92 (0.72-1.17)		
DeVita et al ²⁹	143776	930	55248	290	8.54	0.81 (0.71-1.93)		
Hillman et al ²¹	56756	93	68376	90	9.28	0.94 (0.79-1.13)		
Jones et al ²⁰	16246	66	104001	198	8.00	0.47 (0.35-0.62)		
Dacey et al ¹²	5667	44	17090	52	6.57	0.39 (0.26-0.58)		
Baxter et al ¹²	7820	43	11271	38	6.20	0.61 (0.40-0.95)		
Chan et al ⁹	24193	147	24978	77	6.58	0.59 (0.40-0.89)		
Overall adult (<i>I</i> ² =80.5%, P<001)	380969	11753	414908	1080	82.49	0.66 (0.54-0.80)		
Pediatric studies								
Brilli et al ²⁶	16255	25	9615	6	0.25	0.41 (0.00-0.86)		
Sharek et al ²⁵	22037	53	7257	5	2.50	0.29 (0.10-0.65)		
Zenker et al ¹⁴	22561	181	11682	60	7.72	0.64 (0.47-0.87)		
Hunt et al ³⁵	7504	16	7503	8	2.45	0.49 (0.18-1.20)		
Tibballs and kinney et al ³⁷	104780	20	138424	24	4.58	0.91 (0.50-1.64)		
Overall pediatric (<i>I</i> ² =10.2%, P=35)	173137	295	174481	103	17.51*	0.62 (0.46-0.84)		
Overall (<i>I</i> ² =73.9%, P<001)	554106	2058	589389	1183	100.00	0.65 (0.55-0.77)		

0.25 0.5 1 2 4
RR (95% CI)

CONCEPT OF RRS DOSE

Decline in hospital serious adverse events and mortality with increasing dose of RRS calls is an interesting observation.¹⁵ Hospitals with sustained improvement after

RRS recorded 25.8 and 56.4 calls per 1,000 admissions RRS calls. Year on year improvement was associated with increased numbers of RRS calls.

Table 5: Pooled data from studies showed trend toward decline in hospital deaths after implementation of RRS both in pediatric and adult population. Results are more encouraging in pediatric population. CI indicates confidence interval (Modified from systemic review of RRT by Chan et al)

	Control group		Intervention group		Weight,%	RR (96% CI)	Lower after RRT	Higher after RRT
	Patients, No.	Deaths, No.	Patients, No.	Deaths, No.				
Adults studies								
Bristow et al (hospital 1 vs 2)	13059	240	18338	243	7.17	0.93 (0.77-1.12)		
Bristow et al (hospital 1 vs 3)	19545	295	18338	243	7.28	1.20 (1.00-1.43)		
Bristow et al	19317	380	22847	393	7.31	0.87 (0.71-1.01)		
Bellomo et al	21090	302	20921	222	8.51	0.74 (0.70-0.79)		
Kenward et al	53500	1070	53500	1054	8.36	0.99 (0.91-1.07)		
Priestely et al	1336	76	1456	73	3.54	0.52 (0.32-1.85)		
Hillman et al	56756	67	68376	72	6.85	0.03 (0.84-1.28)		
Dacey et al	5667	123	17090	398	6.96	1.07 (0.88-1.32)		
Jones et al	25334	873	100243	4070	8.43	1.18 (1.10-1.27)		
Baxter et al	7820	279	11271	400	7.55	0.99 (0.81-1.16)		
Chan et al	24193	780	24978	773	7.56	0.95 (0.81-1.11)		
Overall adult (<i>I</i>²=91.4%, P<001)	247617	4485	357358	7941	79.62	0.96 (0.84-1.09)		
Pediatric studies								
Brilli et al	16255	11	9615	3	1.10	0.55 (0.00-2.10)		
Sharek et al	22037	547	7257	158	7.62	0.82 (0.70-0.95)		
Zenker et al	22561	97	11682	53	4.86	1.05 (0.73-1.50)		
Tibbals and kinney et al	104780	459	138424	398	7.80	0.65 (0.57-0.75)		
Overall pediatric (<i>I</i>²=66.0%, P=03)	165633	1114	166978	612	20.38*	0.79 (0.63-0.98)		
Overall (<i>I</i>²=90.3%, P<001)	413250	5599	524336	8553	100.00	0.92 (0.82-1.04)		

0.25 0.5 1 2 4
RR (95% CI)

DeVita et al first showed that increased call rate from 13.7 to 25.8 per 1000 admission reduced cardiac arrest by 17 percent. Recently Buist et al also reported long-term benefit of increased dose of RRS calls by recording 24 percent reduction in cardiac arrest every year. Study from a Melbourne hospital has suggested that 17 additional RRS calls could prevent 1 unexpected cardiac arrest.

Studies from Canada and Sydney have also reported RRS dose (call rate) of 40.3 and 56.5 per 1000 admissions respectively. It is interesting to know that incidence of serious adverse events was also reported to be 5.6 percent in later study. Studies have also shown that cardiac arrests were most common during night time when RRS review rate was lowest. Similarly incidence of cardiac arrests was minimal in evening when RRS usage was highest.

HOW TO IMPLEMENT RRS

RRS is a pan organizational phenomenon and its aim is to reorganize the whole concept of management of sick

patient. RRS thrives on change in the culture in institute and by making every staff member a stakeholder in preventing clinical deterioration at much early stage.

It is an extremely challenging task to change stakeholders' mindset and need sustained efforts over the years. Previous experience has shown that it takes 2 to 3 years to establish RRS in a large hospital.

Implementation of RRS is a complex interaction of various factors. This is about empowering each and every staff member and challenging the very hierarchy of health care system. Various components of implementation process have been summarized in tables below (Tables 6 to 8).

How to Design "Trigger Score" and "Pediatric Early Warning Scores"?

Currently there is no standard trigger or pediatric EWS. Over 30 pediatric EWS are in use in pediatric wards in the UK. All of them use combination of physiological, diagnostic or therapeutic criteria.

Table 6: How to implement RRS

Define the outcomes and measure	First step toward implementing RRS is to establish the baseline incidence adverse events and mortality in hospital as shown in Table 5
Bring hospital leadership on board	Needs coordinated efforts, consensus, willingness to cooperate and understanding the need for change at all levels of leadership. This requires strong, focused and highly motivated leadership.
Standard, uniform and observation and monitoring policy	Monitoring parameters, measurement frequency and way of conducting observation must be clearly defined and uniform all over the hospital.
Standardized and uniform observation charts	A study in Birmingham Children Hospital, UK observed that 30 different charts were in use in different wards before implementation of RRS. Trigger mechanism and age specific thresholds (Single criteria or EWS) should be incorporated with in observation charts. Separate charts for different age groups should be developed. (Divide into 4 age groups: 0-1, 1- 4, 5- 12, Over 12 years)
Educating staff	Sustained efforts to educate both medical and nursing staff in assessing and recognizing early signs of clinical deterioration. All staff must be aware of standard procedures regarding RRS. There should be uniform teaching methodology. Specific course for all staff would be helpful but resuscitation-training course as platform to create uniformity and awareness RRS can be useful.
Communication	Once patient at risk is identified communication is the key to initiate response. This needs; Dedicated, 24×7 telephone number Standard communication format all across the hospital - <i>SBAR</i> (<i>Situation, background, assessment and response/request</i>)
Intervention policy	Defined timeline for assessment and intervention Uniform way of assessing patient once call is activated (A - G as explained in Table 6) Accurate and clear documentation There should be standard hospital wide RRS documentation sheet and all documentation be done on RRS sheet. Ideally it should be colored and clearly visible sheet in patient notes.
Monitoring and feedback	All calls and primary outcome should be monitored and assessed individual. All deaths and cardiac arrests and unplanned ICU admission should be reviewed in detail to identify any preventable event before adverse event. Primary team should be kept in the loop. Two way and regular feedback procedure is required for successful implementation

Table 7: What we should measure before and after implementation of RRS

<i>Measure Primary Outcome</i>	<i>Secondary Outcome</i>	
<i>Adverse events</i>		
Cardiac Arrest	NonDNR cardiac arrest per 1000 admissions (Utstein criteria)	Proportion surviving cardiopulmonary arrest <ul style="list-style-type: none"> • 30 days after arrest • 180 days after arrest
Hospital deaths	No of deaths per 1000 admissions	
Unplanned ICU admissions	Proportion of unplanned ICU admissions that have experienced suboptimal care or had untimely referral	
Satisfaction survey		
Patient/Family		<ul style="list-style-type: none"> • Response time • Quality of response team • Overall quality of acute care services
Nurses		<ul style="list-style-type: none"> • Work load • Perception • Support structure • Staff retention and turnover
Physicians		<ul style="list-style-type: none"> • Work load • Perception • Support structure

Table 8: Structured assessment of RRS call

A	Ask How we can help, Why a call is being made Assess the patient
B	Begin basic and specific investigation
C	Call for further help if required, Communicate with primary team
D	Discuss: Involve primary team and work in partnership Decide - Needs admission to ICU? If not why? Intervention - Make clear plan Document: Clear and standard documentation
E	Explain the plan to staff member and explain etiology
F	Follow-up: If not admitted to ICU then agree a clear plan with primary team for further management regarding frequency of monitoring, warning signs, threshold for considering admission or “Not for Resuscitation” order if appropriate
G	Gracious thank you

Table modified from Findings of the 1st Consensus Conference on Medical Emergency Teams, DeVita et al

Choosing criteria for designing a trigger or aggregate score should be based on local reasons for unexpected deteriorations in children. A baseline audit/study should be conducted before to find out the most common cause. Patient population should also be taken into consideration while designing a trigger score for local use. An audit done in Alder hay children hospital, Liverpool, UK²¹ showed that most common cause of unexpected PICU admission was respiratory distress (55%) followed by respiratory arrest (5%), cardiopulmonary arrest (5%), airway obstruction (5%), uncontrolled seizures and shock (5%). A UK survey of EWS showed a total of 36 different parameters (Duncan ADC 2007) (Tables 9 to 11).

Rapid Response System and Relevance in India

Cost of critical care services is increasing every year and requiring up to 10 percent of national health care resources in developed countries. This is unsustainable and impact on Indian health care system could be highly detrimental

as out of pocket expenditure on health care from individuals/family is up to 65 percent of total national health care expenditure. Direct effect of affordability and inefficient use of resource could seriously impact both public and fast growing private health care system.

Western studies have shown encouraging sign and in India this system has potential to produce even better results. Currently, no study from India has been published for hospital ward based RRS but implementing RRT and EWS as concepts has a huge appeal and sound basis.

Change in Culture

The biggest potential impact RRS can bring is change in culture.

RRS improves coordination and communication among various teams and probably this is the biggest benefit of an RRS system. This was cited as one of the reason why MERIT study failed to show any difference between control and intervention arm as number of cardiac arrest deceased significantly in control group hospitals as well.

Table 9: Characteristics of an aggregate/trigger score

<ul style="list-style-type: none"> • Simple to use for bedside carer • Incorporate aggregate score/trigger score with in observation chart • Embedded trigger mechanism and communication information • Clear communication strategy — a dedicated telephone number • Separate age specific charts to avoid age related confusion with upper and lower and threshold limits (4 age groups: 0-1, 1-4, 5-12, and over 12 years) • Ideally should be colored charts using red, yellow and green colors for normal and abnormal ranges for better differentiation • Avoid too many trigger criteria's • Criteria's should depend on local circumstances and population characteristics
--

Table 10: Comparison of different Pediatric EWS—Aggregate scores

<i>Criteria used</i>		
Cardiff and Vale EWS Wales, UK	Heart rate, respiratory rate, blood pressure, oxygen saturation, consciousness level, temperature, work of breathing, airway threat and staff concern	Single criteria, sensitivity 90%, specificity 64% Two criteria - sensitivity 70%, specificity 90%
Duncan et al	Heart rate, respiratory rate, blood pressure, oxygen saturation, consciousness level, temperature,	Sensitivity 78%, specificity 95%
Toronto study bedside PEWS (Single center)	Systolic blood pressure, capillary refill time, respiratory rate, respiratory effort, transcutaneous oxygen saturation and oxygen therapy	Sensitivity - 82%, specificity - 93%, Trigger score 8, max score - 26, min score -0
Bedside PEWS (Multicenter study)	Systolic blood pressure, capillary refill time, respiratory rate, respiratory effort, transcutaneous oxygen saturation and oxygen therapy	Case mean score - 8, control mean score - 2, P<0.0001 Each hour closer to the event the max PEWS score was 0.13 units higher p<0.0001

Table 11: Trigger scores—Criteria for activation (Any single abnormal criteria to activate call)

Tibballs et al	1. Nurse or doctor worried
Sharek et al	2. Airway threat
Brilli et al	3. Hypoxemia
	• SpO ₂ <90% in any amount of oxygen
	• SpO ₂ <60% in any amount of oxygen (Congenital heart disease)
(Almost similar criteria's were used in three studies)	4. Severe respiratory distress, apnea or cyanosis
	5. Tachypnea - Age specific
	6. Tachycardia or bradycardia - Age specific
	7. Hypotension - Age specific
	8. Acute change in neurology or convulsions
	9. Cardiac or respiratory arrest

Let Us Find Out the Problem

There is a wise saying: you can only manage what you measure.

We cannot solve the problem if we do not know it. Currently, there are not many studies regarding adverse events, patient safety and acute care outcomes in India. Implementing RRS would give every hospital an excellent opportunity to know the extent of problem.

In absence of robust studies it is hard to estimate and compare number of cardiopulmonary arrest with western countries' hospitals but we may not be accused of being wrong if we assume that number would be significantly higher. Knowing the incidence would be the first step toward implementation.

Bigger Impact Where Incidence of Adverse Events are High

Studies have shown that impact of RRT in reducing mortality and unplanned ICU admissions would be felt more

where incidence of cardiopulmonary arrest or unplanned ICU admissions is high.

Invaluable Learning Resource for New/Inexperienced Nursing Staff

Study from Birmingham Children Hospital, UK showed that only 67 percent nurses could assess respiratory rate accurately and only 25 percent nurses could palpate pulse rate. Number increased to 90 percent during RRS implementation process due to enhanced and sustained training and education. High nursing staff attrition and shortage of skilled staff nurse is a well-known problem in large private and public hospitals in India. Small hospitals struggle even more to attract senior and experienced nursing staff.

RRS brings objectivity and standardizes patient assessment and monitoring. RRS improves coordination and supports junior staff at an early stage. A survey in a UK hospital has shown that 88 percent staff felt that RRS increased their confidence in caring for child at risk of deterioration.

Better Use of Resources

RRT has potential to make health care system more affordable and bring the cost down for the organization. RRT system changes the focus and emphasis on preventing clinical deterioration. This way RRT system can decrease the cost of health care by reducing morbidity related with delayed recognition of clinical deterioration and also prevents ICU admissions. RRT also helps with and supports primary care physician to put “Do not resuscitate” order at an early stage if appropriate. This improves overall efficiency of the system and saves precious resources for better utilization.

Improved Patient Experience and Better Health Outcome

It would not be difficult to imagine how RRT would help to establish better client-provider relationship. RRT system has huge potential to improve patient satisfaction. RRT may help to establish and strengthen much needed trust factor. Some institutions have encouraged family members to call the RRT and have found this, a useful adjunct that is not misused (see E Hunt's papers for reference).

Research Opportunities

RRT inevitably needs more research to assess current system and scenario. Such system has not been validated or tested for Indian populations. So, this is an excellent opportunity to improve research in acute care pathways in India. High patient numbers and large populations would help us to design a highly effective scoring system to implement a robust RRT system.

Quality Improvement and Patient Safety

It may not be too harsh to say that incidence of adverse events/negligence and incidence of adverse event related deaths could be much higher in India than developed countries' hospitals. RRS would be of immense help to improve patient safety and quality improvement culture in Indian hospitals. RRT and EWS would bring more accountability and objectivity to the system. The implementation process of RRS and reinforcement of standards of care also leads to better education and training for staff members. Studies have shown that better training would motivate staff and make them more confident, leading to higher standard of care and a safer environment.

SUMMARY

There is an urgent need for good quality studies to validate RRS in India. RRS can also provide us to establish strong database for future health care planning and resource allocation to improve hospital outcomes.

So we strongly recommend use of RRS in pediatric wards. Before that, we must measure the current

practice and outcome as described in Table 5. Implementation of RRT would help to redefine care of sick children. EWS should be based on local circumstances and should be adapted to suit local needs. In absence of evidence to support either single trigger or aggregate score, it is hard to make any recommendation for trigger mechanism. We believe for large hospitals with limited resources single trigger may be more useful. We recommended a 24×7 RRT and PICU fellow should lead rapid response team. Sustained education program, constant monitoring, auditing and feedback mechanism should be established.

In 21st century, critical care physicians need to redefine the concept of intensive care. There is an urgent need to take life saving critical care skills to general wards. This will need a sustained and structured hospital wide implementation of RRS, driven by highly motivated and focused leadership and team of skilled people.

Prevention is always better than cure (Figs 1 to 3).

Date	Rate/min	Time	Time
Respiratory Rate	85		
	80		
	75		
	70		X
	65	X	
	60		
	55		
	50		
Score	45		
4	40		
2	35		
1	30		
	25		
	20		
	15		
	10		
	5		
Score		1	2

Fig. 1: Sample figure of PEWS chart (only respiratory component is shown for ease of demonstration.) Example of respiratory rate documentation on an embedded pediatric early warning score for infants less than one year of age. Thresholds of increasing physiological derangement are embedded into the observation chart to provide a visual and cumulative numeric trend to deterioration. In this example, the threshold bands accrue 1, 2, or 4 points for respiratory rate and other parameters (respiratory distress, pulse oximetry, inspired oxygen, heart rate, systolic blood pressure and capillary refill time) would accrue similar scores. The sum or aggregate of these different parameters gives the PEW score that is trended over time

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OBSERVATION SHEET

		date 11/09						
		1000	1030	1100	1130	1200	1230	
	zero							
	one							
	two							
	four							
Respiratory Rate • RR/min		value						
	zero							
	one							
	two							
	four							
Heart Rate • HR/min		value						
	v systolic	value						
	* mean	value						
	^ diastolic	value						
	Blood Pressure (Score Systolic)	value						
	>91%							
	92-94%							
	<95%							
	any NP Oxygen room air							
	severe							
	moderate							
	mild							
	none							
	>3 sec							
	<3 sec							
	PEWS Score							
	Position value							
	Axilla							
	Tympanic							
	temperature							
	AVPU							
	Pain Score							
	Board sugar							
	Event							
	Eyes open							
	Best verbal / grimace							
	Best motor							
	Coma score							
	Right - size / reaction							
	Left - size / reaction							
	Left Arm							
	Left Leg							
	Right Arm							
	Right - size / reaction							
	Right Arm							
	Right Leg							
	Limb Power & Movement							

Birmingham Children's Hospital NHS Foundation Trust 0 - 1 years

Patients Name: Holly M. MacC...
Hospital No.: ...
Date of Birth: 24.1.12.2008
Consultant: ...
or small patient label

Patient Specific Parameters	Alarm Limits
HR	HR
RR	RR
BP	BP
SpO ₂	SpO ₂
PEWS	Other
OTHER	Type of monitor:
Date & Name:	

PEWS Response		
Score 1-4 or ↓ in GCS of 1 point	Score 5-8 or ↓ in GCS of 2 points or concern	Score ≥9, GCS ≤11 or VERY concerned
Discuss with nurse in charge and consider increasing frequency of observations	Inform nurse in charge, call pt's own team (day) or call H @ N (after hours)	Call pt's own team, or H @ N. If no response or unable to attend immediately call PICU 9652, Bleep 55006

LIFE THREATENING - CALL 2222

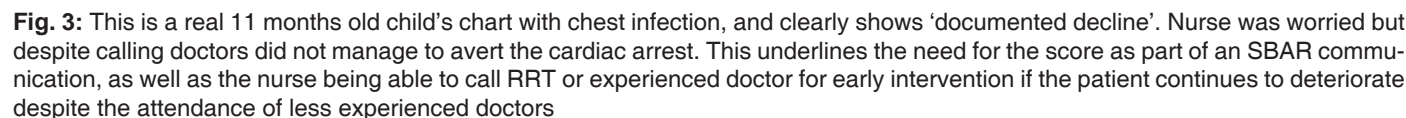
Guide to Levels of Respiratory Distress		Guide to Oxygen Delivery
Mild:	Nasal flaring Intercostal recession	NP - Nasal Prongs FM - Face Mask HB - Head Box
Moderate:	Head bobbing Subcostal recession Inspiratory or expiratory noises Tracheal tug	AVPU A - Alert V - Voice P - Pain U - Unresponsive
Severe:	Sternal recession Exhaustion Impending respiratory arrest	

Modified Paediatric Glasgow Coma Scale	
Adult/ Child according to usual ability	Child infant
Eye Opening (E) E4 Spontaneous E3 To Verbal Stimuli E2 To Painful Stimuli E1 None to painful stimuli C. Eyes closed by swelling/bandage	As for older child
Verbal (V) V5 Orientated (person, place or address) V4 Confused V3 Inappropriate words V2 Inappropriate sounds V1 None S. Silent or mute T. Intubated	V5. Alert, babbles, coos, words or to normal ability V4. Less than usual ability or spontaneous irritability cry V3. Cries inappropriately V2. Occasionally whimpers and/or moans V1. As for older child
Grimace (G) G5 Spontaneous normal facial/motor activity G4 Less than usual spontaneous ability or only response to touch stimuli G3 Vigorous grimace to pain G2 Mild grimace to pain G1 No response to pain NA. Not Applicable	As for older children
Motor (M) M6 Obeys commands M5 Localise to painful stimuli M4 Withdraws to painful stimuli M3 Abnormal flexion to pain (ie. clonus) M2 Abnormal extension to pain (ie. cerebrate) M1 No response to pain NA. Not Applicable	M6 Normal spontaneous movements M5 Withdraws to touch M4 As for older children

Pupil Scale (mm)	Power	Movement
8 7 6 5 4 3 2 1	N = Normal MW = Mild Weakness SW = Severe Weakness	S = Spontaneous PS = Painful Stimuli NR = No Response

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Fig. 2: This is a simulated (made-up) patient's chart to show an example of observation chart with an embedded pediatric early warning score. (Birmingham Children Hospital, UK)



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Arterial Blood Gases: Systematic Approach

Sunil Dutt Sharma

Arterial blood gases (ABG) are one of the first tests done on any critically ill patient, because the results give useful information about A-oxygenation, B-ventilation, and C-perfusion. Arterial blood gas measurements are the gold standard by which the adequacy of oxygenation and ventilation is assessed. A large group of children who are mild to moderately ill can benefit from acid-base status determination for assisting in diagnosis, management and progression of illness. Blood gas values can be directly measured from indwelling arterial catheters or estimated from intermittent arterial punctures, arterialized capillary blood samples and central venous samples. Continuous monitoring devices, particularly the pulse oximeter, play an essential role in respiratory management of patients by giving an ongoing estimate of blood gas values; but it may not give accurate measurements in active patients or very sick hypotensive or edematous patients.

Correct interpretation of blood gases and acid base disturbances requires a familiarity with basic physiology in this field. Intelligent and in depth interpretation leads to a more rational management of the patient as a whole.

TERMINOLOGY OF ARTERIAL BLOOD GASES AND ABBREVIATIONS

The terminology of ABG is complex and confusing. It is made worse by the printouts generated by recent micro-processors. Basically the machines measure pH, CO_2 and O_2 . All other parameters are derived from software in machine, which can be obtained manually if one knows how to use Siggard-Anderson Nomograms.

PaO_2 : Partial pressure of O_2 in arterial blood
 PaCO_2 : Partial pressure of CO_2 in arterial blood
 PAO_2 : Partial pressure of O_2 in alveoli
 PH_2O : Water vapour pressure
 HCO_3 : Bicarbonate

SBC : Standard bicarbonate
 SBE : Standard base excess
 ABE : Actual base excess
 BB : Buffer base
 FiO_2 : Fraction of inspired O_2
 AaDO_2 : Alveolar to arterial O_2 gradient

ACIDOSIS VS ACIDEMIA

Acidemia: pH <7.35

Alkalemia: pH >7.45

The suffix “emia” refers to changes in blood pH

Acidosis: It is an abnormal state leading to increased acid or decreased alkali in the body.

Alkalosis: It is an abnormal state leading to increased alkali or decreased acid in the body.

The suffix “osis” is applied to clinical condition that may or may not imply that change in blood pH has occurred.

Hypercapnia : $\text{PaCO}_2 > 50$ mm Hg
 (alveolar hypoventilation)

Hypocapnia : $\text{PaCO}_2 < 30$ mm Hg
 (alveolar hyperventilation)

Hypoxia : $\text{PaO}_2 < 60$ mm Hg

Hyperoxia : $\text{PaO}_2 > 100$ mm Hg

Goals of ABG

- To characterise the type of disorder.
- Quantify the magnitude
- Assess the nature and extent of compensation

Indications of ABG

- Severe respiratory or metabolic disorders
- Clinical features of hypoxia or hypercarbia

- Shock
- Sepsis
- Decreased cardiac output
- Renal failure
- Ideally any patient on oxygen therapy

Collection of Samples

Sites for Sample Collection

- Radial artery (Ideal)
- Umbilical artery (Neonates)
- Posterior tibial
- Dorsalis pedis
- Any arterial line
- Femoral/Brachial artery: *should never be used if alternative exists*
- Arterialised capillary
 - Laterointernal aspect of heel
 - Ear lobe
- Venous samples: It is good for HCO_3^- -elimination, but bad for pCO_2 , pH and pO_2 .

Ideal artery for sampling is radial artery but in newborns umbilical artery is also a good option. Posterior tibial artery and ulna artery are other alternatives.

Precautions: One must perform the “Allen test” to ensure collateral blood supply by ulnar artery before puncturing radial artery.

Any sample from the continuous A-line is being taken, one should assure free flow of blood and remove three to four times dead space volume before sample is taken. Indwelling arterial line may only be put if round the clock facilities for ABG estimation are available considering this as a potent source of infection.

Arterialised capillary samples are comparable to arterial blood. These should be taken from peripheries of a pre-warmed heel, let the capillary fill from the tissue site from where blood is oozing out. Avoid squeezing and the first drop of blood. Rotate the capillary in palm. Seal both ends of the capillary till processed. Care should be taken not to include any air bubbles in the capillary. Capillary samples are good for pH and PCO_2 when peripheral perfusion is good but pO_2 is 10 to 20 mm less than actual values.

Venous blood is good for HCO_3^- estimation but bad for pH, pCO_2 and pO_2 . While drawing venous blood, sample should be drawn against the flow of blood towards the heart, no tourniquet should be applied and the artery should not be compressed. Conditions where we can rely on venous blood gas analysis are patients with following diseases, e.g. renal disorders, diabetic ketoacidosis, intoxications, liver failure, and metabolic disorders such as inborn errors of metabolism and renal tubular disorders (prerequisite is stable oxygen saturation on pulse oximetry with oxygen requirement $<50\%$). And conditions where arterial blood gas cannot be replaced by venous blood gas are respiratory failure or dysfunction, any disorder with oxygen requirement of $>50\%$ percent and unconscious, i.e. GCS <8 .

To summarise an arterial sample is preferable to a venous sample to evaluate the respiratory system, i.e. for pCO_2 and pO_2 , however HCO_3^- is very similar in arterial and venous blood. A venous blood will give information on HCO_3^- and a tendency on the pCO_2 . For example if pCO_2 is decreased on the venous side, then it must be decreased on arterial side (respiratory alkalosis) (Table 1).

Precautions to be taken for collection of blood sample:

- Wait for steady state.
- Heparin is acidic and lower pH. Use heparin of lower strength (1000 units/ml).
- Use small volume of heparinised saline just for lubricating syringe and plunger. If volume is more, dissolved oxygen in heparinised saline may increase pO_2 .
- Avoid air bubble and let syringe fill spontaneously.
- Carefully mix the blood after sampling.
- Transport in ice.
- Sample may be collected in heparinised capillary from hub of needle used to puncture artery.
- Process within 20 minutes, 1 to 2 hours in ice.
- Discard few drops of blood before testing.

The sample must be processed immediately, preferably within 20 minutes. Blood is a living medium and cells consume O_2 and CO_2 is produced. Drop in pO_2 depends on initial pO_2 . If CO_2 is very high, significant drop may be noticed. Slush of ice (not cubes) should be used for storing sample till processing. The sample should be shaken and homogenised before putting in machine. *Maximum allowable time delay in these conditions is 2 hours and even then PaO_2 is doubtful (Table 2).*

It is obvious that blood sample should be stored at 4°C immediately if it cannot be processed for minimal error.

The average pH at delivery is 7.26. There is relatively high CO_2 and lower HCO_3^- in the neonatal period (Tables 3 and 4).

Problems with ABG Sampling³

Air Bubble in Sample

Partial pressure of oxygen in air is 150 mm Hg and pCO_2 is negligible—so it causes pO_2 values to shift towards 150

Table 1: Comparison of blood gas analysis at different sites

	Arterial	Capillary	Venous
pH	Same	-----	Same
pO_2	Higher	→	Lower
pCO_2	Lower	→	Higher
HCO_3^-	Same	-----	Same
Recommendation	Good	Fair	Bad

Table 2: Changes of ABG every 10 min *in vitro*

	37°C	4°C
pH	0.01	0.001
pO_2	0.1 mm Hg	0.01 mm Hg
pCO_2	0.1 mm Hg	0.01 mm Hg

Table 3: Normal values of ABG (FiO₂ of 0.21)¹

	<i>pH</i>	<i>PaCO₂</i>	<i>PaO₂</i>	<i>BE</i>	<i>HCO₃</i>
Umbilical vein	7.33	43	28		22
Capillary (1-25 days)	7.40	40	52		
Arterial - NB					
1-4 hours	7.30	39	62		19
12-24 hours	7.30	33	68		20
24-48 hours	7.39	34	63-87	-6	20
96 hours	7.39	36	63-87	21	
Infant (1-24 months)	7.40	34	90	-3	20
Child (7-19 years)	7.39	37	96	-2	22
Adult	7.40	40	100	0	24

Table 4: Target ABG value in neonates²

	<i>< 28 weeks</i>	<i>28-40 weeks</i>	<i>Term infant with PPHN</i>	<i>BPD /CLD</i>
PaO ₂	45-65	50-70	80-120	60-80
PaCO ₂	40-50	40-60	30-35	45-70
pH	>7.2->7.25	>7.2->7.25	>7.4-7.5	7.35-7.45
SpO ₂	88-92	88-92	95-100	88-92

and pCO₂ falls precipitously. Effect on pH is negligible however it may be falsely high. Effect is a function of duration of exposure and surface area of air bubble. Mixing/agitation increases surface area for diffusion and hence more erroneous results.

To overcome this expel the air bubble or sample with froth, do not agitate the syringe, and seal it with cork/ cap immediately after sampling.

Venous Sampling or Admixture

Venous sample shows low pH and pO₂ and high pCO₂ in comparison to arterial blood.

Venous contamination of arterial sample produces following results:

Blood	Volume	pO ₂
Arterial	4.5	86
Venous	0.5	31
Mixed	5.0	56

(Admixture of 1/10 part of venous blood to arterial sample produce 25% decrease in pO₂)

Normal mixed venous gases is having normal values as shown below:

pH	7.38
PvCO ₂	48
PvO ₂	40
SvO ₂	75%

To overcome this problem cross check and repeat sample from same venous site with one arterial sample, or repeat sample by expert clinician. Saturation of 90 percent with

pulse oximetry and blood gas saturation of 78 percent strongly suggest that the gas sample may not be arterial.

Excess Heparin in Sample

Dilutes the sample and results in falsely low values of pCO₂, i.e. fall in pCO₂ is more than fall in pO₂ because of difference in solubility coefficient between two gases in liquid phases. pH may become acidic or alkalotic (but generally negligible effect on pH). Dilutional effect on sample results in decreased HCO₃⁻ and pCO₂.

To overcome this use minimal heparin, i.e. 1/1000 U/ml and more so lithium heparin (Lithium Heparin> Sodium Heparin (increase Na-3 MEq/L). Syringe must be emptied of heparin after flushing. Risk of alteration of results increases with increase in size of syringe/ needle and decreased volume of sample. Blood gas results shows 25 percent lower values if 1 ml sample taken in 10 ml syringe (0.25 ml heparin in needle). Hence syringe must be >50 percent full with blood sample.

Metabolism

Cellular components of blood (reticulocytes and immature leukocytes) continue to consume O₂ and produce CO₂. Hence their blood gases will have falsely low pO₂ and falsely high pCO₂, effect on pH is negligible but have generally falsely low pH. This is significant in leukocytosis patients, e.g. acute leukemias with high TLC. 0.1 ml of O₂ consumed/dl of blood in 10 minutes in patients with normal TLC.

To overcome this immediate chilling/ analysis is essential.

If Processed Late

pCO₂ increased by 3 to 10 mm Hg/hour and pO₂ values decreased at a rate related to initial value and dependant on hemoglobin saturation.

To overcome this we have to place the sample in ice if not analyzed within 20 minutes, as iced sample preserves till 1 to 2 hours and un-iced sample is invalid if not processed immediately.

Effect of Temperature on Blood Gases

There is direct relationship between temperature and pressure, at high temperature both pO₂, pCO₂ increased and reverse is also true. When blood is cooled, CO₂ becomes more soluble reducing its pCO₂ by about 4.5 percent per °C fall in temperature and the pH rises by about 0.015 per °C fall in temperature. Available evidence suggests that homeostatic mechanisms center around protein buffers and enzymes, specifically the alpha imidazole group on histidine residues, the so called alpha stat regulation. This mechanism requires that, with hypothermia the pH rises and pCO₂ falls, whereas the HCO₃ concentration remains unchanged. The alpha stat concept refers to the use of 37°C temperature-uncorrected pH and pCO₂ values, whereas the pH stat concept refers to the use of pH and pCO₂ values corrected to the patient's core temperature, i.e. ALPHA- Stat when blood gases taken at 37°C and pH - Stat when blood gases taken at patient's actual temperature.

Hiramatsu et al have used the pH stat strategy in deep hypothermic circulatory arrest (DHCA) and found that cerebral blood flow (CBF) was greater during cooling with a better preservation of cytochrome values. With few exceptions, the appropriate clinical interpretation of blood gas values is better accomplished using the alpha stat strategy and this is a universal practice. Combination of pH stat and alpha stat is adopted in complex congenital cardiac lesions along with DHCA.

Example: Hypothermic (28°C) mechanically ventilated.

Alpha stat	pCO ₂ 40	pH 7.4
pH stat	25	7.52

Normalization of pH stat would create relative respiratory acidosis at 28°C. Oxyhemoglobin dissociation curve will shift to left with hypothermia causing CaO₂ and SaO₂ to rise for any given PaO₂ as temp falls. Measured SaO₂ and true SaO₂ *in vivo* are equal as temp changes. No correction is required.

USE OF ALPHA STAT IS SUGGESTED IN ICUS

To summarise changes in PO₂ values with temp predictable. No significant change of HCO₃⁻, O₂ saturation, O₂ capacity/content, CO₂ content values with temperature and no consensus regarding reporting of ABG values especially pH and PCO₂ after doing 'temperature correction'.

Type of Syringe

Plastic syringes are inferior to glass syringes as PO₂ values drop more rapidly in plastic syringes (only if PO₂ >400 mm Hg) but pH and PCO₂ values are unaffected. Also plastic syringes are gas permeable and small air bubbles adhere to sides of plastic syringes and hence are difficult to expel. Other advantage of glass syringes include minimum friction of barrel with syringe wall and usually no need to 'pull back' barrel hence less chance of air bubbles entering syringe. Though glass syringes preferred, differences usually not of clinical significance so plastic syringes can be continued to be used.

Changes in Altitude

FiO₂ at high altitude remains at 0.21 percent but PaO₂ and barometric pressures fall.

Altitude-Barometric Pressure-PaO₂ in air

0 ft	760	159
50,000 ft	87	18

Thus, normal PaO₂ at high altitude is much lower than the sea level.

Checking Accuracy of the ABG

We should always keep clinical status in mind while interpreting ABG report. Always check predicted pH which can be calculated from the formula (Predicted pH = 7.40 + 0.08 (40 - PaCO₂)/10. Be cautious about mixed disorders. Calculate H⁺ from the given formula by taking into account the PaCO₂ and HCO₃ in your ABG and with help of Table 5 we can see the normal pH for that ABG and hence can check the accuracy of the ABG.

$$(H^+) = 24 \times \frac{PaCO_2}{(HCO_3^-)}$$

pH 7.40 = 40 nEq/L (H⁺)

0.01 change in pH within range of 7.20 to 7.50, there is 1 nEq/L inverse change in (H⁺)

Table 5 : pH is inversely related to [H⁺]; a pH change of 1.00 represents a 10-fold change in [H⁺]

pH	[H ⁺] in nm/L
7.00	100
7.10	80
7.20	65
7.30	50
7.40	40
7.50	30
7.60	25
7.70	20
7.80	15
8.00	10

To check whether the report is reliable calculate

$$H^+ = 24 \times CO_2/HCO_3^-$$

Example

pH = 7.30	PCO ₂ = 26 mm Hg
PO ₂ = 105 mm Hg	HCO ₃ ⁻ = 22 mmol/ L
BE = - 2	SaO ₂ = 99%
Na ⁺ = 138 mmol/ L	K ⁺ = 3.8 mmol / L
Cl ⁻ = 104 mmol/ L	Anion Gap = 12

- Calculate H⁺ = $24 \times 26/22 = 28.36$
- pH should be 7.5
- This ABG is showing wrong pH

UNDERSTANDING THE ABG PRINTOUT**BARO**

It denotes the barometric pressure at site where the machine is installed, varies from place to place. It is required to calculate the alveolar oxygen gradient.

THbA

This is the Hb of the patient. A few machines measure Hb, others need this information to be fed. Hb is required to calculate the oxygen content of the blood (O₂CT).

Temp

Patient temperature needs to be fed into the machine because it measures all values at 37°C. Temperature affects the pH, pCO₂ and pO₂. It is desirable to have values corrected for patient temperature.

BE (ABE), BeEc (SBE), BB

BE refers to the actual base excess in variance from (above or below) total buffer base (BB). Normal BB is 48 to 49 mmol/ L.

HCO₃ (ABC), st HCO₃⁻ (SBC), TCO₂

TCO₂ is the sum of HCO₃⁻ and the amount of CO₂ dissolved in plasma. For each mm Hg pCO₂, 0.03 ml CO₂ is dissolved per 100 ml of plasma. As HCO₃⁻ value changes with CO₂ levels, st HCO₃⁻ is used to denote value of HCO₃⁻ independent of CO₂ changes (i.e. at pCO₂ of 40 and temp of 37°C).

StpH

It is the pH adjusted for temperature of 37°C and PCO₂ of 40 mm Hg. This would reflect pH value purely due to metabolic status.

CH⁺

Concentration of H⁺ ions in mmol/L at 37°C and patient temperature.

O₂CT

It is the sum of oxygen bound to Hb and oxygen dissolved in plasma.

For each gm of saturated Hb, 1.34 ml of O₂ is bound to hemoglobin and for each mm Hg PCO₂, 0.003 ml oxygen is dissolved per 100 ml of plasma.

O₂ Sat

Proportion/ percentage of Hb which is saturated with oxygen.

AaDO₂

Alveolar to arterial oxygen gradient. Normal value is 5 to 15 mm Hg.

FiO₂

Inspired oxygen fraction concentration required for calculation of alveolar oxygen concentration. This is to be fed to the machine.

DBE/ d THB

This is called Hb indicator. Normal values of this parameter are 0.32. If this value is more than 0.32 then it indicates the Hb of the patient should be measured accurately in order to calculate the exact base excess.

Details about pH⁴

pH = pK + log (HCO₃/H₂CO₃) -----Henderson-Hasselbach equation

pK = Constant, it is the pH value at which H₂CO₃ is 50 percent dissociated, i.e. concentration of HCO₃⁻ and carbonic acid in body are equal.

pK = 6.1 for H₂CO₃

Normal ratio HCO₃⁻/H₂CO₃ = 20/1 and hence

$$\text{pH} = 6.1 + \log 20 = 6.1 + 1.3 = 7.4$$

Therefore, ideal pH = 7.4 ± 2 S.D

Severe acidosis = pH < 7.2

If pH < 7.25 it leads to stimulation of respiratory center but if pH < 7.0 it leads to respiratory depression.

Relationship of pH and pCO₂

pCO₂ elevation of 10 mm Hg decrease pH by 0.08 while pCO₂ decrease of 10 mm Hg increase pH by 0.08.

Relationship of pH and HCO₃

Decrease of HCO₃ by 10 will increase pH by 0.15, while increase of HCO₃ by 10 will decrease pH by 0.15.

The Effect of Buffers on pH

Buffers stabilize pH. Hemoglobin, bicarbonate and protein are the principal buffers of blood. Extravascular space does not have hemoglobin and hence the buffering capacity is less than that of blood. Because we have no measure

of extra and intracellular buffering capacity, it is difficult to predict how much pH will change when the concentration of acid or CO_2 change. The equation $\text{CO}_2 + \text{H}_2\text{O} = \text{H}_2\text{CO}_3 = \text{H}^+ + \text{HCO}_3^-$ shows that any addition or subtraction of H^+ or of HCO_3^- ions cause a change in CO_2 level. By changing ventilation, CO_2 concentration can be altered. The Henderson Hasselbach equation can be used to calculate one variable only if the other two are known; for example we can calculate HCO_3^- if pH and H_2CO_3 are known. The equation cannot be used to predict what will happen if only one variable changes and if we know nothing about the other two. Although we can estimate what might happen in response to an acid load or ventilatory change, we cannot be accurate.

PaCO_2

Partial pressure of carbon dioxide in arterial blood. Normal value is 35 to 45 mm Hg (*Ideal 40 mm Hg*)

Normal PaCO_2 of venous blood = 45 mm Hg

PaCO_2 is indicative of alveolar ventilation

If $\text{PaCO}_2 < 30$ = Respiratory alkalosis

If $\text{PaCO}_2 > 50$ = Respiratory acidosis

High CO_2 is the most important respiratory center stimulant. If $\text{PaCO}_2 > 65$ the respiratory center becomes insensitive to CO_2 .

Actual Bicarbonate ($\text{HCO}_3(\text{n})$)

HCO_3^- in plasma = 22 to 24 mEq/L (Normal)

<20 = acidosis

>24 = alkalosis

CO_2 up and down rule: Partial pressure of CO_2 may change the levels of HCO_3^- depending on degree and duration of CO_2 rise.

Relationship between HCO_3^- and PaCO_2

- For acute elevation of PaCO_2 over 40 mm Hg, HCO_3^- increases by 1 mEq/L for each 10 mm Hg PaCO_2 .
- For acute decrease in PaCO_2 below 40 mm Hg, HCO_3^- decrease by 2 mEq/L for each 10 mm Hg decrease in PaCO_2 .
- For chronic elevation in PaCO_2 over 40 mm Hg, HCO_3^- increases by 4 mEq/L for each 10 mm Hg increase in PaCO_2 .

Standard Bicarbonate Concentration (SBC): 22 to 26 mEq/L

It is the concentration of HCO_3^- in the plasma from blood which is equilibrated to bring the PaCO_2 to 40 mm Hg at 37°C, i.e. it overcomes the changes in HCO_3^- due to respiratory causes and reflects a nonrespiratory acid base change.

Under ideal conditions $\text{SBC} = \text{HCO}_3(\text{n})$ variation = + 2 mEq/L. If respiratory acidosis is present, $\text{HCO}_3^- > \text{SBC}$ (because this blood will have $\text{PaCO}_2 > 40$ mm Hg and therefore when equilibrated to 40 mm Hg, some of the CO_2 will leave the blood, hence SBC will be lowered).

If respiratory alkalosis is present $\text{HCO}_3^- < \text{SBC}$ (because during equilibration to 40 mm some CO_2 will get absorbed and therefore SBC will increase).

REMEMBER THIS

SBC low: Metabolic acidosis

SBC high: Metabolic alkalosis

If $\text{HCO}_3(\text{n}) > \text{SBC}$: Respiratory acidosis

If $\text{HCO}_3(\text{n}) < \text{SBC}$: Respiratory alkalosis

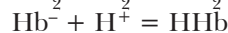
If $\text{HCO}_3^- = \text{SBC}$ respiratory balance present

If both are low but $\text{HCO}_3^- = \text{SBC}$ then compensated metabolic acidosis

Actual Base Excess (ABE)

Refers to actual base excess above or below total buffer base (BB). It is *in vitro* expression which mainly reflects nonrespiratory portion of acid base.

When CO_2 accumulates as a result of impaired respiration, the following reactions occur:



The decrease in amount of Hb^- buffer is equal to the amount of HCO_3^- released in the reaction. Therefore total amount of buffer anion content will not change. Therefore change in the PaCO_2 will not change base excess. Hence ABE is an indicator of metabolic status. It attempts to quantify the patient's total base excess or deficit. Expressed as mmol/L of base above or below the Normal buffer base range. The base excess allows an estimate how much base or acid is necessary to bring a liter of blood to pH 7.4.

$$\begin{aligned} \text{Formula for calculation of BE} &= (\text{Actual pH} - \text{Predicted pH}) \times 67 \text{ or} \\ &= 1.2 \times (24 - \text{measured bicarbonate}) \end{aligned}$$

Standard Base Excess (SBE), Buffer Base (BB)

SBE is same as ABE except that it is an *in vivo* measurement, which is dependent on the equilibrium of the interstitial or ECF compartment of the body and not only the blood with CO_2 .

Unlike the ABE which is the BE in the whole blood *in vitro*, where buffering capacity is due to bicarbonate and hemoglobin, the *in vivo* buffering capacity is less than *in vitro* because actually equilibration to the new level CO_2 takes place not only in the blood but also in interstitial space. Since the extracellular volume of the body contains about three times more extravascular (free of Hb buffer) than intravascular (rich in Hb buffer) volume some clinicians like to report the SBE, a base excess assuming Hb of 5 g/dl. This represents the average buffering capacity of the total extracellular volume. Intracellular buffers play an important role after a disturbance has persisted for some time, particularly in severe acid base derangements. In such situations standard base excess does not provide a useful guide to therapy, one has to titrate until the desired result is achieved.⁴

Significance of Base Excess

Total buffer base (BB) is 48 to 49 mmol/L. Half of this is due to HCO_3^- , 25 percent due to Hb buffer and another 25 percent due to protein, sulphate, phosphate buffers.

A value of $\text{BE} + 3$ is considered as normal. Abnormal pH with $\text{BE} > -5$ (base deficit < 5) without any decompensation in a stable condition does not need any treatment. Abnormal pH with $\text{BE} < -5$ with significant imbalance needs treatment. Treatment of neonatal metabolic acidosis consists of general supportive care and specific measures directed to treat underlying cause. Treatment of hypothermia, hypovolemia, anemia, hypoxia and electrolyte disturbance will usually correct metabolic acidosis secondary to asphyxia or poor tissue perfusion. Antibiotics should be given if sepsis is suspected. Many infants require ventilatory support. Bicarbonate is considered to be unnecessary and even harmful, leading to changes in cerebral blood flow and paradoxically to increased CSF or intracellular acidosis.

$$\text{Amount of buffer to be administered/ Total base deficit} \\ = \text{Base deficit (mEq/L)} \times \text{body weight} \times 0.3$$

Interpretation of ABG^{3,5}

Simple disorders: In simple acid base disorder pCO_2 and HCO_3^- levels change in the same direction.

Simple disorder	pH	PCO_2	HCO_3^-
Metabolic acidosis	↓	↓	↓
Metabolic alkalosis	↑	↑	↑
Respiratory acidosis	↓	↑	↑
Respiratory alkalosis	↑	↓	↓

Mixed disturbances: In patient with respiratory insufficiency develop metabolic acidosis, he loses his ability to compensate and a mixed respiratory-metabolic acidosis supervenes. Correspondingly, a mixed respiratory-metabolic alkalosis is also possible (Table 6).

Mixed disorder	pH	HCO_3^-	pCO_2
Mixed acidosis	↓↓	↓	↑
Mixed alkalosis	↑↑	↑	↓

This demonstrates that compensation cannot take place when respiratory and metabolic disturbances conspire. In mixed disturbances, both metabolic (HCO_3^-) and respiratory (pCO_2) factors pull in the same direction and pH changes are exaggerated (double arrows). We should alert for mixed acid base disturbances whenever there is absence of compensation or excessive compensation, if child is on respiratory assistance or there are any temporal inconsistencies, beware in case of long standing pulmonary or renal disease and in settings conducive to mixed disorder.

Table 6: Common settings of mixed acid-base disorders:

Metabolic acidosis/ Respiratory acidosis
Cardiopulmonary arrest
Severe pulmonary edema
Poisonings
Metabolic acidosis/ Respiratory alkalosis
Sepsis
Severe liver disease
Salicylate intoxication
Metabolic acidosis/ Metabolic alkalosis
Renal failure with vomiting
Ketoacidosis with vomiting
Metabolic alkalosis/ Respiratory acidosis
Chronic lung disease with vomiting or diuretics
Metabolic alkalosis/ Respiratory alkalosis
Severe liver disease
Inappropriate use of soda bicarb in hyperventilating patient

Compensation Mechanisms

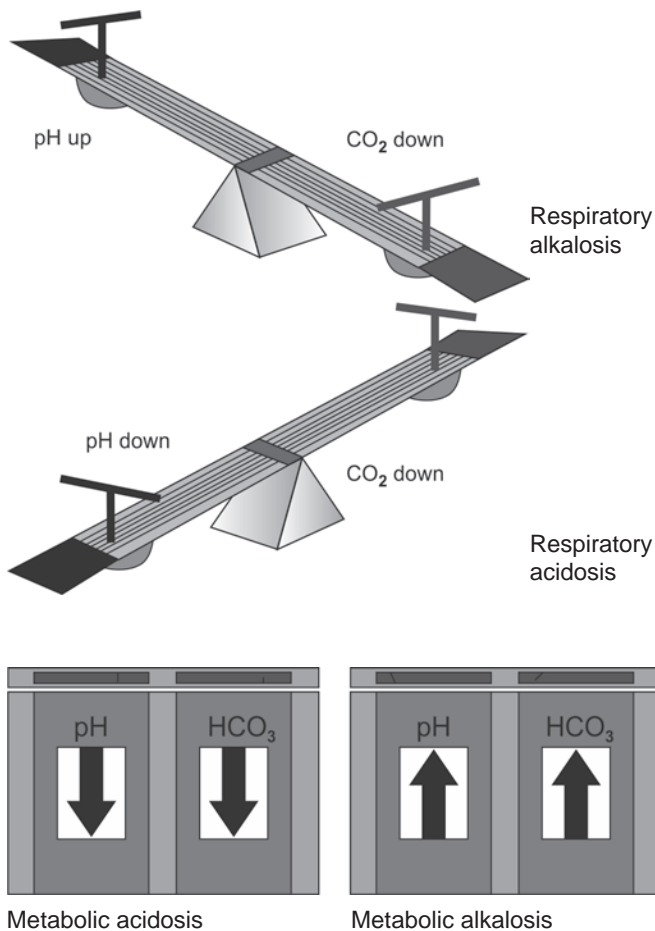
When disturbances in acid base balance persist, the body can call into play compensatory efforts through an organ not primarily affected; for example, pulmonary disturbances resulting in respiratory acidosis or alkalosis will lead to compensation by the kidney. Conversely, primary disturbances of renal function or metabolism with acid base imbalance lead to compensation by the lungs.

The body's compensatory efforts are governed by complex intracellular and extracellular stimuli and responses. Assume that a respiratory acidosis triggers a renal compensatory effort. Compensation will return the abnormal pH toward normal. It does not re-establish completely normal values or when complete compensation and correction of respiratory acidosis succeeds, the drive that sustains the compensatory effort would cease.

Direction for Compensatory Mechanisms, Bicarbonate and pCO_2

	pH	HCO_3^-	pCO_2	Compensation
<i>Respiratory</i>				
Acidosis	↓	↑↑	↑	Renal effect on HCO_3^-
Alkalosis	↑	↓↓	↓	
<i>Metabolic</i>				
Acidosis	↓	↓	↓↓	Respiratory effort on CO_2
Alkalosis	↑	↑	↑↑	

Double arrow shows direction of compensation. The pH change will be less pronounced in the presence of compensatory mechanism than in their absence.



Remember: “See saw effect” seen in *respiratory* disturbances, i.e. pH and pCO₂ move in *Opposite* direction.
And *Metabolic* disturbances show an “Elevator effect”, i.e. pH and HCO₃ move in *same* direction

For all calculation take HCO₃ as 20 mEq/L and pCO₂ as 40 mm Hg.

Prediction of Compensatory Mechanisms

Compensation is the body's ability to correct acidosis or alkalosis. For metabolic disorders, metabolic compensation occurs through the kidneys. It is a much slower process, starts within a few hours and takes about 2 to 5 days to complete. Compensation is said to be complete if normal pH is attained even though the pCO₂ and HCO₃⁻ are abnormal. In partial compensation pH, pCO₂ and HCO₃⁻ are all abnormal but pH is not appropriate for PCO₂/HCO₃⁻ levels.

Metabolic acidosis
HCO₃⁻ ↓ 1 mEq/L
Metabolic alkalsis
HCO₃⁻ ↑ 1 mEq/L

Factor of 1
CO₂ ↓ 1 mm Hg (1-1.5)
Factor of 1
CO₂ ↑ 1 mm Hg (0.5-1.0)

Respiratory acidosis
pCO₂ ↑ 10 mm Hg
Respiratory alkalosis
pCO₂ ↓ 10 mm Hg

Factor of 10
HCO₃⁻ ↑ 1 mEq/L (0.08-1)
Factor of 10
HCO₃⁻ ↓ 1 mEq/L (1-3)

Metabolic: Factor of 1
Change of HCO₃⁻ by 1 will change pCO₂ also by 1
Respiratory: Factor of 10
Change of pCO₂ by 10 will change HCO₃⁻ by 1

Prediction of Compensation

Disorder	Prediction of compensation
Metabolic acidosis	PaCO ₂ = (1.5 X HCO ₃ ⁻) + 8 or PaCO ₂ = HCO ₃ ⁻ + 15 or PaCO ₂ will ↓ 1.25 mm Hg per 1 mEq/L ↓ in HCO ₃ ⁻
Metabolic alkalosis	PaCO ₂ will ↑ 0.75 mm Hg per 1 mEq/L ↑ in HCO ₃ ⁻ or PaCO ₂ = HCO ₃ ⁻ + 15
<i>Respiratory alkalosis</i>	
Acute	HCO ₃ ⁻ will ↓ 2 mEq/L per 10 mm Hg ↓ in PaCO ₂
Chronic	HCO ₃ ⁻ will ↓ 4 mEq/L per 10 mm Hg ↓ in PaCO ₂
<i>Respiratory acidosis</i>	
Acute	HCO ₃ ⁻ will ↑ 1 mEq/L per 10 mm Hg ↑ in PaCO ₂
Chronic	HCO ₃ ⁻ will ↑ 4 mEq/L per 10 mm Hg ↑ in PaCO ₂

Maximum Compensation

Metabolic Acidosis : PaCO₂ = Up to 10?
Metabolic Alkalosis : PaCO₂ = Maximum 60
Respiratory Acidosis : BICARB = Maximum 40
Respiratory Alkalosis : BICARB = Up to 10

Anion Gap⁴

Measurement of anion gap gives a clue to the cause of metabolic acidosis. Anion gap is the difference between the unmeasured anions and cations. This is calculated as difference between measured anions and cations.

Serum (Na⁺ + K⁺) — Serum (Cl⁻ + HCO₃⁻)

Normal value of anion gap is 8 to 12 mmol/L. A normal anion gap acidosis suggests a HCO₃⁻ loss or rapid dilution of ECF. Chloride is proportionately increased in such conditions- GIT, Renal loss of HCO₃⁻ (Table 7). Increased anion gap suggest an addition of strong acid in the system as occurs in lactic acidemia, ketonemia, renal failure, excessive salt therapy (ringer lactate, acetate), etc.

(Table 8). A decrease in serum K^+ , Ca^{++} , Mg^{++} or falsely high serum Na^+ or serum protein can also increase the anion gap. This may occur with low serum protein or increased plasma chloride due to bicarbonate loss by intestine or kidneys. True abnormal value of anion gap is not known. Although anion gap more than 30 mmol/L signifies that organic acidosis is always present. If anion gap is more than 25 and $HCO_3^- < 20$ mmol/L is highly predictive of organic acidosis and renal failure. Anion gap of more than 20 and $HCO_3^- < 8$ mmol/L is virtually diagnostic of organic acidosis. Remember 50 percent of sick patients with hyperlactatemia may present as no anion gap metabolic acidosis because of hyperchloremia and hypoalbuminemia. Calculation of AG does not control for changes in PCO_2 and albumin, decrease in albumin by 1 gm/dL decreases BE by 3.7 mEq/L and AG by 2.75 mEq/L. High PCO_2 may result in falsely low AG (tCO_2 used in calculation is not equivalent to std. HCO_3^-). We use figge formula for that, i.e.

$AG_{adjusted} = AG + 0.25 \times (\text{normal albumin} - \text{Obs. albumin})$ (Normal albumin = 44 gm/L)

Use of adjusted AG prevents underestimation of anion gap. Use leads to 7 fold increase in the detection of high AG in ICU patients.

Increased anion gap is also seen with decreased K^+ , Ca^{++} , Mg^{++} , increased Na^+ , total proteins and high PO_4^{3-} (Table 9).

To diagnose normal anion gap acidosis; later on urinary anion gap is also indicated $UAG = \{(Na + K) - Cl\}$ (indirect evidence of urinary ammonium excretion), Normal values range from = -10 to + 10. In extra renal causes of normal anion gap acidosis UAG is largely negative (> -10) and in renal causes of NAG metabolic acidosis UAG is largely positive ($> +10$).

If anion gap is increased >20 (high anion gap acidosis) we have to see if there a superimposed nonanion gap acidosis? For this we have to see two more things.

Gap-Gap Phenomenon

$\Delta AG / \Delta HCO_3^-$
 $(AG - 12/24 - HCO_3^-)$
 < 1 : superimposed nonanion gap metabolic acidosis
 > 1.6 : superimposed metabolic alkalosis

$HCO_3^- + (\text{Anion gap} - 12) = 24$

If this value is less than 24 there is a hidden nonanion gap acidosis

If this value is more than 24 then there is a metabolic alkalosis hidden in the numbers.

Bicarbonate Gap (Delta Gap)

If anion gap acidosis is the only abnormality, there is 1 to 1 correlation between the rise in AG and the fall in bicarbonate (Serum tCO_2). Normal bicarbonate gap is ZERO. But no accepted abnormal value (deviation >6 or 8 mEq/L)

Table 7: Metabolic acidosis with normal anion gap⁶

Diarrhea
Renal tubular acidosis (RTA)
<ul style="list-style-type: none"> • Distal (type I) • Proximal (type II) RTA • Hyperkalemic (type IV) RTA
Posthypocapnia
Small bowel, biliary, pancreatic tube or fistula
Drainage
<ul style="list-style-type: none"> • Ureteral diversion • Bowel augmentation cystoplasty
Intake of $MgCl_2$, NH_4Cl , Cholestyramine, arginine HCl, $CaCl_2$
TPN
Carbonic anhydrase inhibitors—Acetazolamide
Mineralocorticoid deficiency
Dilution

Table 8: Metabolic acidosis with increased anion gap [Na - (Cl + HCO_3^-)]

MUDPILES⁶
Methanol
Uremia (renal failure)
Diabetic ketoacidosis (other also, e.g. starvation and alcoholic ketoacidosis)
Paraldehyde and phenformin
Isoniazid and iron
Lactic acidosis (tissue hypoxia, shock, severe anemia, liver failure, malignancy, intestinal bacterial overgrowth, inborn error of metabolism, drugs, e.g. metformin and)
Ethanol and ethylene glycol
Salicylates

Table 9: Low anion gap: No help in diagnosis of acid-base disorder

Hypoalbuminemia
High K^+ , Ca^{++} , Mg^{++}
Low PO_4
Bromide intoxication
Lab error

Elevated AG with significant variation of bicarbonate gap from zero either + or -, suggest mixed acid base disorder.

$BG = \Delta AG - \Delta tCO_2$
 $\Delta AG = \text{Patient's AG} - 12 \text{ mEq/L}$
 $\Delta tCO_2 = 27 \text{ mEq/L} - \text{patient's } tCO_2$
 $BG = Na^+ - Cl^- - 39$ (Short cut method)

If a patient is having positive (+) bicarbonate gap (>6 mEq/L) means serum $t\text{CO}_2$ reduced less than predicted by the change in AG and is seen in:

- Metabolic alkalosis and/ or
- Bicarbonate retention as compensation for respiratory acidosis

If a patient is having negative (-) Bicarbonate Gap (< -6 mEq/L) means serum bicarbonate reduced more than predicted by change in anion gap and is seen in:

- Hyperchloremic metabolic acidosis and/ or
- Bicarbonate excretion as compensation for respiratory alkalosis

Examples

1. 12-year-old male presented with several days of vomiting, nausea and abdominal pain. He has severe dehydration with hypotension.

$\text{Na}^+ - 144, \text{Cl}^- - 95, \text{K}^+ - 4.2, \text{CO}_2 - 14$

$$\text{BG} = 144 - (95 + 39) = +10$$

Impression: Metabolic Acidosis + Metabolic Alkalosis

2. 14-years-old with acute renal failure

$\text{Na}^+ - 140, \text{K}^+ - 4, \text{Cl}^- - 115, t\text{CO}_2 - 5, \text{pH} - 7.12, \text{PaCO}_2 - 13, \text{HCO}_3^- - 4.$

$$\text{BG} = 140 - (115 + 39) = -14$$

Impression: AG increased metabolic acidosis with hyperchloremic acidosis

Systematic Approach to ABG^{3,7}

Keep clinical condition, previous ABG and therapeutic interventions in mind while interpreting the ABG report. Compensation by kidneys is slow in neonates, while a sick neonate with respiratory disease has limitation for CO_2 excretion and kidneys may be ineffective for HCO_3^- conservation (Flow chart 1).

It Consists of (Flow chart 2)

Step 1: Is acidosis or alkalosis present?

$\text{pH} < 7.35 = \text{acidosis}$

$\text{pH} > 7.45 = \text{alkalosis}$

Step 2: Is the imbalance respiratory or metabolic in origin?

Look at the PaCO_2

- If the CO_2 provides a cause for abnormal pH, i.e. low pH and High PaCO_2 (acidosis) or high pH and low PaCO_2 (alkalosis) then the picture is respiratory acidosis or alkalosis.
- If the CO_2 does not provide a cause for the pH, it is compensating for a metabolic abnormality.

Remember for each \uparrow/\downarrow of PaCO_2 by 10 mm Hg, the pH increases or decreases by 0.08 units.

- Use this to calculate the predicted pH.
- If measured pH > predicted pH then an associated metabolic alkalosis is present.

- If measured pH < predicted pH then an associated metabolic acidosis is present.

Step 3: Now look at HCO_3^- and BE.

- If the BE and HCO_3^- provide a cause for the abnormal pH, i.e. low pH and low HCO_3^- and BE (acidosis) or high pH and + BE and high HCO_3^- , then the overall picture is a metabolic acidosis or alkalosis.

If the BE or HCO_3^- does not provide a cause then it is compensating for a respiratory abnormality.

Remember for pH changes that are primarily of metabolic origin, for every 0.1 unit change in pH there is a 6.7 mEq/L change in HCO_3^- .

Step 4: What is PaO_2 ?

Normal : 80 to 100 mm Hg

Mild hypoxemia : 60 to 80 mm Hg

Moderate hypoxemia : 40 to 60 mm Hg

Severe hypoxemia : <40 mm Hg

(corrected, undercorrected or overcorrected hypoxemia is used to explain the ABG if child is with respiratory support or on oxygen).

Step 5: Identify possible cause of the acid base imbalance and what is the management for the imbalance?

Step 6: If the compensation is not what is expected, be on the hunt for a mixed disorder.

As an example: A patient has the following blood gas, pH - 7.1, pCO_2 - 35 mm Hg, Na-145 mEq/L, K-5 mEq/L, Cl- 97 mEq/L, HCO_3^- - 12 mEq/L.

With acidemia and low bicarbonate the primary disorder is a metabolic acidosis. The expected compensation is a change of $1.2 \times$ the Bicarbonate. The pCO_2 was much higher than expected so, a respiratory acidosis must also be present.

Step 7: As they say on the London subway, MIND THE GAP!

Gap 1

The anion gap: $\text{Na} - (\text{Cl} + \text{CO}_2) = 10 \pm 4$

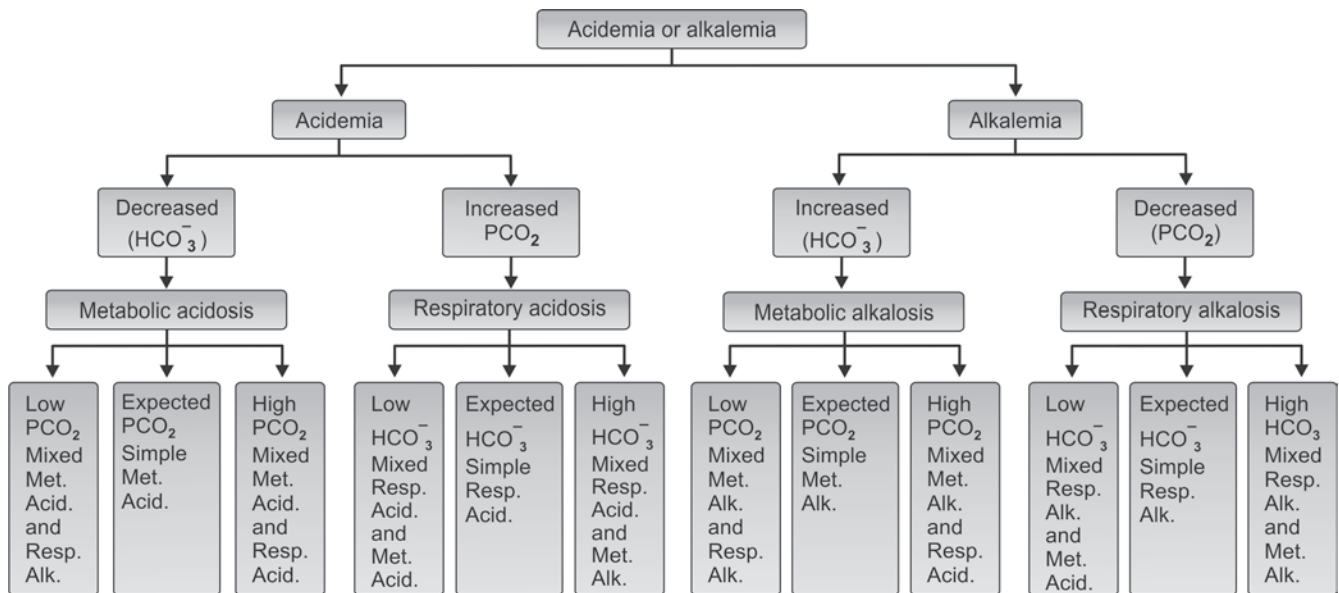
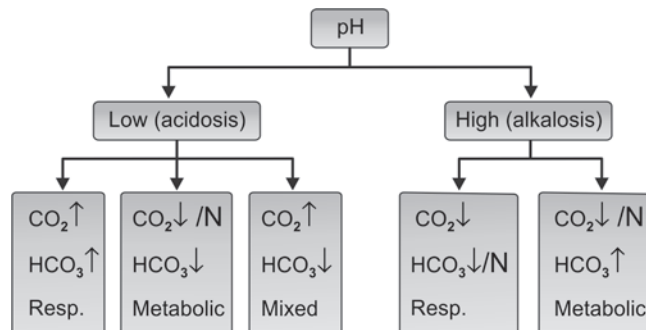
Calculate the gap on each patient. If there is a high anion gap consider an underlying acidosis even if the pH is elevated. (an anion gap of 20 or more is always a problem) The expected compensation will not be present but the anion gap can lead you to where the discrepancy lies. Also, the gap will obviously differentiate between an anion gap and non-anion gap acidosis.

Gap 2

The delta anion gap (aka: delta/delta, bicarbonate gap)

$$\text{Delta AG} = (\text{anion gap} - 10) / (24 - \text{HCO}_3^-)$$

The delta anion gap can be used to detect the presence of additional acid-base disorders in patients with a high anion gap acidosis. The delta averages between 1

Flow chart 1: Schematic presentation to approach to acid-base disorders:**Flow chart 2:** Interpretation of blood gas: flow diagram

and 1.6. If the delta is less than 1 suspect a concomitant non-anion gap acidosis, if greater than 1.6, look for a concomitant metabolic alkalosis.

Gap 3A

The Osmolal Gap

First calculate the osmolality - $(2 \times \text{Na}) + (\text{glucose}/18) + (\text{BUN}/2.8)$

Osmolal gap = Measured Osmolality - Calculated Osmolality (any number over 20 implies an unmeasured osmole) Unmeasured osmoles are usually alcohols. In the presence of a metabolic acidosis think Ethylene glycol or methanol, with a normal pH ethanol or isopropyl alcohol is likely.

Gap 3B

Urine Anion Gap

This gap has limited utility (a history from the patient usually solves this conundrum). It can help differentiate

between diarrhea and RTA as a cause of a non-anion gap acidosis.

UAG = urinary Na + urinary K - urinary Cl

Normal is = 20 - 0

In diarrhea the UAG is typically highly negative (-20 - -50) due to increase NH_4^+ production with diarrhea. With an RTA the UAG is typically positive because of the decrement in NH_4^+ production.

Possible Simple Disorders in Pediatric Patients

Metabolic acidosis

- Under perfusion
- Hypothermia
- Anemia
- Intraventricular hemorrhage
- Hypoxemia
- Sepsis
- Renal immaturity - loss of bicarbonate

- Renal failure
- Hyperkalemia
- Hyperglycemia
- Metabolic disorder- inborn error of metabolism
- Decreased cardiac output, PDA
- Use of excessive PEEP, increase work of breathing
- Drugs, e.g. acetazolamide

Metabolic Alkalosis

- Iatrogenic – bicarbonate therapy
- Use of diuretics
- Following blood transfusion
- Persistent vomiting- congenital adrenal hyperplasia
- Prolonged gastric aspiration
- Urea cycle disorder
- Acute correction of persistent hypercapnia
- Contraction alkalosis

Respiratory Acidosis

- Tube block
- Tube dislodgement
- Increased dead space- long ET, small bore tube
- Opening of PDA
- PIE
- Pulmonary air leak
- Collapse, consolidation

- Asphyxia: damage to respiratory centre
 - Apnea
 - RDS

Respiratory Alkalosis

- Asphyxia: over stimulation of respiratory center
- Over ventilation while on mechanical ventilation.

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Recognition and Management of Acute Respiratory Failure, Including ARDS

Vivek Bhaganagare, Bala Ramachandran

INTRODUCTION^{1,2}

Respiratory distress and failure are part of a spectrum of conditions and sometimes it can be difficult to clinically differentiate one from the other. Failure to recognize and manage respiratory failure appropriately can result in death or long-term disability. Therefore, early recognition of respiratory distress and respiratory failure prevents cardiac arrest and improves neurological outcome.

PHYSIOLOGIC ROLE OF RESPIRATORY SYSTEM¹⁻³

Oxygenation is the diffusion of oxygen across alveoli into the blood and its attachment to hemoglobin.

Hypoxemia is inadequate oxygenation of arterial blood.

Tissue hypoxia is inadequate oxygenation at the tissue level. Early compensation for tissue hypoxia happens with increase in breathing rate and efforts, along with increase in heart rate (which eventually increases cardiac output to maintain oxygen delivery). Tissue oxygenation depends on the following factors: Hb, PaO₂, SaO₂, and Cardiac Output.

*Inadequate oxygenation*³ is defined as PaO₂ <60 Torr or SpO₂ <90 percent in room air and is expressed as PaO₂/FiO₂ ratio <300 or Alveolar-Arterial PO₂ Gradient (aADO₂) >300 Torr with FiO₂ of 1.0.

Due to high oxygen requirement in children (6 to 8 ml/kg/min), hypoxemia and tissue hypoxia develops faster in children than in adults.

Ventilation is the diffusion of carbon dioxide across capillaries into the alveoli for expiration.

Hypercarbia is due to inadequate alveolar ventilation that decreases CO₂ elimination, resulting in a rising level of PaCO₂ in the blood, eventually resulting in respiratory acidosis.

Hypercarbia is difficult to detect clinically and requires invasive measurement for confirmation.

*Inadequate ventilation*³ is defined as a PaCO₂ >45 mm Hg with arterial pH <7.35 in the absence of chronic hypercapnia.

Inadequate ventilation is seen in airway disease, lung parenchymal disease and central hypoventilation.

Respiratory distress^{1,2} is defined as a clinical state with increased respiratory rate and efforts (Nasal flaring, Retractions, Accessory muscle use) with other associated changes in airway sounds, skin color and mental status.

Respiratory failure^{1,2} is defined as a clinical state of inadequate oxygenation or inadequate ventilation or both. It is often the end stage of respiratory distress.

*Hypoxic respiratory failure*⁴ (type 1 respiratory failure) is hypoxia without hypercapnia and with an arterial partial pressure of oxygen (PaO₂) of <60 mm Hg on room air at sea level.

Hypercapnic respiratory failure⁴ (type 2 respiratory failure) is hypoxia with an arterial partial pressure of carbon dioxide (PaCO₂) of >50 mm Hg on room air at sea level.

*Respiratory failure*² usually is defined biochemically as an arterial partial pressure of carbon dioxide (PaCO₂) greater than 50 mm Hg, an arterial partial pressure of oxygen (PaO₂) of less than 60 mm Hg, or both.

COMMON CAUSES OF RESPIRATORY FAILURE IN CHILDREN²

- *Airway/Lung Dysfunction*: Usually associated with signs of increased respiratory drive
 - *Central Airway Obstruction (Pathophysiology: Hypoventilation)- Causes*: Croup, Foreign body, Anaphylaxis, Bacterial tracheitis, Epiglottitis, Retropharyngeal abscess, bulbar muscle weakness/dysfunction.
 - *Peripheral Airways/ Parenchymal Lung Disease (Pathophysiology: Disordered gas exchange) - Causes*: Status

asthmaticus, Bronchiolitis, Pneumonia, Acute respiratory distress syndrome, Pulmonary edema, Pulmonary contusion, Cystic fibrosis, Chronic lung disease (e.g. bronchopulmonary dysplasia).

- *Respiratory Pump Dysfunction (Pathophysiology: Hypoventilation)*: May be associated with signs of decreased respiratory drive.
 - *Decreased Central Nervous System (CNS) drive*: Head injury, Ingestion of CNS depressants, Adverse effect of procedural sedation, Intracranial bleeding, Apnea of prematurity.
 - *Peripheral Nerve/Neuromuscular Junction*: Spinal cord injury, Organophosphate/ carbamate poisoning, Guillain-Barre' syndrome, Myasthenia gravis, Infant botulism.
 - *Muscle Weakness*: Respiratory muscle fatigue due to increased work of breathing, Myopathies/ Muscular dystrophies.

SIGNS AND SYMPTOMS PERTINENT TO RESPIRATORY FAILURE¹⁻⁴

Increased Respiratory Drive

Increased rate/depth of breathing, Anxiety, Dyspnea, Retractions, Accessory muscle use.

Decreased Respiratory Drive

Decreased rate/depth of breathing, lethargy, confusion
Respiratory muscle fatigue: Paradoxic (see-saw) respiration, Grunting, Irregular or uncoordinated breathing.

Hypoxemia

Cyanosis, digital clubbing.

Evidence of Lung Disease

Wheezing/rhonchi/rales, retractions.

Evidence of Respiratory Muscle Weakness

Paradoxical, shallow breathing, Ineffective cough.

Hypercapnia

Throbbing morning headaches, disrupted sleep, decreased level of consciousness.

Evidence of Loss of Airway Protective Reflexes

Absent gag and cough reflexes, Gurgling respirations.

Evidence of Critical Upper Airway Obstruction

Stridor, Drooling, Muffled/absent breath sounds

Clinical Recognition of Respiratory Failure

Early Signs—Tachypnea, Tachycardia, Nasal flaring, Retractions.

Late Signs—Bradycardia, bradypnea, apnea, variable (Increased/decreased/no) respiratory efforts, cyanosis, Poor/absent distal air movement, stupor, coma.

Confirmation of Respiratory failure – requires arterial blood gas analysis.

Impending Respiratory Failure³

It is seen with progressively worsening respiratory distress with rapidly rising (out of proportion to the respiratory efforts) PaCO₂ or fatigue of respiratory muscles.

When respiratory efforts are inadequate, respiratory failure may occur without typical signs of respiratory distress.

Degree of hypoxemia is a sign of respiratory failure in a child with normal baseline cardiopulmonary physiology.

MANAGEMENT OF RESPIRATORY DISTRESS AND FAILURE

Patients with acute respiratory failure are at risk of developing imminent cardiac arrest, as opposed to those with chronic respiratory failure. The latter are at risk of developing pulmonary hypertension and cor pulmonale.²

The primary goal of initial treatment for respiratory distress or failure is to support or restore adequate oxygenation and ventilation. The first priority therefore, remains a rapid focussed assessment to categorize (type and severity) the condition. Later, targeted management may be implemented after identification of the cause of respiratory dysfunction.

INITIAL STABILIZATION AND MANAGEMENT¹

Airway

- Support airway with position of comfort.
- Open airway with either a jaw thrust maneuver without extension in suspected cervical spine injury and head tilt, or chin lift with head extension.
- Clear airway with suction nose and mouth and/ or foreign body removal if present.
- Insert airway adjuncts like oropharyngeal airway or nasopharyngeal airway as needed.

Breathing

- Assist ventilation by Bag/ mask ventilation.
- Provide oxygen by non-rebreathing mask.
- Monitor oxygen saturation by pulse oximeter.
- Prepare for endotracheal intubation, if necessary.
- Use medications as needed like nebulisation with epinephrine, bronchodilators.

Circulation

- Monitor heart rate and rhythm.
- Initiate vascular access for fluid therapy and medications.

Once oxygenation and ventilation are stabilised, the cause of respiratory dysfunction can be identified and treated accordingly.

OXYGEN SUPPLEMENTATION^{1,2}

Any respiratory distress/failure condition with desaturation including cyanosis, tachypnea with intercostals retractions, stridor, wheezing etc. requires oxygen. The devices should be used according to requirement (age, flow, type, condition) including intranasal catheter, nasal cannula, face mask, head-box, venturi mask, non-rebreathing mask etc.

NIPPV⁵⁻⁷

Noninvasive positive pressure ventilation provides ventilatory assistance to the respiratory system with nasal/facial interface, without an artificial airway. It provides IPAP and EPAP and breaths are allowed by the patient. It can be used in various conditions of respiratory distress including pneumonia, early pulmonary edema, asthma, aspiration. This therapy is indicated in the alert, oriented, cooperative, hemodynamically stable child, and potentially can prevent intubation and mechanical ventilation, reduces nosocomial infection and shortens hospital stay. Other indications are children with chronic respiratory insufficiency, sleep associated abnormality, hypoventilation.

VENTILATORY MANAGEMENT^{3,8,9}

Indications for intubation are mainly:

- Respiratory Failure (inadequate oxygenation, ventilation or both).
- Cardiovascular Dysfunction (septic shock, myocardial failure).
- Neurologic and Neuromuscular Disorders (GCS <8 or fall by >3 over one hour, raised intracranial pressure).

Initial settings depend on clinical condition and underlying pathologic process. Mode can be pressure or volume control. Tidal volume (usually 6 to 8 ml/kg) and ventilator rate (physiological rate at start) are set to provide normal minute ventilation and to maintain normocarbia.

PEEP

Lower PEEP is useful in lower airway obstruction and in conditions with raised intracranial pressure. Higher (optimum) PEEP is required in conditions with diminished lung compliance, such as pneumonia and ARDS, to recruit alveoli to improve oxygenation. Higher PEEP is also useful in diseases with abdominal distension.

I:E ratio is usually kept in the range of 1:1 to 1:3. Alternatively, the inspiratory time is set between 0.6 to 1 second (lower for younger patients). Inspiratory time is increased in order to improve oxygenation. Prolonged expiratory time is useful in lower airway obstruction.

Fractional inspired oxygen is generally started at 1 and then adjusted downwards to the lowest level required to maintain adequate oxygen saturation.

Adequate sedation and muscle paralysis is required to prevent asynchrony with ventilator and to decrease metabolic demand.

SPECIFIC MANAGEMENT IN CERTAIN COMMON CONDITIONS

Upper Airway Obstruction

Reduce airway swelling with nebulized adrenaline (0.5 ml/kg 1:1000 solution, up to a maximum of 5 ml), IM dexamethasone according to severity. Avoid unnecessary agitation and decide on airway adjuncts or advanced airway/surgical airway (tracheostomy).

Lung Tissue Disease (Parenchymal Lung Disease)

Causes can be infectious pneumonias, chemical pneumonitis, aspiration pneumonitis.

- Initial stabilization of airway, breathing and circulation, as described above.
- Use of *positive expiratory pressure* (CPAP, BiPAP, or mechanical ventilation with PEEP).
- Administer *nebulisation with bronchodilators* if wheeze/airway obstruction is present.
- If suspecting infectious pneumonia, administer *antimicrobial therapy* to treat potential gram positive organisms (pneumococcus and MRSA) and consider coverage for Mycoplasma and Chlamydia with a macrolide antibiotic. Gram-negative coverage may be required in special situations, such as when a hospital acquired infection is suspected.
- If suspecting aspiration pneumonitis (form of chemical pneumonitis where toxic effects of gastric acids and enzymes induce lung tissue inflammation), use of CPAP or BiPAP reduces the need for mechanical ventilation. Consider administration of antibiotics if an infiltrate is present on chest X-ray and there is fever. Prophylactic antibiotic is not indicated in aspiration pneumonitis.
- Monitor clinical signs of cardiac output and tissue perfusion and support as necessary.

ACUTE LUNG INJURY AND ACUTE RESPIRATORY DISTRESS SYNDROME¹⁰⁻¹⁹

ALI/ARDS may follow pulmonary or nonpulmonary insults¹⁰ that injure the alveolar capillary unit and trigger release of inflammatory mediators. Pulmonary causes commonly found include pneumonia, pulmonary aspiration, pulmonary contusion, fat embolism, submersion injury, inhalational injury. Extra-pulmonary causes include sepsis, shock, burns, cardiopulmonary bypass, transfusion-related lung injury, severe trauma, pancreatitis, crush

injury, polytrauma, following upper airway obstruction, following bone marrow transplantation.

*American European Consensus Conference criteria*¹¹ for ALI/ARDS conditions are as follows: Acute onset, bilateral infiltrates of chest X-ray, $\text{PaO}_2/\text{FiO}_2 < 200$ regardless of PEEP for ARDS and < 300 for ALI, with no evidence for cardiogenic cause for pulmonary edema and no clinical evidence of left atrial hypertrophy or pulmonary artery occlusion pressure ≤ 18 mm Hg.

Early recognition and treatment of shock and respiratory failure may effectively minimize the process that precipitates ARDS.

Specific Ventilatory Goals and Other Supportive Management in ARDS¹²⁻¹⁹

Indications for ventilation include worsening clinical condition with worsening radiographic disease, hypoxemia refractory to high O_2 concentration. Use of cuffed ET tube to prevent glottic air leak is recommended.

Tidal volumes of > 10 ml/kg body weight should be avoided and target tidal volumes should be kept around 6 ml/kg. Adult trials have shown increased survival with lower tidal volumes (lung protective ventilation).

Recommended ventilation parameters are *plateau pressure* of less than 30 cm H_2O , *arterial pH* of 7.35 to 7.45, and *PaO_2* target of 55 to 80 mm Hg (*SpO_2* target 88–95%).

Permissive hypercapnia is a well accepted consequence of lung protective strategies of ventilatory support. Goals of management are to allow gradual increase in PaCO_2 , that is, no more than 5 mm Hg increase per hour, and to avoid acute severe acidosis. Permissive hypercapnia should be avoided in conditions where there is increased intracranial pressure or pulmonary hypertension.

High Frequency Oscillatory Ventilation¹³

HFOV is a form of ventilation in which very high rates are combined with extremely low tidal volumes. The mean airway pressure in HFOV is usually higher than with conventional mechanical ventilation (CMV). HFOV avoids the high peak inspiratory pressures and the tidal swings with each respiratory cycle seen in CMV. This technique is useful to recruit collapsed alveoli and to keep them open during the entire respiratory cycle.

HFOV should ideally be used earlier rather than later, before prolonged exposure to injurious levels of conventional ventilation (mean airway pressure > 20 –25 cm H_2O).

Supportive Care

Good supportive care is the key to improved outcomes. This includes close attention to fluid balance (avoid fluid overload), adequate suctioning, chest physiotherapy when required, proper sedation, analgesia (with neuromuscular blockade only when required), nutrition (enteral pre-

ferred), treatment of infection, prevention of skin ulcers and stress ulcer prophylaxis.

Hemoglobin concentration should be maintained within the normal range for age (> 10 g/dl) in children with profound hypoxia or shock, otherwise the hemoglobin transfusion threshold can be lowered to 7 g/dl in critically ill stable children.

Corticosteroids: The anti-inflammatory and anti-fibrotic properties of corticosteroids suggest that they might have a role in modulating the course of ARDS. The available clinical trials of prolonged glucocorticoid treatment show favourable effects on clinical outcomes, including ventilator-free days, ICU-free days, and mortality. However, the exact dose and duration of steroid therapy in children with ARDS are as yet undetermined.

In children with ALI *prone positioning* (20 hr/day for 7 days) showed improved oxygenation but no significant effects on either ventilator free days or survival.

Extracorporeal membrane oxygenation has been used as a rescue therapy for over two decades in children with ALI/ARDS, with reported survival rates of > 50 percent. Its use is not without risk, but it is a crucial consideration that can be life saving when patients fail traditional therapies for severe respiratory failure.

Inhaled nitric oxide is a potent pulmonary vasodilator and doses as low as 1ppm can improve oxygenation in ALI/ARDS. However, no survival benefit has been demonstrated.

Surfactant: A PALISI (*Pediatric Acute Lung Injury and Sepsis Investigators*) Network randomized trial of *Calfactant* in children with ALI/ARDS caused by direct forms of pulmonary injury showed improved oxygenation and decreased mortality but no improvements in the course of respiratory failure (ventilator days, hospital, or intensive care unit length of stay).

CONCLUSION

Management of acute respiratory failure and ARDS remains a challenge. Mortality in children with ARDS has fallen over the past two decades to approximately 30 percent now. The major reasons for this are overall improvements in the quality of intensive care and meticulous attention to the daily details of the patient, and the institution of lung protective ventilation. Even though a variety of newer technologies have become available, none have as yet proven to have a survival benefit.

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Newer Modes of Ventilation

Anil Sachdev, Sanjeev Kumar Arora

Newer ventilators can be set to modes other than the pressure-control and volume-control modes of older machines.¹ The alternative modes of ventilation were developed to prevent ventilator lung injury, patient-ventilator asynchrony, promote better oxygenation and faster weaning, and be easier to use. However, evidence of their benefit is scant. Until now, we have lacked a standard nomenclature for mechanical ventilation, leading to confusion. Regardless of the mode used, the goals are to avoid lung injury, keep the patient comfortable, and wean the patient from mechanical ventilation as soon as possible.^{1,2} In this article, we review several of these alternative modes (APC, ASV, PAV, APRV, biphasic PAP, MMV, and HFOV), explaining how they work and contrasting their theoretical benefits and the actual evidence of benefit (Flow chart 1).

Pressure Regulated Volume Control

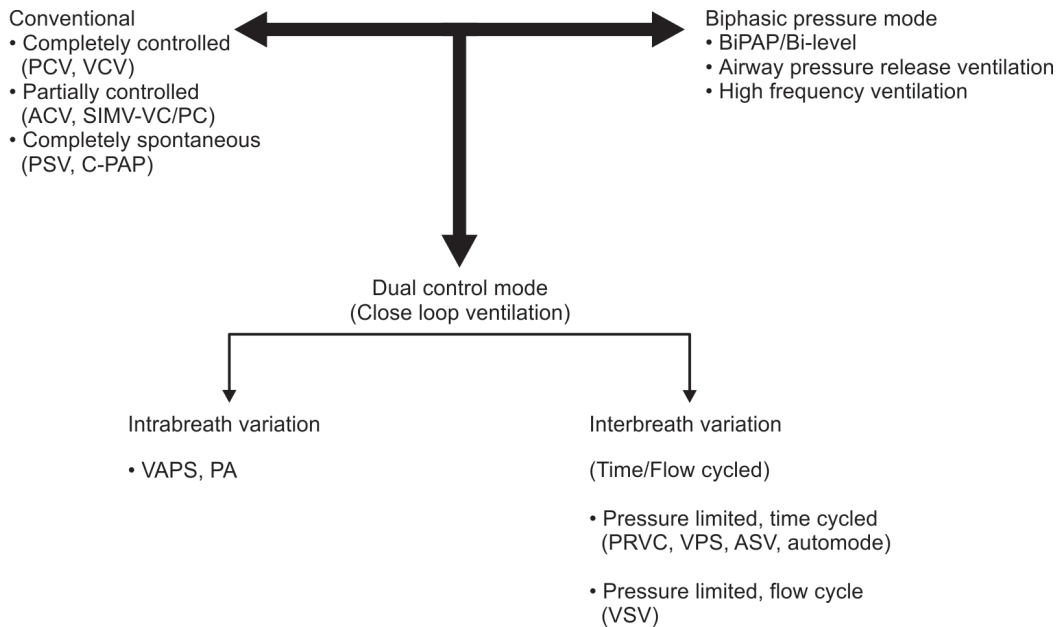
Pressure regulated volume control (PRVC) ventilation is an example of a dual control ventilation mode, also known as hybrid modes of ventilation. This mode is a form of closed loop ventilation that has combined the features of volume and pressure ventilation. First introduced on the Servo 300 ventilator, it is now available on most modern ventilators under different names, e.g. Autoflow (Dräger Evita), Volume guarantee (Datex- Ohmeda, Dräger Babylog), Adaptive pressure ventilation (Hamilton Galileo), Variable pressure control (Venturi).³

This dual mode combines the benefits of decelerating flow of pressure controlled ventilation with the safety of a volume guarantee. In essence, the clinician sets a target tidal volume and maximal pressure level. The ventilator attempts to achieve the volume target using a pressure-control gas-delivery format at the lowest possible airway pressure. This is achieved by altering the peak flow and inspiratory time breath-to-breath in response to changing airway resistance

or compliance characteristics. PRVC breaths have a variable decelerating flow pattern. The breaths are time-cycled. During PRVC, the pressure and volume are regulated. All breaths are volume targeted, with pressure adjusted to reach that volume target. PRVC often incorporates a “compliance curve” that is developed within the ventilator computer, as it gives several initial breaths at varying tidal volumes that increase incrementally up to the set value (Flow chart 2). From this information, the ventilator computes the pressure target required to deliver the desired tidal volume.⁴

When activated, the first delivered breath is a “test breath” at some minimal pressure level (5–10 cm H₂O), along with an inspiratory “hold” maneuver, which is used to calculate patient compliance. The program in the ventilator then determines the plateau pressure required to achieve the desired tidal volume. The next few breaths may be delivered at a pressure below the calculated pressure needed to deliver the target tidal volume as a further test. This is also done anytime ventilation has been interrupted, (opening the ventilator circuit, suctioning, etc.) Using this information, the calculated pressure is applied to deliver breaths (Flow chart 2).

Depending on the respiratory system compliance, the pressure associated with the tidal breath can vary over time. If the tidal volume is exceeded, the pressure limit is decreased by 1 to 3 cm H₂O on each breath until the target tidal volume is reached. Similarly, if the volume is low, pressure is increased by 1 to 3 cm H₂O on each breath until the target volume is met. The pressure required to ensure the volume breath can be increased up to a maximum of within 5 mmHg of the set pressure alarm limit.¹⁻³ Thus, specific tidal volume and minute ventilation is assured, while pressure-induced lung damage is minimized. The duration of inspiration is determined by the respiratory rate and the I:E ratio or inspiratory time (i.e.

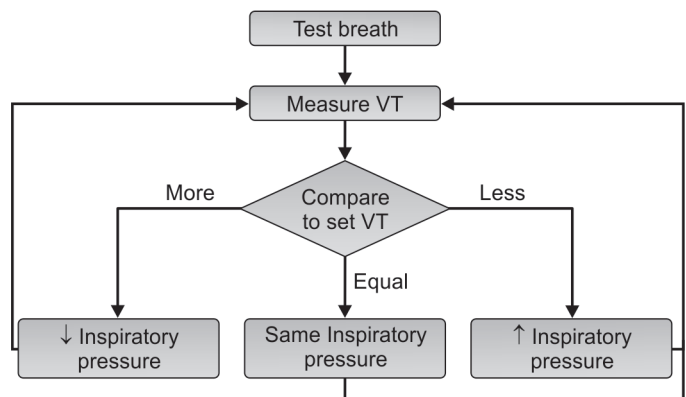
Flow chart 1: Classification of mode of ventilation^{1,2}

PCV- Pressure control ventilation, VCV- Volume control ventilation, ACV- Assist control ventilation, SIMV- Synchronized intermittent mandatory ventilation, PSV- Pressure support ventilation, CPAP- Continuous positive airway pressure, BiPAP- Bi-level Positive airway pressure, PRVC- Pressure regulated volume control, ASV- Assist control ventilation, VAPS- Volume assured pressure support, PAV- Proportional assist ventilation, NAVA- Neurally adjusted ventilatory assist, PA- Pressure augmentation, VSV- Volume support ventilation.

this is a time-cycled mode of ventilation). In the Siemens 300 ventilator, PRVC is only active during CMV whereas in other ventilators, this type of dual-control mode is also active in SIMV. The proposed advantage of this mode is a constant tidal volume with automatic weaning of the pressure limit as the patient's compliance improves.³⁻⁵

Initial settings: Ventilatory setting will depend on type and severity of disease.⁴

- Respiratory rate—physiological for age
- If patient's spontaneous respiratory rate is less than set rate, then ventilator gives additional control breaths to make up difference, whereas if patient's spontaneous rate > set rate, no control breaths are provided
- Target tidal volume—initial setting: 6-8 ml/kg predicted body weight
- Upper pressure limit—since ventilator delivers pressure of up to 5 cm H₂O below upper pressure alarm limit set to 35 to 40 cm H₂O to ensure "safe" pressures.
- Inspired oxygen concentration—initial setting 100 percent
- I:E ratio- initial setting: 1:2 (inspiratory time of 33%)
- PEEP—initial setting 5 to 10 cm H₂O

Flow chart 2 : Breath to breath pressure adjustments to deliver target tidal volume

- Rise time—5 percent of inspiratory time usually satisfactory.

PRVC is one of the recommended modes of ventilation in patients with acute lung injury (ALI)/acute respiratory distress syndrome (ARDS).³ During ARDS if volume control ventilation is used, higher peak inspiratory pressures would be required to ensure delivery of set tidal volume. Conventional ventilation may lead to over distention of the normally functioning lung while expanding collapsed parts. Thus, mechanical ventilation may exacerbate the pulmonary pathology and/or delay recovery. In two studies of patients with ARDS, it was concluded that survival is better when high ventilation pressures are avoided. In another study Sachdev et al⁵ comparing PRVC and volume control ventilation in two groups of children with acute lung diseases concluded that significantly lower

mean airway pressure was required to improve oxygenation parameters in PRVC group. A study by Guldager et al⁶ showed the advantage of using the PRVC mode for ventilation during acute respiratory failure. In this study, PIP was lower for all patients using the PRVC mode compared to the VC mode, (statistically significant difference in peak pressures of 4 cm H₂O) and alveolar ventilation was unchanged as indicated by the constant PaCO₂. They concluded that though this difference in peak pressure is small, it may be more relevant in situations where larger tidal volumes are contemplated. D'Angio et al⁷ in a study comparing synchronized intermittent mandatory ventilation versus PRVC found no differences in time to extubation or pulmonary outcomes. Piotrowski et al⁸ also found in a study comparing intermittent mandatory ventilation versus PRVC in neonates with RDS that there was no decrease in duration of mechanical ventilation or incidence of bronchopulmonary dysplasia. Kallet et al⁹ also found that during lung-protective ventilation, PRVC offered no advantage in reducing work of breathing, compared to volume controlled ventilation with a high flow rate, and in some patients did not allow control of tidal volume to be as precise as expected. But some other small studies have found that PRVC resulted in faster weaning.¹⁰

Advantages

It "guarantees" tidal volume with minimum risk of barotraumas and decelerating flow pattern, that provides better distribution of ventilation and oxygenation.^{3,4}

Disadvantages

In this mode, pressure delivery to achieve target tidal volume will depend on the character of previous breath. If patient makes intermittently significant inspiratory effort, it can result in variable tidal volume.

To conclude, PRVC is a new dual mode of ventilation that is becoming increasingly popular as it offers advantages of both target volume ventilation with pressure control, but specific studies on whether it allows for easier, faster weaning, better patient comfort or improved outcomes, are currently conflicting and need to be explored further.

Airway Pressure Release Ventilation

Airway pressure release ventilation (APRV) is a mode of ventilation that was described in 1987 by Stock et al.¹¹ It has gained popularity recently due to the decreased need of sedation and neuromuscular blockade while using this mode of ventilation. It has also been identified as safe mode of ventilation for ARDS and ALI.³ APRV has also been shown to facilitate spontaneous breathing, decrease peak airway pressures, and improve oxygenation and ventilation compared to other modes of ventilation. (Table 1)¹² It has been described as continuous positive pressure ventilation

(CPAP) with intermittent, regular and brief release of pressure. The release phase results in alveolar ventilation and removal of carbon dioxide (CO₂). Airway pressure release ventilation, unlike CPAP, facilitates both oxygenation and CO₂ clearance and originally was described as an improved method of ventilatory support in the presence of acute lung injury (ALI) and inadequate CO₂ ventilation.^{11,12} Technically, APRV is a time-triggered, pressure-limited, time-cycled mode of mechanical ventilation.

Physiological Effects

Oxygenation is better with APRV with spontaneous breathing than with mechanical ventilation alone. This effect is at least attributable to recruitment of collapsed lung tissue and increased aeration in dependant areas of lung. Putensen et al¹⁴ showed improved ventilation perfusion matching and increased systemic flow in APRV with spontaneous breathing. APRV with spontaneous breathing increased ventilation in the juxta-diaphragmatic regions, predominantly in the dependent areas. Spontaneous breathing had a significant effect on the spatial distribution of ventilation and pulmonary perfusion. It has been shown to improve cardiac output, renal blood flow, glomerular filtration, and achieve high mean airway pressure with low peak airway pressure. APRV was associated with increases in lung compliance and oxygenation and reduction of shunting (Fig. 1).¹⁰

Initial Ventilator Settings^{15,16}

There are 4 commonly used terms in APRV: pressure high (P high), pressure low (P low), time high (T high), and time low (T low) (Flow chart 1).

P high: It is the baseline airway pressure and is higher of the two airway pressure. Initial P high is kept same as plateau pressure measured on volume control mode provided it is lower than 30 cm H₂O.

P low: It is the airway pressure level resulting from pressure release. Other authors have described P low as the PEEP level, the release pressure, or the P₂ pressure. It is usually set at 0 cm of H₂O.

T high: It is the time during which P high is maintained. It is set at 3 to 4 sec. then adjusted if necessary.

T low: It is the time for which P low is held or pressure is released. It is probably the most difficult variable to set because it needs to be short enough to avoid de-recruitment but still long enough to allow alveolar ventilation. It is usually set at 0.6 to 0.8 seconds.

Adjustments

- **Hypoxemia:** Adjust these ventilator settings to improve oxygenation
 - Increase pressure gradient (P high minus P low) — increase P high by 2 to 5 cm H₂O.

Table 1: Summary of advantages and disadvantages of airway pressure release ventilation¹¹⁻¹⁶

Advantages	Disadvantages
High MAP with low peak pressure	Pressure targeted mode, variable tidal volume delivery
Maintain normal cyclic decrease in pleural pressure	CO ₂ elimination depends on spontaneous breaths
Allow inverse ratio ventilation, increases oxygen delivery	Increase in airway resistance hampers CO ₂ elimination
Augment venous return, increases cardiac index	Increase work of breathing with asynchrony between spontaneous and pressure release breathe
Reduces need for sedation/paralysis	Not useful in large bronchopleural fistula and raise intracranial pressure
Improves renal perfusion, increase osmolar clearance, increases urine output	Limited experience
Decreased basal atelectasis, may decrease dead space	Auto-PEEP is usually present, contraindicated in high expiratory resistance
Improve patient ventilatory synchrony with spontaneous respiration	

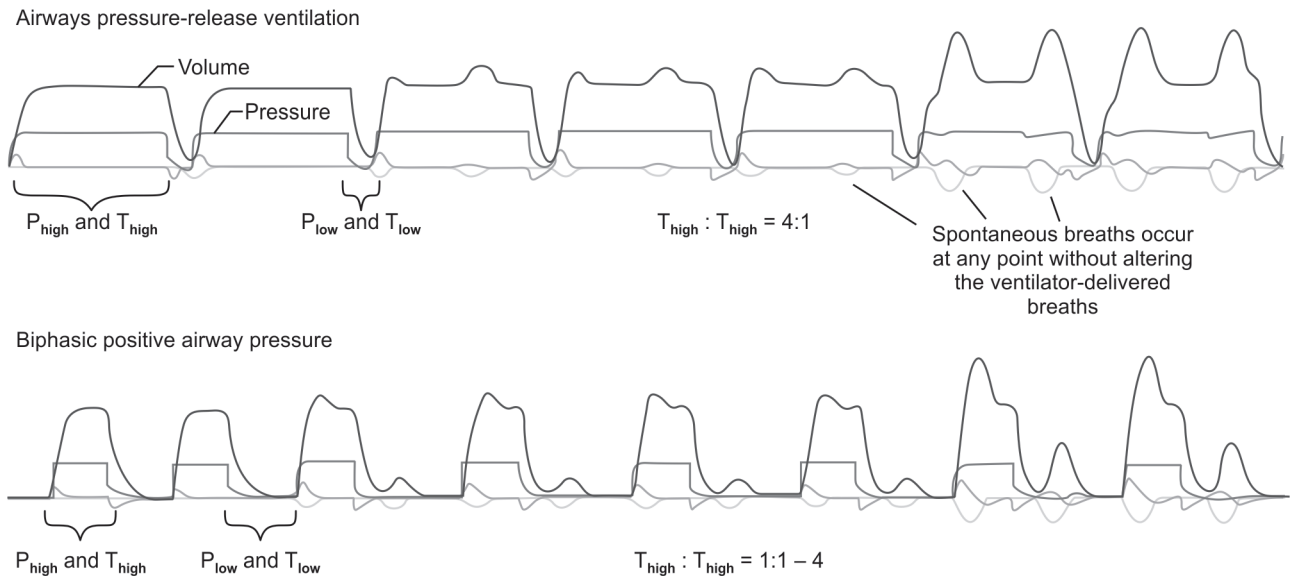


Fig. 1: Differences between APRV and biphasic positive airway pressure modes. APRV (top) and biphasic positive airway pressure (bottom) are forms of pressure controlled intermittent mandatory ventilation in which spontaneous breaths can occur at any point without altering the ventilator-delivered breaths. The difference is that the time spent in high pressure is greater in airway pressure-release ventilation¹³

- Airway pressure release frequency = 60/cycle time (T_{high} + T_{low}) - decrease frequency of pressure release (prolong T_{high} by 0.5–1 sec) (if T_{low} remains constant)
- Increase FiO₂
- **Hypercapnia:** Adjust these ventilator settings to relieve hypercapnia
 - Tolerate “permissive hypercapnia” (pH ≤ 7.15).
 - Reduce T_{high} by 0.5 to 1 sec; it may affect recruitment by lowering the P_{aw}.

Volume Support Ventilation

In volume support ventilation (VSV) patient triggers every breath. Ventilator automatically adjusts the inspiratory pressure to ensure the lowest possible inspiratory pressure to deliver the preset tidal volume. Tidal volume is used as feedback control to adjust the pressure support level.

Inspiratory pressure is maintained constant during inspiration. Inspiratory flow is decelerating. Patient determines the breathing rate and the inspiratory time.^{3,4} If there is apnea, there is automatic back-up with PRVC mode of ventilation. Inspiration stops and expiration starts when the peak flow drops to 5 to 15 percent of initial flow (Fig. 2). As the upper pressure limit is reached, the ventilator immediately changes to expiration and gives alarm for “high airway” pressure. If the difference between the upper pressures limit and peak airway pressure is less than 5 cm of H₂O, a “limited pressure” alarm is given. The tidal volume delivered will be less than the preset. Maximum inspiratory time is 80 percent of the respiratory cycle. VSV indicated in postoperative patient recovering from anesthesia, spontaneous breathing patient who requires minimum tidal volume, patients who are asynchronous with the ventilator, and as a weaning mode especially in

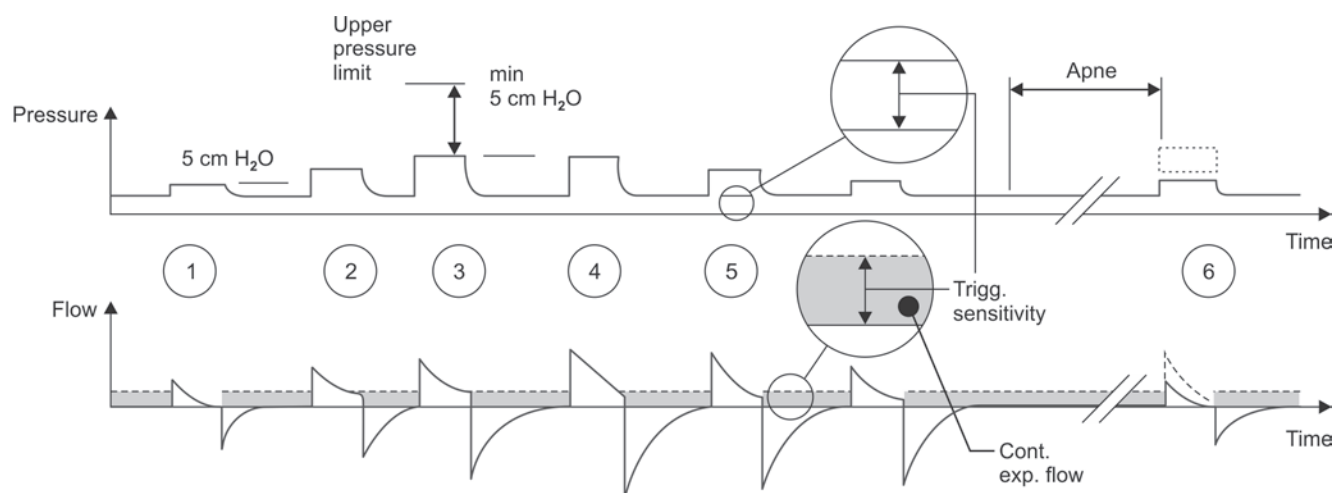


Fig. 2: Breath-to-breath analysis of patient in pressure time and flow time waveform with volume support ventilation¹⁷

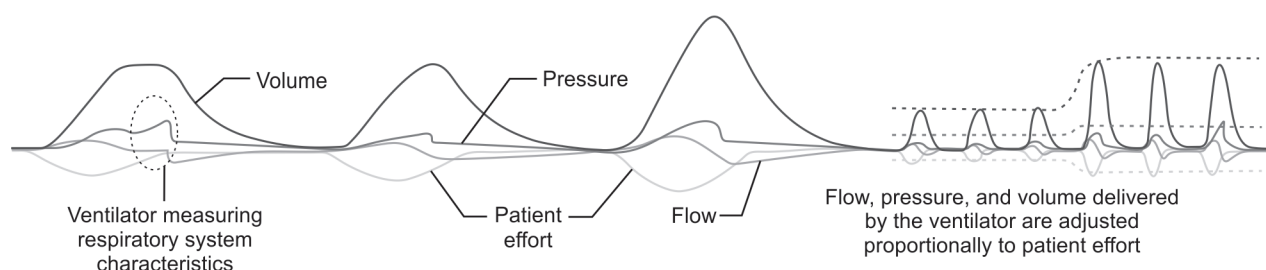


Fig. 3: Volume delivery adjusted proportionally to the patient's effort in PAV mode.

patient with neuromuscular weakness. Volume support is a PRVC-like modification of pressure support. The difference between this and PRVC is the difference between PCV and PS—volume support is flow-cycled.¹⁷

- Test breath (5 cm H₂O)
- Pressure is increased slowly until target volume is achieved
- Maximum available pressure is 5 cm H₂O below upper pressure limit
- VT higher than set VT delivered results in lower pressure
- Patient can trigger breath
- If apnea, ventilator switches to PRVC (automode).

Advantages: Automatic weaning of pressure support as tidal volume matches minimum required tidal volume.

Disadvantages: Sustain spontaneous effort required, tidal volume selected may be too large or small for patient, auto-PEEP may affect proper functioning, varying mean airway pressure with each breath, sudden increase in respiratory rate and demand may result in a decrease in ventilator support.

Proportional Assist Ventilation

Patients who have normal respiratory drive but who have difficulty in sustaining adequate spontaneous ventilation

are often subjected to pressure support ventilation (PSV), in which the ventilator generates a constant pressure throughout inspiration regardless of the intensity of the patient's effort (Fig. 3). In 1992, Younes and colleagues developed proportional assist ventilation (PAV) as an alternative in which the ventilator generates pressure in proportion to the patient's effort. PAV became commercially available in Europe in 1999 and was approved in the United States in 2006, available on the Puritan Bennett 840 ventilator. PAV has also been used for noninvasive ventilation. Other names for PAV are Proportional Pressure Support (Dräger Medical).¹⁸

Both PSV and PAV are spontaneous modes. The patient controls the timing and size of the breath. There are no preset pressures, flow, or volume goals, but safety limits on the volume and pressure delivered can be set. With PSV, the pressure applied by the ventilator rises to a preset level that is held constant until a cycling criterion is reached. The inspiratory flow and tidal volume are the result of the patient's inspiratory effort, the level of pressure applied, and the respiratory system mechanics. In contrast, during PAV, the pressure applied is a function of patient effort—the greater the inspiratory effort, the greater the increase in applied pressure. The operator sets the percentage of support to be delivered by the ventilator.

The ventilator intermittently measures the compliance and resistance of the patient's respiratory system and the instantaneous patient-generated flow and volume, and on the basis of these it delivers a proportional amount of inspiratory pressure.

Ventilator Settings in PAV

- Airway type (endotracheal tube, tracheostomy)
- Airway size (inner diameter)
- Percentage of work supported (assist range 5–95%)
- Tidal volume and pressure limit
- Expiratory sensitivity (normally, as inspiration ends, flow should stop; this parameter tells the ventilator at what flow to end inspiration).

Advantages

In theory, PAV should reduce the work of breathing, improve synchrony, automatically adapt to changing patient lung mechanics and effort, decrease the need for ventilator intervention and manipulation, decrease the need for sedation, and improve sleep. The probability of

spontaneous breathing without assistance was significantly better in critically ill patients ventilated with PAV than with PSV.¹⁸ No trial has reported the effect of PAV on deaths.¹⁹

Volume Assured Pressure Support

VASP is also based on closed loop ventilation but in this mode intrabreath variation is present rather than inter-breath variation. It means character of breath changes within the breath from pressure control to volume control if minimum tidal volume has not been achieved. It combines high initial flow of pressure-limited breath with a constant volume delivery of volume-limited breath within same breath. In this mode ventilator use both type of breaths (Pressure and volume limited) within the same breath to achieve target minimum tidal volume. Type of breath will depends on the adequacy of the patient's effort. If patient had adequate respiratory effort, then pressure supported breath will be delivered. If patient had inadequate respiratory effort, then controlled breath (flow targeted and volume cycled) will be delivered rather than pressure supported (Fig. 4).^{3,4}

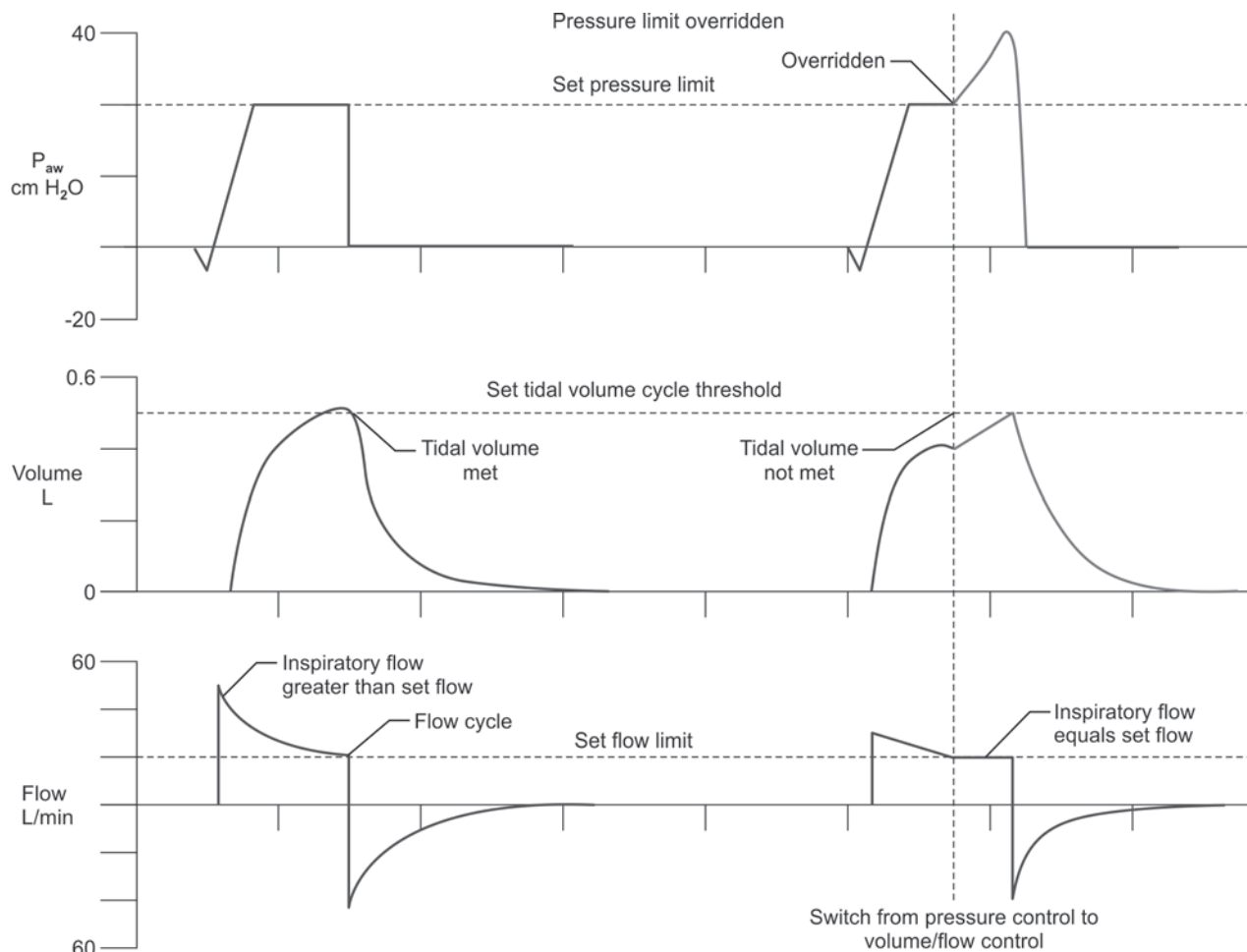


Fig. 4: Pressure, volume and flow time waveforms in VASP mode showing change in mode of ventilation within same breath to achieve target minimum tidal volume²⁰

Table 2: Comparisons between different modes of ventilation^{3, 4, 20}

<i>Pressure regulated volume control</i>	<i>Volume support ventilation</i>	<i>Volume assured pressure support</i>
Interbreath variation	Interbreath variation	Intrabreath variation
Use the set tidal volume as the “target” for each breath	Use the set tidal volume as the “target” for each breath	Use the set TV as a minimum
Normal cycling may stop inspiration below or above set tidal volume	Normal cycling starts when the peak flow drops to 5–15% of initial flow	Normal cycling occurs at or above the set tidal volume
Pressure used based on mechanics measurements	If inspiratory demand decreases, ventilator can increase up to 150% of set tidal volume in next breath by increasing inspiratory pressure up to a limit	Character of breath changed within the breath from pressure control to volume control if minimum tidal volume has not been achieved
	Tidal volume/pressure mechanics measured	Tidal volume mechanics not measured

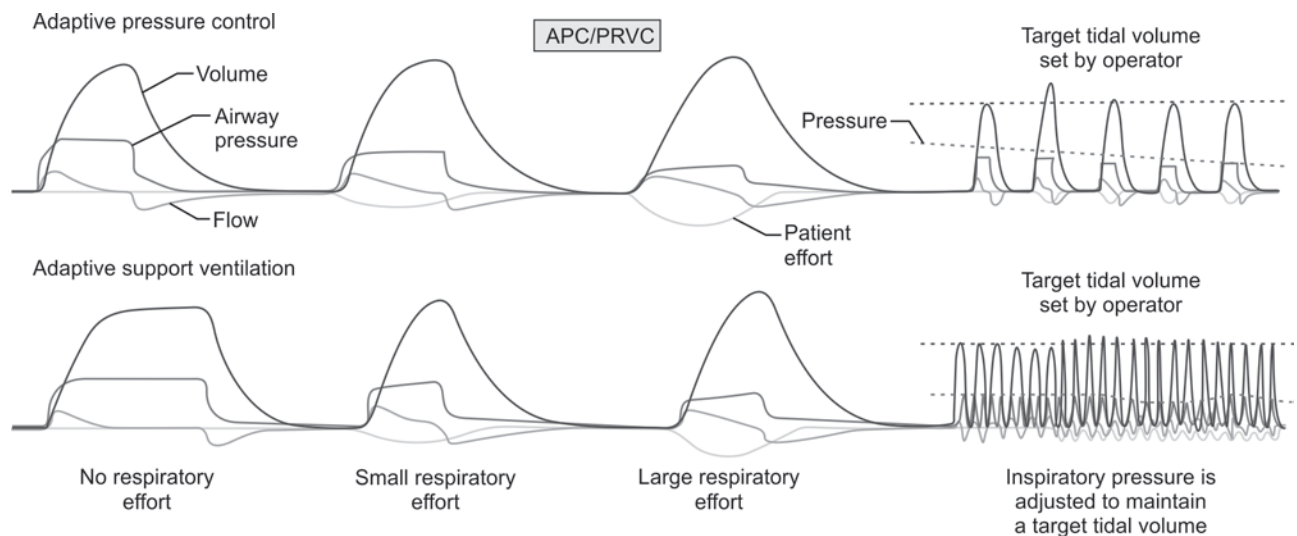


Fig. 5: Differences between PRVC (APC) and ASV mode. Adaptive support ventilation (bottom) automatically selects the appropriate tidal volume and frequency for mandatory breaths and the appropriate tidal volume for spontaneous breaths on the basis of the respiratory system mechanics and the target minute ventilation^{21,22}

Advantages

Patient will receive minimum pressure support and peak flow to achieve minimum tidal volume. Decrease work of breathing in comparisons to conventional ventilation (Table 2).

Adaptive Support Ventilation

Adaptive support ventilation (ASV) is a positive pressure mode of mechanical ventilation that is closed-loop controlled. ASV evolved as a form of mandatory minute ventilation implemented with adaptive pressure control. Mandatory minute ventilation is a mode that allows the operator to preset target minute ventilation, and the ventilator then supplies mandatory breaths, either volume- or pressure-controlled, if the patient's spontaneous breaths generate a lower minute ventilation. ASV automatically selects the appropriate tidal volume and frequency for mandatory

breaths and the appropriate tidal volume for spontaneous breaths on the basis of the respiratory system mechanics and target minute alveolar ventilation. In the ASV mode, every breath is synchronized with patient effort if such an effort exists, and otherwise, full mechanical ventilation is provided to the patient. Targeted tidal volume will be given as pressure control or pressure support breaths (Fig. 5).²¹

Initial ventilatory settings: It is first commercially available mode that automatically selects all the ventilator settings except PEEP and FiO₂.

- Sex and height (to calculate the ideal body weight)
- Percent of normal predicted minute ventilation goal. Delivers 200 ml/min/kg of minute ventilation for children. It can be set from 20 to 200 percent.
- FiO₂ and PEEP
- *High-pressure alarm:* 5 cm H₂O above PEEP to 10 cm H₂O below set P max.

Advantages

It provides decelerating flow waveform to improved gas distribution with guaranteed tidal volume. It also decreases work of breathing. Automatic weaning is possible with disease reversal.

Mandatory Minute Ventilation

Mandatory minute ventilation (MMV) was first described by Hewlett et al in 1977. MMV is the first closed loop mode which simply means that the ventilator changes its output based on measured input variables. This mode allows the patient to breathe spontaneously with guaranteed minimum minute ventilation preset by clinician. This can be accomplished by the use of increasing levels of pressure support or by delivery of mandatory breaths (time triggered, volume controlled). If spontaneous breathing is used, breaths are pressure controlled; pressure, flow or volume triggered; pressure limited; and flow cycled. Essentially the patient is receiving pressure support ventilation with varying pressure support level. In contrast to SIMV, MMV gives mandatory breaths only if spontaneous breathing has fallen below pre-selected minimum ventilation.²³

Advantages

Major difference with SIMV mode is that it decreases mechanical breaths and it may reduce some long-term complications associated with mechanical ventilation.

Neurally Adjusted Ventilatory Assist (NAVA)

It is a unique mode of ventilation which is based on neural respiratory output. The act of taking a breath is controlled by the respiratory center in the brain, which decides the characteristics of each breath, timing and size. The respiratory center sends a signal along the phrenic nerve, excites the diaphragm muscle cells, leading to muscle contraction and descent of the diaphragm dome. As a result, the pressure in the airway drops, causing an inflow of air into the lungs. With NAVA, the electrical activity of the diaphragm (Edi) is captured, fed to the ventilator and used to assist the patient's breathing in synchrony with and in proportion to the patient's own efforts, regardless of patient category or size. As the work of the ventilator and the diaphragm is controlled by the same signal, coupling between the diaphragm and the ventilator is synchronized simultaneously. As the work of breathing increases and the respiratory center asks the diaphragm for more effort, the neurally controlled system increases the amount of ventilator support.^{24,25}

Automode

This mode design to allow the ventilator to be interactive with the patient's needs by making breath-by-breath adjustments in both control and support modes. In the absence of triggering, the machine functions in a control

mode. When the patient begins to make satisfactory inspiratory efforts (two consecutive triggered breaths), the ventilator switches to the support mode. All breaths are patient triggered, pressure limited, and flow cycled. A switching of modes is indicated by a blinking light. Ventilator automatically shifts between controlled, supported, and spontaneous ventilation as required. When patient was shifted from time cycled to flow cycled ventilation, which can lead to decrease in mean airway pressure and hypoxemia.²⁶

High Frequency Oscillatory Ventilation (HFOV)

Different modes are available in high-frequency ventilation. Here we will discuss only high-frequency oscillatory ventilation (HFOV), which is most commonly used.¹¹ HFOV is a form of pressure controlled intermittent mandatory ventilation. In contrast to conventional pressure-controlled intermittent mandatory ventilation, in which relatively small spontaneous breaths may be superimposed on relatively large mandatory breaths, HFOV superimposes very small mandatory breaths (oscillations) on top of spontaneous breaths (Fig. 6). HFOV can be delivered only with a special ventilator. The ventilator delivers a constant flow (bias flow), while a valve creates resistance to maintain airway pressure, on top of which a piston pump oscillates at frequencies of 3 to 15 Hz. This creates a constant airway pressure with small oscillations. For appropriate amplitude settings "chest wiggle factor" is assessed clinically.²⁷

It is an attractive mode of ventilation because of its unique ability to provide adequate gas exchange using tidal volumes below dead-space volume in the setting of continuous alveolar recruitment. Theoretically, HFOV should provide the ultimate open-lung strategy of ventilation, with preservation of end expiratory lung volume (EELV), minimization of cyclic stretch, and avoidance of parenchymal over distension at end-inspiration, amounting to ventilation on the most compliant portion of the volume-pressure curve while avoiding extremes of lung volume. Oxygenation is achieved with high mean airway pressure to achieve lung recruitment and ventilation is achieved with an oscillating piston that creates cycles of pressure above and below the mean airway pressure at a supraphysiologic respiratory rates (180–900/min), resulting in small tidal volumes (1–2.5 ml/kg). Exhalation is active rather than passive process as occurs in all other conventional and high frequency mode. In this mode control of oxygenation and ventilation are independent.^{27,28} The initial ventilatory settings in HFOV depend on age, type and severity of the disease (Table 3).
Ti- Inspiratory time, Hz- Hertz, Paw/Map- Mean airway pressure.

Adjustment: After initial ventilator settings, the oxygenation and ventilation are adjusted independently. Mean airway pressure is adjusted to achieve $\text{SaO}_2 > 90$ percent, while CO_2 elimination is increased by adjusting the amplitude and decreasing frequency on machine.^{2,27,28}

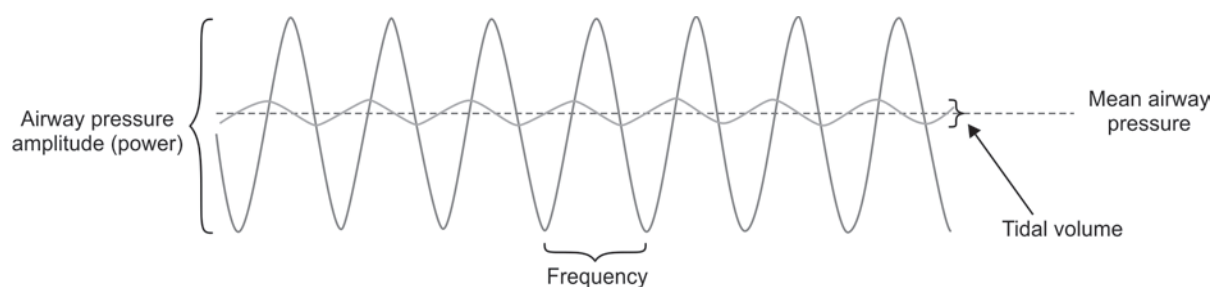


Fig. 6: High-frequency oscillatory ventilation delivers very small mandatory breaths (oscillations) at frequencies of up to 900 breaths per minute

Table 3: Initial ventilator settings in HFOV

	FiO_2	Bias flow	Ti	Hz	P_{aw}	Power
Neonate (not preterm)	1.0	20 L/min	33%	13–12		0–2
< 10 kg	1.0	20 L/min	33%	12–10	3–5 cm above	0–4
10 – 30 kg	1.0	20–30 L/min	33%	12–8	CMV P_{aw}	4
> 30 kg	1.0	≥ 30 L/min	33–(50)%	6		4–6

Weaning

- Decrease FiO_2 , MAP, and amplitude
- Switch to conventional ventilation when
 - Reversal of disease process
 - Adequate gas exchange and improving oxygenation indices
 - MAP < 15 (12–18 cm H₂O)
 - FiO_2 < 0.5 (0.4–0.6)

HFOV should not be used in patients with shock, severe airway obstruction, intracranial hemorrhage, or refractory barotraumas. It must be used cautiously with severe acidosis, because CO₂ excretion may be limited. Different studies have found no differences in survival or duration of mechanical ventilation between the 2 groups while comparing conventional and HFOV, but few children who receive HFOV remained dependent on supplemental O₂ at 30 days. It has been suggested that HFOV should be employed early in the course of severe ARDS.²⁸

CONCLUSION

Regardless of the mode, our goals are to avoid lung injury, keep the patient comfortable, and wean the patient from mechanical ventilation as soon as possible. Conventional modes are passive and operator dependant, but newer modes are adaptively interactive, goal oriented and patient centred. Further clinical trials are needed to make a recommendation for various modes of ventilation according to disease and patient status.

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CHAPTER 100

Acute Asthma and Asthma Like Conditions in Emergency

Kundan Mittal

Twelve year girl child came in accident and emergency department with history of cough and cold three days and shortness of breath 2 days. She is conscious but anxious looking and her respiratory rate is 36/min with intercostal retraction and heart rate 120/min with pulsus paradox. Auscultation of chest revealed decreased air entry associated with diffuse expiratory wheeze and oxygen saturation of 90 percent in room air. She was on inhaled salbutamol and steroid. There is history of similar episodes in past and snoring during sleep. There is also history of hospitalization in the past in PICU and required ventilatory support. There is family history of atopy in mother and father has taken treatment for tuberculosis 2 years back.

- Would you consider it acute exacerbation of asthma?
- Does this child require admission in Emergency Department or PICU?
- What is the modality of treatment of asthma in emergency department?
- How will you differentiate from other conditions that mimic asthma?
- Role of NIV versus invasive mechanical ventilation.

Asthma is a chronic inflammatory disorder of the lung airways characterized by an obstruction of airflow, which may be completely or partially reversed with or without specific therapy. Airway inflammation is associated with airway hyper-reactivity or bronchial hyper-responsiveness, which is defined as the inherent tendency of the airways to narrow in response to various stimuli. It nearly affects 300 million people annually. The diagnosis of asthma is primarily made on the basis of clinical history, physical examination, and lung function test. There is no gold standard test to diagnose asthma. We have to understand that all wheezes are not asthma. The condition has to be differentiated from following conditions to avoid wrong management at different stages of life.

Conditions which mimic asthma at various stage of life:

- Left heart failure
- Foreign body
- Aspiration syndromes
- Endobronchial tuberculosis
- Obliterative bronchiolitis
- Tracheal stenosis
- Cystic fibrosis
- Bronchopulmonary dysplasia
- Neuromuscular diseases
- Pulmonary embolism
- Prematurity in neonates
- Ciliary dyskinesia
- Gastroesophageal reflux
- Hyperventilation syndrome
- Recurrent viral infections of lower airway
- Pneumothorax
- Viral pneumonias
- Aspiration pneumonia, bronchiolitis and viral pneumonias in smaller children.

Acute severe asthma is life-threatening problem.

Classification of Severe Asthma

- *Acute severe asthma*: PEFR 33 to 50 percent of predicted best, RR >25/min, HR >110/min
- *Life threatening asthma*: PEFR <33 percent, SpO₂ <90 percent, PaO₂ <8pKa, silent chest, bradycardia or hypotension, cyanosis and poor respiratory efforts
- *Near fatal asthma*: Rising CO₂ level and requiring mechanical ventilation

Arterial blood gas marker of acute severe asthma are normal or increased pCO₂, hypoxia PaO₂ <60 despite oxygen therapy and low pH.

Factors that Exacerbate Acute Asthma

- Infections mostly viral
- Smoke
- Weather
- Cold room
- Pollution
- Allergens
- Drugs
- Noncompliance of drug therapy
- Features suggestive of asthma
- Previous history of hospitalization.

Management of Acute Exacerbation of Asthma

Goals of management are to relieve hypoxemia, airflow obstruction and preventing further progression.

- Admit patient in emergency department and attach vital sign monitor
- Start oxygen therapy (40–60%) with face mask/non-rebreathing mask targeting oxygen saturation >92 percent
- Oxygen driven nebulization with salbutamol 0.15 mg/kg minimum 2.5 mg dissolved in 3 ml saline every 20 minutes for three doses or 2 to 8 puffs of MDI (spacer and or mask as per need) and repeat up to three times and monitor for response
- If poor response or no response start nebulized salbutamol 0.15 to 0.3 mg/kg 1 to 4 hour or 0.5 mg/kg/hr as continuous nebulization and monitor response to therapy or one can use MDI as above
- Levo-salbutamol may also be used in place of salbutamol 0.075 mg/kg (1.25 mg) up to three doses followed by 0.075 to 0.15 mg/kg 1 to 4 hour or 0.25 mg/kg/hour for continuous nebulization
- Short course of steroids for 3 to 7 days prednisolone 0.5 to 1.0 mg/kg 6 to 12 hour for 48 hour and later 1 to 2 mg/kg for 3 to 7 days
- Adrenaline or terbutaline may also be used SC/IM
- If no response to therapy intravenous magnesium sulphate should be given
- Intravenous aminophylline may also be used.

If no response to treatment one may try noninvasive ventilation in BIPAP mode. If patient is hemodynamically unstable, unable to protect airway, or unconscious non-invasive ventilation should not be used. If oxygenation is issue increase IPAP and EPAP in increment of 2 and see the response and perform acid base analysis after 30 minutes. If ventilation is a concern increase IPAP in increment of 2.

Indications of Mechanical Ventilation

- Severe respiratory distress
- Potential respiratory failure
- Poor response to treatment
- Hypoxia $\text{PaO}_2 < 60$ mm Hg
- Hypercarbia
- Exhaustion
- Coma
- Hemodynamic instability.

Ventilatory Settings

- *Mode*: Volume control, A/CMV some may prefer dual mode (volume and pressure)
- *Tidal Volume*: 6 to 8 ml/kg (permissive hypercapnia is acceptable)
- *Rate*: Less than physiological rate
- *I:E ratio*: 1:3
- *Flow*: High
- *Pplat*: <30 to 35 mm
- *FiO₂*: Target oxygen saturation >92 percent
- Set alarm limits
- *Monitor*: PIP/Pplat, resistance, compliance
- *Sedation*: Ketamine and benzodiazepines.

Complications of Severe Asthma

- Aspiration pneumonia
- Pneumothorax
- Pneumomediastinum
- Hypoxic brain injury
- Respiratory failure
- Rhabdomyolysis.

Pediatric Septic Shock: Guidelines and Beyond

Praveen Khilnani

Pediatric sepsis is a commonly encountered global issue with serious consequences of multiple organ failure and high mortality.¹⁻⁴ Existing guidelines for sepsis seem to be applicable to the developed countries.² An expert representative panel drawn from all over India, under aegis of Intensive Care Chapter of Indian Academy of Pediatrics (IAP) met to discuss and draw guidelines for clinical practice and feasibility of delivery of care in the early hours in pediatric patient with sepsis, keeping in view unique patient population and limited availability of equipment and resources.

Besides factors such as limited resources, lack of equipment, trained personnel, lack of awareness, treatment delay, late arrival to medical facility occurs frequently due to inadequate critical care transport services⁵, mostly rural infrastructure, and traffic congestion. A significant number of children with sepsis are malnourished who tend to be sicker,⁶ and there are concerns about the adverse effects of aggressive fluid therapy in these children. The current WHO guidelines on the management of severe malnutrition have recommended small fluid boluses and thereafter use of blood transfusion.⁷ Free availability and rampant misuse of broad spectrum antimicrobials makes it even more challenging to treat sepsis with emerging drug-resistant organisms.

In this chapter management of sepsis in pediatric age group is discussed. Standard accepted pediatric sepsis definitions (2005)⁵ are described followed by currently accepted evidence based guidelines to treat sepsis in children. Finally controversial and newer therapies will also be discussed.

Sepsis definitions: Definitions of sepsis based on International Consensus Conference 2005⁸ are presented as follows:

SYSTEMIC INFLAMMATORY RESPONSE SYNDROME

The presence of at least two of the following four criteria, one of which must be abnormal temperature or leukocyte count:

- Core (oral or rectal) temperature of $> 38.5^{\circ}\text{C}$ or $< 36^{\circ}\text{C}$
- Tachycardia, in the absence of external stimulus, chronic drugs, or painful stimuli; or otherwise unexplained persistent elevation over a 0.5 hour time period or for children < 1 year old: bradycardia, in absence of external vagal stimulus, β -blocker drugs, or congenital heart disease; or persistent depression over a 0.5-hour time period.
- Tachypnea for an acute process not related to underlying neuromuscular disease.
- Leukocyte count elevated or depressed for age (not secondary to chemotherapy-induced leukopenia) or $> 10\%$ immature neutrophils.

INFECTION

A suspected or proven infection caused by any pathogen or a clinical syndrome associated with a high probability of infection. Evidence of infection includes positive findings on clinical examination, imaging, or laboratory tests (e.g. leukocytes in a normally sterile body fluid, perforated viscus, chest radiograph consistent with pneumonia, petechial or purpuric rash, or purpura fulminans) or a positive culture, tissue stain, or polymerase chain reaction test.

SEPSIS

Systemic inflammatory response syndrome (SIRS) in the presence of or as a result of suspected or proven infection

SEVERE SEPSIS

Sepsis plus one of the following: cardiovascular organ dysfunction or acute respiratory distress syndrome or two or more other organ dysfunctions.

Organ dysfunctions are defined in Table 1.

SEPTIC SHOCK

In a child with sepsis presence of: hypotension (systolic BP <70 mm Hg in infant; $<70 + 2 \times$ age after 1 year of age) or need for vasoactive drug to maintain BP above fifth centile range (dopamine > 5 mcg/kg/min or dobutamine, epinephrine, or norepinephrine at any dose) or Signs of hypoperfusion—any three of the following: decreased pulse volume (weak or absent dorsalis pedis pulse), capillary refilling time > 3 s, tachycardia heart rate as defined in Table 2, core (rectal/oral) to peripheral (skin-toe) temperature gap $> 3^{\circ}\text{C}$, and urine output < 1 mL/kg/h (< 20 mL/h in > 20 kg child) or sepsis and cardiovascular organ dysfunction as defined in Table 1.

MULTIPLE ORGAN DYSFUNCTION

The detection of altered organ functions in the acutely ill patient constitutes multiple organ dysfunction syndrome (MODS; two or more organs involvement).

Rapid Cardiopulmonary Assessment and Clinical Examination

Assessment should be prompt and comprehensive. General assessment (appearance, respiratory effort and color) and primary assessment (airway breathing, circulation, disability and exposure) are important. Following points must not be missed:

- *Appearance:* Restlessness, agitation, anxiety, progressive lethargy, and decreased responsiveness are signs of impaired mental status.
- *Airway patency and stability.*
- *Breathing:* Respiratory rate is increased in response to tissue hypoxia and to compensate for metabolic acidosis. Progressive worsening of respiratory distress (tachypnea, nasal flaring, suprasternal, intercostal, and subcostal retractions) with bilateral rales or wheezes or unequal breath sounds on auscultation are signs of primary focus of infection in lungs, or early acute respiratory distress syndrome (ARDS).
- *Circulation (Cardiovascular):* Heart rate, adequacy of central and peripheral pulse, systolic and diastolic blood pressure, skin color, capillary refill time (CRT), and temperature of extremities should be noted. Tachycardia occurs early in response to falling cardiac output and is the most significant physical findings in septic shock.

Blood pressure: A fall in blood pressure is a late manifestation of low-cardiac output in children. Children

Table 1: Organ dysfunction criteria

Cardiovascular dysfunction(a)

Hypotension (systolic BP <70 mm Hg in infant; $<70 + 2 \times$ age after 1 year of age) or need for vasoactive drug to maintain BP above fifth centile range (dopamine > 5 mcg/kg/min or dobutamine, epinephrine, or norepinephrine at any dose) or Signs of hypoperfusion—any three of the following: decreased pulse volume (weak or absent dorsalis pedis pulse), capillary refilling time > 3 sec, tachycardia (heart rate as defined in Table 2), core (rectal/oral) to peripheral (Skin-toe) temperature gap $> 3^{\circ}\text{C}$, and urine output < 1 mL/kg/h (< 20 mL/h in > 20 kg child). In early stage, there is an increase in heart rate and poor peripheral perfusion in form of weak pulse and prolonged capillary refill time. Hypotension occurs late, and may lead to precipitous cardiac arrest.

Respiratory dysfunction (b)

Proven need for supplemental oxygen (c) or $> 50\%$ FiO_2 to maintain saturation $> 92\%$ or Need for nonelective mechanical ventilation (d) or $\text{PaO}_2/\text{FiO}_2 < 300$ in absence of cyanotic heart disease or pre-existing lung disease or $\text{PaCO}_2 > 65$ torr or 20 mm Hg over baseline PaCO_2

Neurologic dysfunction

Glasgow Coma Score < 11 or Acute change in mental status with a decrease in Glasgow Coma Score > 3 points from abnormal baseline

Hematologic dysfunction

Platelet count $< 80000/\text{mm}^3$ or a decline of 50% in platelet count from highest value recorded over the past 3 days (for chronic hematology/oncology patients) or International normalized ratio > 2

Renal dysfunction

Serum creatinine > 1 mg/dL

Hepatic dysfunction

Total bilirubin > 4 mg/dL (not applicable for newborn) or, alanine transaminase $2 \times$ upper limit of normal for age

(a) See Table 2.

(b) Acute respiratory distress syndrome must include a $\text{PaO}_2/\text{FiO}_2$ ratio < 200 mm Hg, bilateral infiltrates, acute onset, and no evidence of left heart failure. Acute lung injury is defined identically except the $\text{PaO}_2/\text{FiO}_2$ ratio must be < 300 mm Hg.

(c) Proven need assumes oxygen requirement was tested by decreasing flow with subsequent increase in flow if required.

(d) In postoperative patients, this requirement can be met if the patient has developed an acute inflammatory or infectious process in the lungs that prevents him or her from being extubated.

can prevent reduction in blood pressure by vasoconstriction, and an increase in heart rate and may have features of poor peripheral perfusion in presence of normal blood pressure. Diastolic blood pressure falls early causing wide pulse pressure as vascular tone

Table 2: Age specific upper and/or lower limits of heart rate to define tachycardia and bradycardia, respiratory rate to define tachypnea, and systolic blood pressure to define hypotension*

Age group	HR (bpm) Mean (range)	RR breath/min	Systolic BP, mm Hg (range)	MAP-CVP mm Hg
Up to 1 months	140 (100-190)	> 60	<60	55
2 months to 1 year	130 (80-180)	> 50	<70	60
1 to 5 years	80 (60-140)	> 40	<70+ (2 x age in years)	65
6–10 years	80 (60-130)	> 30	<70+ (2 x age in years)	65
> 10 years	75 (60-100)	> 30	<90	65

* For heart rate lower values are approximate 5th percentile and upper values 95th percentile, for blood pressure the values are 5th percentile and for respiratory rate 95th percentile.

begins to decrease. Systolic blood pressure begins to fall causing narrow pulse pressure once hemodynamic compromise is severe.

Hepatomegaly and jugular venous distension with gallop rhythm may signify predominant cardiac involvement as part of septic myocardial depression or myocarditis. Petechial rash may be present in meningococemia or disseminated intravascular coagulation.

Capillary refill time (CRT): Capillary refill time of more than 2sec is abnormal. In warm phase of septic shock, CRT may be normal; however, signs of hyperdynamic circulation (bounding pulse, widened pulse pressure, and hyperdynamic apex beat) are present. Warm shock if untreated will progress to cold shock. Cold shock is more common than warm shock. In older children, cold peripheries, poorly felt pulses, and prolonged CRT are harbingers of shock.

- **Urine output:** Oliguria is common and may progress to anuria. Assessment of urine output in last 6 hours is helpful. In severe cases, patient may present with cardiopulmonary failure or cardiopulmonary arrest; both situations need endotracheal intubation and ventilatory support as well as aggressive hemodynamic support for survival.

A time-sensitive protocolized approach to resolve shock in severe sepsis should be implemented with an effort to resolve shock in the initial hours of resuscitation as it is associated with steep decline in mortality rate.^{9,10}

Guidelines for Management of Severe Sepsis and Shock

For simplicity sake, components of this Flow chart 1 are divided into four steps (I–IV) to address recommended interventions according to clinical condition, time, and available resources.

STEP I: 0-5 minutes

Recognize depressed mental status and decreased perfusion by rapid cardiopulmonary assessment.

Begin high flow oxygen

Establish intravenous/intraosseous access

Venturi masks or non-rebreathing mask may be used for high flow oxygen therapy.

All of the above are readily achievable in first five minutes

If airway is unstable or the patient is lethargic or unresponsive and adequate oxygenation and ventilation is not achieved, start bag-valve mask ventilation and plan early endotracheal intubation and mechanical ventilation. Other indications for intubation are hypotension on arrival or during therapy, convulsive seizures refractory to 2 doses of benzodiazepine, persistently low Glasgow Coma Scale (GCS) of less than 8 and signs of raised intra cranial pressure. Implementation of this step may take additional time encroaching upon the interventions expected in next 60 minutes as per the guidelines.

STEP II: 5-40 minutes

Initial fluid resuscitation: Rapid infusion of 20 ml/kg isotonic saline each, up to 60 ml/kg, titrated toward achievement of therapeutic goals of shock resolution (Table 3) or unless rales or hepatomegaly develop.

Fluid therapy by peripheral or intraosseous access should be initiated while adequate control of airway and breathing is being accomplished.

Establish a second peripheral IV line or central line if feasible. (for possible inotrope: Dopamine)

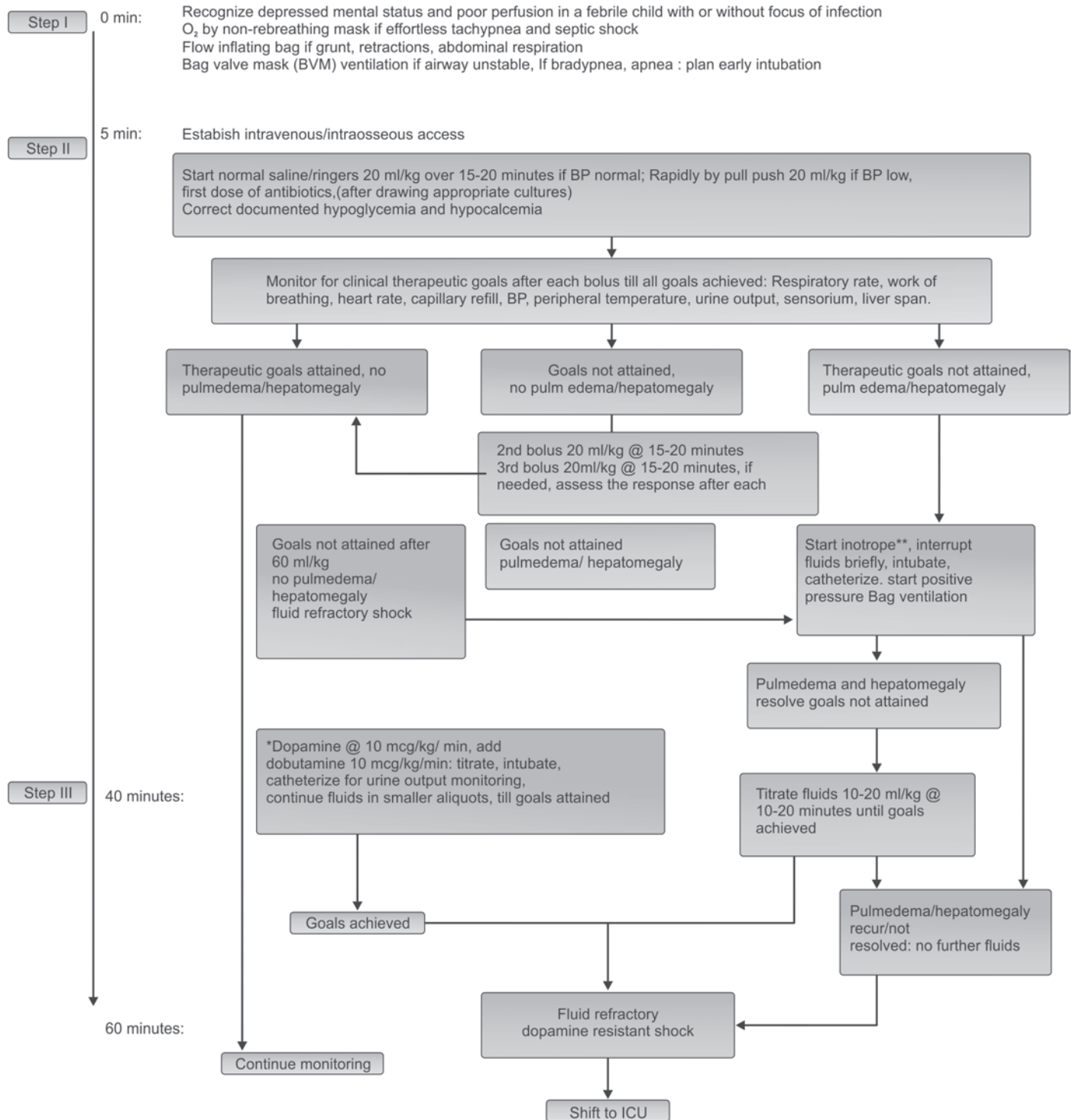
Begin antibiotics (third generation cephalosporin and an aminoglycoside).

Correct hypoglycemia and hypocalcemia.

Volume replacement with 20 ml/kg of isotonic solutions such as normal saline or Ringers lactate can be safely given and repeated if necessary. Typically 40-60 ml/kg

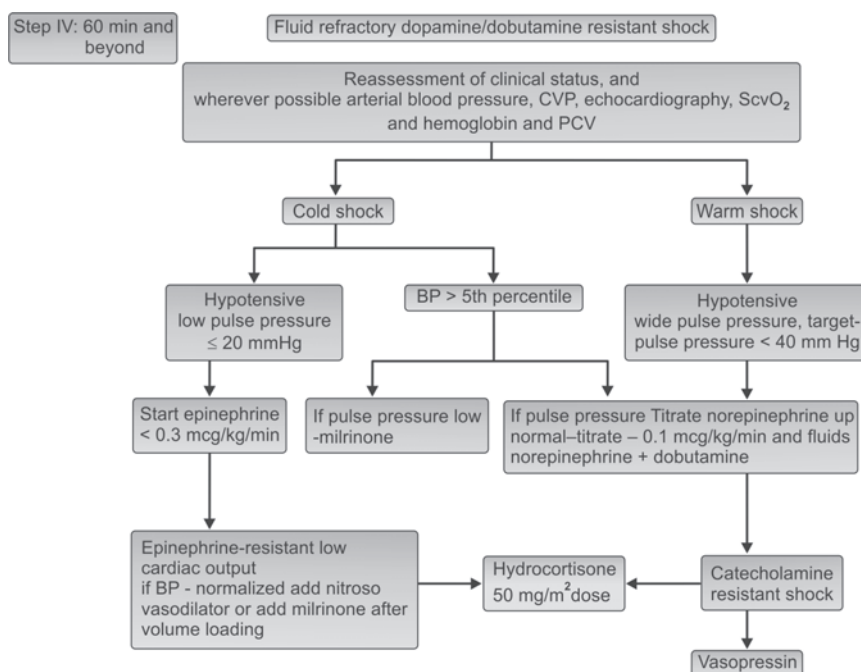
Flow chart 1: Pediatric septic shock

IAP intensive care chapter pediatric sepsis guidelines for resource limited countries



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*Dopamine may be started after 2nd bolus

plan epinephrine infusion early if bradycardia, BP remains low or falls with cold shock at any step¹⁷
Relief of tamponade, such as pneumothorax, or pericardial tamponade, increased intra-abdominal pressure due to fluid should be considered at any point

**Dopamine 10 mcg/kg/min, titrate according to response

PCV: packed cell volume, CVP: central venous pressure, ScvO₂: mixed venous O₂ saturation
maximum dose of both norepinephrine and epinephrine is 1 mcg/kg/min

may be required to correct hypovolemia; in some the need may be as high as 120 ml/kg in first hour. It has been suggested that malnourished child may get fluid overloaded with aggressive volume replacement; caution and a slower rate of infusion is advised. This issue needs to be systematically studied.

Clinical scenarios where larger volumes are needed to achieve therapeutic end points are warm septic shock and shock due to gastro-intestinal sepsis. Presence of pulmonary edema and shock is an indication that more fluids may be needed to resolve shock.¹¹ Repeated assessment helps to decide whether further fluids may be given, or stopped and inotrope initiated and intubation and mechanical ventilation may be initiated. It also helps to decide whether further fluids may be titrated after intubation and inotrope infusion.

Choice of fluid for volume replacement

Guidelines regarding isotonic crystalloid such as Ringers lactate or normal saline be used for the initial fluid resuscitation in septic shock.¹²

Choice of Fluid

Crystalloids: Crystalloids are readily available, cheap, convenient to use, free of side-effects. Crystalloids are rapidly

distributed across intravascular and interstitial spaces. Volume 2-4 times of colloid is required for same volume expansion and the effect may be transient due to leak in the interstitial space.

Colloids (starch, gelatins) produce greater and more sustained increase in plasma volume, but they may not be readily available. Fresh frozen plasma, that is frequently used in patients with disseminated intravascular coagulation to supplement clotting factors may be used, however may not be practical to use as a resuscitation fluid.

Albumin: Albumin should be used only in special circumstances, e.g. burns or documented hypoalbuminemia such as nephrotic syndrome. Recently one study in patients with malaria showed beneficial effect of albumin when compared to normal saline in fluid resuscitation.¹³

In resource limited countries cost of therapy is an issue while considering colloid solutions for expansion of plasma volume. In dengue shock syndrome three studies have looked at different fluid regimens with no significant differences^{12,14,15} in outcomes.

Method of Fluid Administration

Guidelines suggest that fluids be given in boluses of 20 ml/kg; in hypotensive patients as rapidly as possible by pull push method

using a 3 way stop-cock, and in others by gravity method over 15-20 minutes should be preferred.

The ACCM guidelines recommend administration of the boluses as fast as possible which can only be administered by pull push method using a 3 way stop-cock.¹⁶ However, a recent prospective study, from India shows that administration of fluids by pull push method using a 3 way stop-cock increased the incidence of hepatomegaly/pulmonary edema and a greater need for intubation.¹⁰

Development of pulmonary edema and hepatomegaly should be anticipated during fluid administration. In some patients evidence of pulmonary edema and hepatomegaly may be present on arrival, as ARDS and myocardial dysfunction may co-exist in severe sepsis.

Other practical ways to assess fluid overload are jugular venous distension, heart size and pulmonary congestion on chest radiograph. Measurement of CVP and bedside echocardiography should be used at tertiary care centers, if available, to assess adequacy of intravascular volume, cardiac function and signs of fluid overload.

Patients who develop pulmonary edema and hepatomegaly after fluid boluses should be intubated and given positive pressure ventilation. Care must be taken to provide ventilation with PEEP (positive end expiratory pressure).¹⁰ This can be achieved in resource limited setting using the self inflating bag with PEEP valve or Mapleson C-Circuit/Bain's circuit if a mechanical ventilator is not available.

If shock persists' following 60 ml/kg fluid and no signs of pulmonary edema/hepatomegaly are noted, elective intubation should be performed. Since shock can worsen during or following intubation, initiation of an appropriate inotrope infusion often improves the safety profile of this procedure, particularly in warm shock.

Achievement of all therapeutic end points (Table 3) is needed to define shock resolution in fluid and inotrope responsive shock. Discontinuing fluid therapy based on

achievement of some and not all the goals may result in inadequate resuscitation.

Early Antibiotic Therapy and Infection control

*Antibiotics should be administered within 1 hour of the identification of severe sepsis, if possible, after appropriate cultures have been obtained. Early antibiotic therapy is as critical for children with severe sepsis as it is for adults.*¹⁷

Choice of initial antibiotic therapy: The initial empiric antibiotic therapy should include one or more drugs that have activity against the likely pathogens and that penetrate the presumed source of sepsis (Table 4). Commonly used antibiotics include a third generation cephalosporin such as ceftriaxone and an aminoglycoside such as amikacin.

Source control: Every patient presenting with severe sepsis should be evaluated for the presence of a focus of infection that is amenable to source control measures, e.g. drainage of an abscess, debridement of infected necrotic tissue, removal of a potentially infected device, etc.

Hypoglycemia

Hypoglycemia should be checked for and corrected.

Hypoglycemia should be avoided.

Hypoglycemia can have devastating neurological consequences and should be diagnosed early and treated immediately.¹⁸ Hypoglycemia has been shown to be associated with morbidity and mortality in critically ill children with very severe pneumonia,¹⁹ malaria and severely ill malnourished children.²⁰ Hyperglycemia also has been shown to be associated with morbidity and mortality in critically ill as also the hypoglycemia^{21,22} However, the effects of intensive glucose control on mortality in critically ill children are unknown and insulin therapy may result in hypoglycemia²³ one may consider use of insulin only if the child had significant glycosuria and polyuria leading to difficulty in fluid management. Tight control of glucose level 80-120 mg/dl may lead to hypoglycemic episodes, therefore it is suggested to keep blood glucose levels in 120-180 mg/dl range.

Calcium and Hypocalcemia

Before cardiac output and perfusion pressure are restored with drugs, ionized hypocalcemia that might impair cardiac performances should be corrected.

Ionized hypocalcemia is common in neonates and children with sepsis admitted to PICU.^{24,25} Administration of calcium in septic patients with ionized hypocalcemia may transiently improve blood pressure.²⁶ However, there is no evidence to suggest a survival benefit.²⁷ Nevertheless treatment goal should be to keep ionized calcium in the normal limit to avoid any potential morbidity such as hypotension, seizures or tetany.

Table 3: Therapeutic endpoints of resuscitation of septic shock

Normalization of the heart rate
Capillary refill of < 2 sec
Well felt dorsalis pedis pulses with no differential between peripheral and central pulses
Warm extremities
Normal range of systolic pressure and pulse pressure
Urine output > 1 ml/kg/hour
Return to baseline mental status tone and posture
Normal range respiratory rate

Other end-points that have been widely used in adults and may logically apply to children include central venous pressure of 8-12 mm Hg.

Table 4: Choice of empirical antibiotic in patients with septic shock with respect to clinical settings

Clinical setting	Usual pathogens	Preferred therapy	Alternate therapy
Unknown source from the community	<i>Salmonella typhi/paratyphi</i> <i>S. pneumoniae</i> <i>H. influenzae</i> Enterobacteriaceae <i>B. fragilis</i> <i>E. fecalis</i> Think of malaria and dengue	Ceftriaxone plus metronidazole or Piperacillin/tazobactam or Meropenem or Imipenem	Quinolone (Ciprofloxacin/levofloxacin) plus either metroindazole or Clindamycin
Lung source	<i>S. pneumoniae</i> <i>H. influenzae</i> <i>Staphylococcus aureus</i> <i>M. pneumoniae</i>	Ceftriaxone/cefotaxime/ amoxicillin clavulanic and azithromycin/ clarithromycin	Substitute new fluoroquinolone (levofloxacin/gatifloxacin) for macrolide
IV line sepsis	<i>S. epidermidis</i> <i>S. aureus</i> (Methicillin Sensitive <i>S. Aureus</i>) <i>Klebsiella</i> Enterobacter Serratia	Vancomycin plus meropenem or Imipenem or Cefepime or Piperacillin/tazobactam	May substitute linezolid for vancomycin Add antifungals if fungus suspected
Urosepsis	Enterobacteriaceae	Ceftriaxone or Cefotaxime or Quinolone	Aztreonam or Ampicillin + amikacin
Meningitis	<i>S. pneumoniae</i> <i>H. influenzae</i> meningococci	Ceftriaxone or Cefotaxime	Add vancomycin if drug resistant pneumococci suspected
Intrabdominal source	Enterobacteriaceae <i>B. fragilis</i> enterococci	Ceftriaxone plus Metronidazole or Piperacillin/tazobactam or Meropenem or Imipenem	Quinolone (Ciprofloxacin/levofloxacin) plus either metronidazole or Clindamycin

Monitoring and Therapeutic End-points (Table 3)

Meticulous clinical monitoring for therapeutic endpoints without high technology facilities has shown a dramatic reduction in mortality in Vietnamese children presenting with moderate dengue shock syndrome²⁸ and in Indian children treated for septic shock.¹⁰

End-points such as O₂ saturation, and CVP can be monitored at secondary level facilities. Use of cardiac monitor can give reliable continuous heart rate (HR) record. In absence of a monitor, HR could be determined by auscultation periodically; this may be done before, during and after a fluid bolus has been administered.

Blood pressure: BP monitoring assists to regulate rate of fluid infusion, the need for vasoactive agents and further titration. In vasodilatory or warm shock, with wide pulse pressure narrowing of pulse pressure is an additional therapeutic goal.

Limitations of Clinical Therapeutic End-points

All the clinical end-points may not be applicable in some patients.

While normalization of heart rate is one of the most reliable signs of shock resolution, other causes of tachycardia may be fever, anxiety, pain and SIRS. It may also be the only sign of ongoing seizure activity in a sedated, muscle-relaxed child. Anti-pyretic and analgesics, antiseizure medications, source control and mother's close proximity can often help in achievement of normal range of heart rate in appropriate clinical scenarios. On the other hand heart rate, which falls within the normal range for age, in the presence of severe respiratory distress or impending respiratory failure and shock, is an ominous sign (of imminent cardiac arrest).

Poor peripheral perfusion may be the result of cool environmental temperatures in very young infants.

Recognition and resolution of shock in these young patients will depend on normalization of mental status, respiratory rates and heart rates.

There are concerns about the use of capillary refill and pulse volume, as there may be significant inter-observer variability.²⁹

Accurate urine output monitoring by catheterization in fluid unresponsive shock is useful especially in settings without access to CVP monitoring.

Clinical Significance of Mixed Venous Oxygen Saturation (ScvO₂)

Because low cardiac output is associated with increased O₂ extraction²⁸ ScvO₂ saturation can be used as an indirect indicator of whether CO is adequate to meet tissue metabolic demand. If tissue oxygen delivery is adequate, then assuming a normal arterial oxygen saturation of 100%, mixed venous saturation is > 70%. Assuming a hemoglobin concentration of 10 gm/dL and 100% arterial O₂ saturation then a cardiac index (CI) > 3.3 L/min/m² with a normal oxygen consumption of 150 mL/min/m² (O₂ consumption = CI × (arterial O₂ content – venous O₂ content)) results in a mixed venous saturation of > 70% because $150 \text{ mL/min/m}^2 = 3.3 \text{ L/min/m}^2 \times (1.36 \times 10 \text{ gm/dL} + \text{paO}_2 \times 0.003) \times 10 \times (1 - 0.7)$. In an emergency department study in adults with septic shock, maintenance of superior vena cava O₂ saturation > 70% by use of blood transfusion to a hemoglobin of 10 gm/dL and inotropic support to increase cardiac output, resulted in a 40% reduction in mortality compared with a group in whom MAP and CVP were maintained at usual target values without attention to superior vena cava O₂ saturation.³⁰ Since 2002, Oliveira and colleagues reproduced this finding in children with septic shock reducing mortality from 39% to 12% when directing therapy to the goal of ScvO₂ saturation > 70%.

Unresolved Challenging Issues in Achieving Therapeutic End-points

- Time to achieve various therapeutic end-points may be variable. There are no evidence based guidelines for defining expected time frame of response for each of the monitoring parameters.
- ABGs and lactate estimations are available in a few centers; in others this cannot be used. Use of mixed venous oxygen saturations (ScvO₂) is still beyond reach of most centers.
- Ability to place central lines particularly subclavian or internal jugular vein is still limited.
- In children with shock, the non-invasive BP measurements may be unreliable and invasive intra-arterial BP is ideal; it may not be feasible in majority of resource limited centres.
- Echocardiography for determining the cardiac filling is also not practical in many centres.

- Precise therapeutic end-points for severely malnourished children are unknown.

STEP III: 40-60 minutes

Recognize fluid refractory shock: Begin inotrope by intravenous or intraosseous (IO) route. Dopamine up to 10 µg/kg/min.

Obtain central venous access and airway if needed and feasible. Following adequate intravascular volume repletion, continued presence of hypotension and/or poor perfusion (fluid refractory shock) warrants the consideration of vasoactive therapy, which should be goal directed.^{26,27}

The guidelines suggest the use of dopamine as the first line vasopressor for fluid refractory hypotensive shock in the setting of low systemic vascular resistance. Children with septic shock more often have myocardial dysfunction and low cardiac output hence it is preferable to combine inotropy with a vasopressor effect. Dopamine with or without dobutamine can be used as first line drugs for giving this kind of support. In children the age specific insensitivity to dopamine has to be kept in mind before starting dopamine particularly in infants < 6 months.^{28,29}

STEP IV: 60 minutes and beyond

Recognize dopamine resistant shock

Transfer to PICU

If possible, monitor CVP, echocardiography, mean arterial pressure

Titrate fluids and vasoactive drugs to resolve shock based on CVP, echocardiography to achieve therapeutic goals.

Reverse cold shock resistant to dopamine (normal or low blood pressure) titrate central epinephrine (0.05-0.3 µg/kg/min)

Reverse warm shock with wide pulse pressure and/or low blood pressure by titrating central nor-epinephrine (0.05-0.3 µg/kg/min)

Begin hydrocortisone (50 mg/m²/24 hr) if child is at risk for absolute adrenal insufficiency.

When a child in septic shock does not improve and the goals of treatment are not achieved even after dopamine and or dobutamine infusion the shock is labelled as *fluid refractory, dopamine/dobutamine resistant shock*. Dopamine resistant shock may reverse with epinephrine or norepinephrine infusion.

Some of pediatric patients may have adult type manifestation of high cardiac output, vasodilatation and hypotension. Clinically, it will manifest as tachycardia, flush capillary refill, low-to-low normal blood pressure and wide pulse pressure (*warm shock*). A vasopressor such as norepinephrine is the drug of choice in such patients. It should be used only to restore adequate values of mean arterial pressure that is sufficient to restore urine output. The usual dose is 0.05-0.3 µg/kg/min (maximum 1 µg/kg/min).

Children with septic shock more often have myocardial dysfunction with intense compensatory vasoconstriction.

This leads to a state of low cardiac output, with high cardiac filling pressure and high systemic vascular resistance, which clinically manifests as tachycardia, signs of hypoperfusion, prolonged capillary refill, cold extremities and low-to-low normal blood pressure and narrow pulse pressure (*cold shock*). An inotrope such as *Epinephrine* is the drug of choice. The dose range is 0.05-1.00 $\mu\text{g/kg/min}$, usual recommended dose is $< 0.3 \mu\text{g/kg/min}$.

The low cardiac output state, characterized by persistent narrow pulse pressure and/or prolonged capillary refill even after use of dopamine may be improved with addition of dobutamine (up to 20 $\mu\text{g/kg/min}$) or low dose epinephrine ($< 0.3 \mu\text{g/kg/min}$).

At various stages of sepsis or the treatment thereof a child may move from one hemodynamic state to another. Vasopressor or inotrope therapy should be used according to the clinical state.^{31,32}

Characteristics of Various Inotropes

Dopamine³³: It has alpha, beta and dopaminergic (delta) actions that are dose dependant. At low doses ($< 3 \text{ mcg/kg/min}$) it primarily causes weak renal and splanchnic vasodilatation, and at 3 mcg to 10 mcg/kg/min it exerts a positive myocardial inotropic effect. At higher doses ($> 10 \text{ mcg/kg/min}$), it has strong vasoconstricting alpha effect, in addition to positive inotropic effect. So called 'renal dose' of dopamine (2-5 mcg/kg/min) for renal vasodilation has been over emphasized and is of less practical significance in clinical setting. The primary indication for dopamine is the need to increase myocardial contractility after preload restoration. Usual dose is 5-20 mcg/kg/min titrated to desired effect. Dopamine (in doses $> 10 \text{ mcg/kg/min}$) should preferably, be given via central line to prevent ischemic necrosis of the skin.

Dobutamine: It is selective beta 1 agonist. It causes an increase in cardiac contractility and reduces peripheral resistance. The reduction in afterload and improved myocardial performance lowers ventricular filling pressures. Usual dose is 5 mcg to 20 mcg/kg/min. It should not be used alone in septic shock due to risk of further drop in blood pressure. In combination with dobutamine, any of the following: dopamine, adrenaline, or noradrenaline can be used to prevent hypotension due to their vasoconstrictive action.

Adrenaline (Epinephrine): It is an alpha and beta adrenergic agonist. It is used in situations where dominant hemodynamic feature is peripheral vascular failure as in septic shock. At higher doses severe vasoconstriction can lead to lactic acidosis and renal and splanchnic ischemia. The usual dose is 0.05 mcg/kg/min to 0.3 (maximum 1 mcg/kg/min). It should be titrated closely and minimum dose should be used for required effect.

Noradrenaline (Norepinephrine): An alpha and beta agonist (alpha $>$ beta effect). Cardiac contractility is increased

but it also causes massive increase in myocardial oxygen consumption and afterload, so cardiac output may not actually increase. Usual dose is 0.05 -0.3 (maximum 1 mcg/kg/min). In warm septic shock with hypotension despite use of adrenaline secondary to intense vasodilatation, noradrenaline may be useful in increasing peripheral vascular resistance to improve blood pressure.

An alternative approach to improve cardiac contractility and lower systemic vascular resistance is based on the use of type III phosphodiesterase inhibitors (PDEI).

Milrinone and Inamrinone³⁴

These are newer inotropic agents with properties of afterload reduction and myocardial diastolic relaxation (lusotropic effect). This class of agents, which includes milrinone and inamrinone (formerly amrinone, but the name was changed to avoid confusion with amiodarone), has a synergistic effect with beta-adrenergic agonists since the latter agents stimulate intracellular cAMP production while the PDE inhibitors increase intracellular cAMP by blocking its hydrolysis. Since the PDE inhibitors do not depend on a receptor mechanism, they maintain their action even when the beta-adrenergic receptors are down-regulated or have reduced functional responsiveness. The main limitation of these agents is their need for normal renal function (for milrinone clearance) and liver function (for inamrinone clearance). Inamrinone and milrinone are rarely used in adults with septic shock because catecholamine refractory low cardiac output and high vascular resistance is uncommon; however, this hemodynamic state represents a major proportion of children with fluid-refractory, dopamine-resistant shock. Fluid boluses are likely to be required if inamrinone or milrinone are administered with full loading doses. Because milrinone and inamrinone have long half-lives (1-10 hours depending on organ function) it can take 3 to 30 hours to reach 90% of steady state. Milrinone is commonly used for cardiogenic shock which is frequently associated with septic shock.

Levosimendan³⁵⁻³⁶: Levosimendan is a promising new medication that increases $\text{Ca}^{++}/\text{actin}/\text{tropomyosin}$ complex binding sensitivity and also has some Type III PDEI and ATP-sensitive K^{+} channel activity. Because one of the pathogenic mechanisms of endotoxin induced heart dysfunction is desensitization of $\text{Ca}^{++}/\text{actin}/\text{tropomyosin}$ complex binding, this drug allows treatment at this fundamental level of signal transduction overcoming the loss of contractility that characterizes septic shock. It does not increase the myocardial oxygen requirement.

Vasodilators: Both nitroprusside and nitroglycerin lower systemic vascular resistance in children and are useful afterload reducing agents. These agents act via generation of nitric oxide. Nitroprusside has potent peripheral arterial vasodilating effects. Nitroglycerin is more potent venodilator

and pulmonary vasodilator. Close monitoring and volume augmentation are frequently required when vasodilators are used to decrease pulmonary vascular resistance.

Corticosteroids in Septic Shock

Corticosteroids should not be used routinely in all children with septic shock. The guidelines recommend stress doses of hydrocortisone 50 mg/m²/dose (2 mg/kg/dose) every six hours until reversal of shock for pediatric sepsis patients with catecholamine resistant shock and suspected or proven adrenal insufficiency.^{37,38}

Up to this point most of the interventions can be performed in a peripheral setting to be followed as the guideline in resource limited situation. Further management requires transfer of the patient to a PICU, reassessment of the patient's clinical status, arterial blood pressure, CVP, echocardiography and hemoglobin and packed cell volume (PCV). Generally, a low CVP will be an indication for more fluids, low blood pressure for more vasopressors, poor contractility of myocardium on echocardiography for titrating the dose of inotropes and low PCV, an indication for packed cell transfusion.

Further Management and Other Issues

Vasoactive drug therapy: Further titration

At this stage children in shock may be classified into 2 broad categories: warm shock and cold shock.

Children in cold shock may be further categorized in two sub-groups. First are children with low BP. In these children the dose of epinephrine should be titrated to achieve normal mean arterial pressure for age. Once this is achieved but the other goals of therapy are not yet achieved one should consider adding a vasodilator such as nitroprusside and nitroglycerine, with very short half life, or milrinone³⁴ having both vasodilator as well as inotropic effects. Nitroso-vasodilators are used as first line therapy for children with epinephrine-resistant low cardiac output and elevated systemic vascular resistance. Use of milrinone (50-75 µg/kg/min) should be strongly considered if low cardiac output and high vascular resistance state persists in spite of epinephrine and nitroso-vasodilators. Starting milrinone may require additional fluid bolus, and titrating up the dose of epinephrine to check the vasodilatation and maintain BP.

Second category is that of children with normal BP. In these children, further action would depend on the pulse pressure. If the pulse pressure is low milrinone would be the drug of choice. However, if the pulse pressure is normal or high norepinephrine and dobutamine should be titrated up.

Vasopressin in Shock

Vasopressin therapy may be considered as a last resort if patient has warm shock with low blood pressure unresponsive to

norepinephrine.³⁹ In pediatric patients, suggested dose is 0.3 to 2 milliunits/kg/min (equivalent to 0.0003 to 0.002 units/kg/min or 0.01 to 0.12 units/kg/hr). The infusion should be titrated to optimize blood pressure and perfusion.

Drugs—Practice Points

Accurate dose delivery is an important component of vasoactive drug therapy. This can only be achieved with infusion pumps. When infusion pumps are not available the infusions may be given using micro-infusion sets whose drop size has been standardized. Mixing of more than one vasoactive drug in the same infusion set or infusion syringes is not recommended even when limited numbers of intravenous access ports are available. These drugs can be infused through the intraosseous route till the time that an intravenous access becomes available.

A meticulous search for the causes of persistent catecholamine resistant shock should be made if therapeutic goals are not achieved in spite of adequate volume loading and high doses of appropriate vasoactive agents. One must rule out mechanical causes of catecholamine resistant shock such as tamponade due to pericardial effusion, pneumothorax or increased intrabdominal pressure.

Blood and Component Therapy

Optimal hemoglobin for a critically ill child with severe sepsis is not known. A Canadian multicenter trial⁴⁰ strongly argues in favor of a restrictive transfusion strategy recommending RBC transfusions to only those critically ill children whose Hb is ≤ 7g/dl. However, this study excluded children with hemodynamic instability, therefore, the results cannot be extrapolated to children with septic shock.

The adult trial used a goal of 30% PCV (approx 10 gm/dl Hb) during the resuscitation phase of septic shock along with other interventions and showed a clear benefit.⁴¹ Hence, a recommendation for maintaining a somewhat higher Hb level of 10 gm/dl during the resuscitation phase is being made here too.

These recommendations may not apply to premature infants, children with severe hypoxemia, or cyanotic heart disease and to children who are actively bleeding.

Fresh Frozen Plasma

Correction of coagulation abnormalities does not improve outcome in all the patients and unnecessarily exposes the child to the risks of blood product transfusions. Hence, *fresh frozen plasma (FFP) is indicated in patients with coagulation abnormality having any of the following: active bleeding, before surgery, before invasive procedure, and to reverse warfarin effect.* Routine use of FFP to correct laboratory clotting abnormalities is not indicated. When required the FFP infusion should be given relatively rapidly to achieve effective factor levels.

Intravenous Immunoglobulins

Although some pediatric studies have supported use of Intravenous immunoglobulins (IVIG) for severe sepsis.^{42,43} Large clinical trials and recent consensus guidelines⁴⁴ do not recommend the widespread use of IVIG in patients with severe sepsis or septic shock.

Deep Vein Thrombosis (DVT) Prophylaxis

Use of DVT prophylaxis is recommended in postpubertal children with severe sepsis.

Stress Ulcer Prophylaxis

Therapy may be individualized. There are no graded recommendations.

Renal Replacement Therapy

Continuous veno-venous hemofiltration may be clinically useful in children with anuria/severe oliguria and fluid overload. There are no graded recommendations due to lack of pediatric studies. It has been shown in several studies that fluid overload leads to poor prognosis in sepsis and multiple organ failure,⁴⁵ it may be worthwhile considering furosemide infusion or intermittent diuresis once initial resuscitation and hemodynamic stabilization has been achieved.

Key messages

- Immediate recognition of shock state from decreased perfusion state and altered mental status by general and primary assessment
- ABCs with high flow O₂.
- Rapid IV access. IO immediately if IV not available 4.0-40 mins at least 60 ml/kg isotonic non glucose containing fluid must go in.
- Clinical evaluation of improvement of shock by decreasing HR, CRT < 2 secs, improved mental status, improved peripheral pulse/central pulse, improved urine output, warmer extremities and improved age related values of mean arterial pressure. Fluid overload should also be evaluated simultaneously.
- Rapid decision to start dopamine/dobutamine by peripheral line... no waiting for central line
- First hour appropriate antibiotics
- Continue fluid boluses as needed throughout the process. For maintenance fluids add glucose if blood sugar < 120
- Ventilation with sedation and analgesia; CVP and arterial lines at this stage or earlier if possible
- If fluid refractory dopamine resistant shock. Epinephrine for cold shock, nor epinephrine for warm shock. Consider adding vasodilators if poor cardiac contractility and vasoconstricted state.

- Steroids for catecholamine resistant shock at 2 mg/kg/d Q6 hours until hemodynamic stability
- Early goal directed therapy with ScvO₂ 70%, Hb 10, CVP 8-12, adequate age related mean arterial pressure
- Source control for sepsis, drainage, debridement, removal of hardware or surgery as applicable
- Glucose control with insulin if needed > 150 mg/dl.

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Disorders of Sodium Homeostasis

Dhiren Gupta, MA Sheikh

Disorders of sodium and water balance are commonly encountered in critically ill patients. These disorders are generally categorized as either hypo-osmolar or hyperosmolar, depending on the balance (i.e. excess or deficit) of total body water relative to total body sodium content. It is important for physicians to understand the pathophysiologic mechanisms that cause hyponatremia and hypernatremia.

These disorders are often asymptomatic; however, in some patients, they may result in symptoms ranging from minor to life-threatening. The approach to treating these disorders in individual patients involves balancing the risk of treatment versus the risk of the disorder itself.

The challenge in management lies in identifying the cause for the disorder of sodium and water balance. Instituting therapy needs to be carefully monitored as rapid correction can cause neurological sequel.

Under normal circumstances, the serum Na is preserved within a fine physiologic range (138–142 mEq) despite large variations in daily sodium and water intake. Sodium metabolism is tightly regulated by the kidney through the interaction of numerous neurohormonal mechanisms, including the renin–angiotensin–aldosterone system, the sympathetic nervous system, and the presence of atrial natriuretic and brain natriuretic peptides. Sodium regulation is closely correlated with the body's effective circulating volume (ECV), defined as the requisite intravascular volume to provide adequate tissue perfusion. As such, the major determinant of serum Na is in fact the serum water content, and disturbances in sodium balance most often reflect abnormalities in the ECV and serum water content.

HYPONATREMIA

Hyponatremia is defined as a serum sodium concentration less than 135 mEq/L. It is one of the most common electrolyte abnormalities seen in hospitalized patients.¹ It

is a water problem, not a sodium problem; there is always an excess of water relative to sodium when hyponatremia is present. In hyponatremia, water excretion by the kidney is impaired. Hyponatremia may be associated with hypovolemic, euvolemic, or hypervolemic states (Table 1).

Hypovolemic Hyponatremia²

Hypovolemic hyponatremia is caused by loss of sodium in excess of water. Most often this is secondary to extra renal losses, especially gastrointestinal, but sweating (cystic fibrosis), and “third spacing” from burns, trauma, peritonitis, effusions, ascitis, and pancreatitis are other etiologies. Renal salt-wasting is seen in diuretic abuse, osmotic diuresis, salt-wasting nephropathy, renal tubular acidosis (types 2 and 4), and adrenal insufficiency.

Euvolemic Hyponatremia

The most common cause of euvolemic hyponatremia is the inappropriate secretion of ADH (SIADH) with a primary elevation in vasopressin secretion, secondary to CNS pathology (meningitis, trauma) or pulmonary disease (pneumonia, tuberculosis). Drugs, such as nicotine, morphine, barbiturates, isoproterenol, antineoplastic agents, carbamazepine, and acetaminophen have all been implicated as “antidiuretic” agents. Other etiologies are hypothyroidism and water intoxication. Glucocorticoid deficiency can cause euvolemic or hypovolemic hyponatremia.

Hypervolemic Hyponatremia

Hypervolemic hyponatremia is characterized by edema, as in congestive heart failure, cirrhosis, nephrotic syndrome, and renal failure.

Clinical Manifestations

The symptoms attributable to hyponatremia are primarily neurologic and due to water movement into brain cells. The

Table 1: Causes of hyponatremia based upon total body water¹*Hypovolemic hyponatremia*

Extra renal losses

- Gastrointestinal (emesis, diarrhea)
- Skin (sweating or burns)
- (Third space losses)

Renal losses

- Thiazide or loop diuretics
- Osmotic diuresis
- Postobstructive diuresis
- Polyuric phase of acute tubular necrosis
- Juvenile nephronophthisis
- Autosomal recessive polycystic kidney disease
- Tubulointerstitial nephritis
- Obstructive uropathy
- Cerebral salt wasting
- Proximal (type II) renal tubular acidosis

Lack of aldosterone effect (high serum potassium)

- Absent aldosterone
- Pseudohypoaldosteronism type I
- Urinary tract obstruction and/or infection

Euvolemic hyponatremia

- Syndrome of inappropriate antidiuretic hormone
- Nephrogenic syndrome of inappropriate antidiuresis
- Desmopressin acetate
- Glucocorticoid deficiency
- Hypothyroidism
- Water intoxication
 - Iatrogenic (excess hypotonic intravenous fluids)
 - Feeding infants excessive water products
 - Swimming lessons
 - Tap water enema
 - Child abuse
 - Psychogenic polydipsia
 - Diluted formula
 - Marathon running with excessive water intake

Hypervolemic hyponatremia

- Congestive heart failure
- Cirrhosis
- Nephrotic syndrome
- Renal failure
- Capillary leak due to sepsis
- Hypoalbuminemia due to gastrointestinal disease (protein-losing enteropathy)

symptoms mirror the severity of cerebral edema, (Table 2) which in turn is related to the degree of hyponatremia and the acuity of the process. The mechanisms of cellular adaptation include movement of intracellular electrolytes to the extracellular space, which can occur within minutes. Over hours to days, organic solutes move to the extracellular space. Given the ability for cerebral adaptation, the degree of cerebral edema and neurologic symptoms are less severe in chronic hyponatremia. Early neurologic

Table 2: Clinical symptoms of hyponatremic encephalopathy³**Early**

- Headache
- Nausea and vomiting
- Lethargy
- Weakness
- Confusion
- Altered consciousness
- Agitation
- Gait disturbances

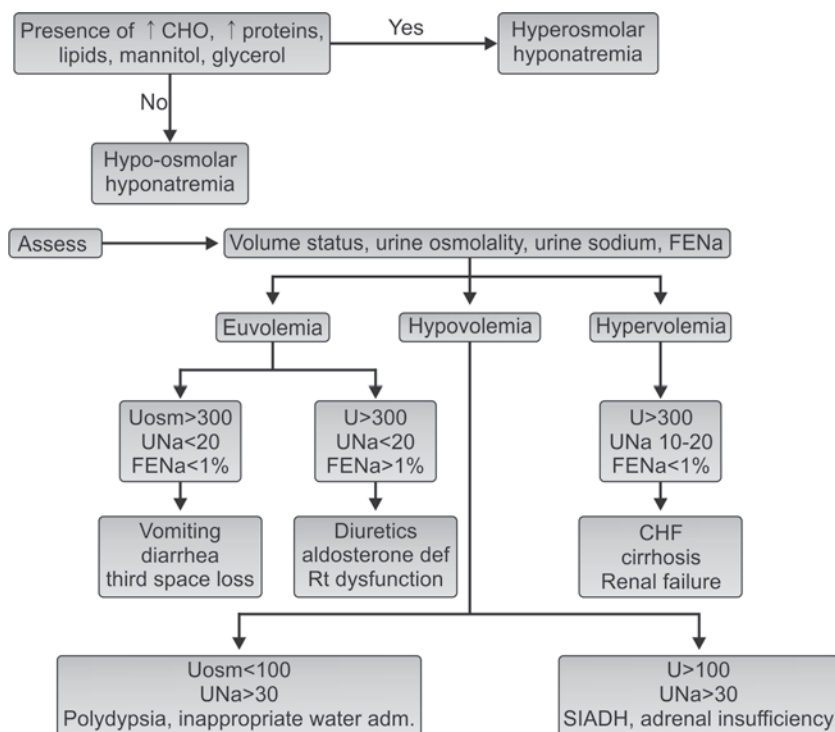
Advanced

- Seizures
- Coma
- Apnea
- Pulmonary edema
- Decorticate posturing
- Dilated pupils
- Anisocoria
- Papilledema
- Cardiac arrhythmias
- Myocardial ischemia
- Central diabetes insipidus

symptoms include nausea and malaise, and may be seen when the serum Na concentration falls below 125 mEq/L. With progressive derangement of cerebral cell volume, symptoms of headache, altered mental status, lethargy, ataxia, and psychosis may ensue. Signs of severe cerebral edema include seizures, coma, and respiratory depression.

Diagnosis

Hyponatremia is usually discovered incidentally, when electrolytes are obtained because of vomiting, dehydration, altered mental status, or seizures. Once hyponatremia is reported (Flow chart 1) rule out pseudohyponatremia as a result of increased serum proteins or lipids; usually the plasma has a milky appearance. Next, consider dilutional hyponatremia secondary to the presence of excess solutes, such as glucose or mannitol, which cause intracellular fluid to shift to the extracellular space. In a diabetic, for every 100 mg/dl increase in glucose over 100 mg/dL, the serum sodium is lowered by 1.6 mEq/L. If true hyponatremia is suspected, the next step is to assess the patient's hydration status and obtain blood for a CBC, electrolytes, and glucose, as well as a urinary sodium. If a euvolemic or hypervolemic state is likely, also obtain a vasopressin, renin, aldosterone, uric acid, cortisol, thyroid function tests, and a lipid panel, as well as urinary osmolality and creatinine. The urinary sodium level can help distinguish among the various etiologies of hyponatremia. With dehydration and volume depletion, the proximal tubular reabsorption of sodium and water will be high, leading to a urinary sodium of less than <10 mEq/L. It will also be low in most hypervolemic states; a urine sodium >20 mEq/L

Flow chart 1: Evaluation of child with hyponatremia

suggests renal saltwasting, SIADH (Table 3) and other euvolemic conditions. With renal failure the urine sodium may be >40 mEq/L, except in acute glomerulonephritis (when it is typically low).³

Table 3: Criteria for the diagnosis of syndrome of inappropriate antidiuretic hormone secretion (SIADH)**Major**

Decreased extracellular fluid osmolality (<275 mOsm kg^{-1} H_2O)
 Inappropriately elevated urine osmolality (>100 mOsm kg^{-1} H_2O and usually >300 mOsm kg^{-1} H_2O) in the context of normal kidney function
 Clinical euvoolemia
 Urine $[\text{Na}]$ 40 mEq L^{-1}
 Absence of hypothyroidism, hypocortisolism (primary or secondary), and diuretic use
 Relatively normal serum $[\text{creatinine}]$
 Normal acid-base and potassium balance
 Low serum $[\text{urea}]$ and serum $[\text{uric acid}]$

Minor

Abnormal water load test
 Inappropriately elevated plasma $[\text{AVP}]$ relative to plasma osmolality
 No significant correction of plasma $[\text{Na}^+]$ with volume expansion, but improvement after fluid restriction
 AVP arginine vasopressin

Patients with decreased effective intravascular volume caused by CHF, cirrhosis, nephrotic syndrome, or lung disease will present with signs of their underlying disease, which often includes peripheral edema. Patients with primary salt loss will also appear volume depleted. If the salt loss is from the kidney (e.g. diuretic therapy or polycystic kidney disease), urinary sodium will be elevated, as may be the urine volume. Salt loss from other regions (e.g. the gut in gastroenteritis or the skin in cystic fibrosis) will cause urine sodium to be low, as in other forms of systemic dehydration. Cerebral salt wasting is encountered with central nervous system insults, and results in high serum atrial natriuretic peptide concentrations, leading to high urine sodium and urine excretion. The syndrome of inappropriate antidiuretic hormone (vasopressin) secretion (SIADH) exists when a primary elevation in vasopressin secretion is the cause of hyponatremia. It is characterized by hyponatremia, an inappropriately increased urine osmolality (>100 mOsm/ kg), normal or slightly elevated plasma volume, and a normal to high urine sodium level (because of volume-induced suppression of aldosterone and elevation of atrial natriuretic peptide). Serum uric acid is low in patients with SIADH, whereas it is high in those with hyponatremia owing to systemic dehydration from other causes of decreased intravascular volume. Consider drug-induced hyponatremia in patients taking potentially contributory medications. A careful search for a tumor (thymoma, glioma, bronchial, carcinoid) causing SIADH is necessary if there is not an obvious cause.

Management

Principles of clinical management³

There are a few essential questions that should be asked in the approach to the clinical management of the patient with hyponatremia:

- What is the underlying diagnosis of hyponatremia, and if known, is there an etiology-specific treatment?
- What rate of serum [Na] correction is considered safe, given the clinical context?
- What is the risk of central pontine myelinolysis (osmotic demyelination)?
- What is the optimal method for raising the serum [Na]?
- What is the management approach when the serum [Na] has been corrected too rapidly?

For children with hyponatremia associated with hypovolemia, isotonic solutions should be provided to restore intravascular volume. In cases of severe hyponatremia (i.e. serum Na less than 125 mEq/L), symptoms of neurologic dysfunction due to cerebral edema may evolve. Children with symptomatic hyponatremia require urgent treatment to avoid progressive neurologic complications. Symptoms are more likely to develop if hyponatremia evolves rapidly, as water will move along an osmotic gradient from the extracellular space to the intracellular space. Given the effect of cell volume regulatory mechanisms, an important goal is to control the rate of rise in serum Na to prevent rapid fluid shifts into the extracellular space and avoid the development of osmotic demyelination. The general recommendation for a child with severe hyponatremia is to increase the serum Na no more rapidly than 12 mEq/L in the first 24 hours or an average of 0.5 mEq/L/hour. An exception to this guideline would be symptomatic hyponatremia and evolving cerebral edema. Symptomatic hyponatremia would call for a more aggressive initial correction of the serum Na of approximately 2 mEq/L/hour for 2 to 3 hours, which should result in clinical improvement. This can be achieved with hypertonic or 3 percent saline (513 mEq/L of sodium). As an example, the calculation for the dose of sodium required to increase the serum Na by 4 mEq/L in a symptomatic patient is $\text{Na (mEq)} = \text{TBW(c)} \times 4 \text{ mEq/L}$. Once the dose of sodium is estimated, the volume of 3 percent saline can be calculated as each ml contains approximately 0.5 mEq of sodium. After the initial correction is achieved, the goal for the daily correction remains approximately 12 mEq/L in the first 24 hours (including the initial emergent correction). Frequent assessment of serum Na is necessary to avoid rapid correction, which may lead to the osmotic demyelination syndrome.

Patients who have asymptomatic hyponatremia and euvolemia do not require urgent intervention.^{4,5} The care of these patients should be carefully planned and based upon the underlying diagnosis with the aim of gradual correction. If hyponatremia is associated with an edema-forming

state, providing supplemental sodium will worsen the state volume excess, and the goal of therapy would be to achieve negative water balance in excess of negative sodium balance. To achieve this effectively, the underlying pathophysiology must be considered, though initial water restriction is generally indicated. Sodium restriction and diuretic therapy may also be warranted. The treatment of SIADH begins with water restriction, though this may be insufficient. Some cases of SIADH require the administration of salt supplements and loop diuretics to achieve the desired negative water balance. Loop diuretics interfere with the counter-current concentrating mechanism in the loop of Henle and impair the renal responsiveness to ADH.⁵

Acute Symptomatic Hyponatremia

- Three percent hypertonic saline
- Correct no more than 2 mEq/L/h
- Correct no more than 12 to 15 mEq/L/h over first 24 hours

Chronic Symptomatic Hyponatremia (>48 hours, or Unknown Duration)

- Three percent hypertonic saline
- Correct no more than 1.5 mEq/L/h initially
- Correct to resolution of symptoms or 10 percent correction of serum sodium:
- Correct no more than 12 mEq/L/24 hours
- Close monitoring of electrolytes and neurologic status.

Asymptomatic Hyponatremia

Euvolemic

- Treat underlying cause
- Water restriction
- Occasionally loop diuretic or demeclocycline to lower urine osmolality
- Hypertonic saline rarely indicated.

Hypovolemic

- Treat underlying cause of fluid loss
- Normal saline.

Hypervolemic

- Treat underlying cause of decreased effective circulating volume:
- Salt and water restriction
- Loop diuretics for some patients.

New Therapies for Hyponatremia⁶

Recently, conivaptan, a V1A/V2-receptor antagonist, was approved for treating hospitalized patients with euvolemic hyponatremia in adults. Because most hyponatremia is caused by the nonosmotic release of vasopressin, the availability of vasopressin antagonists is exciting

and may change the management of hyponatremia completely. From a pathogenesis point of view, V2-receptor antagonists are ideal drugs for hyponatremia involved in the nonosmotic release of vasopressin, except those with volume depletion. With this therapy, the risk of rapid correction is still present; therefore, frequent checks of serum Na are needed. In addition, V2-receptor antagonists are not suitable for certain causes of hyponatremia, such as cerebral salt wasting syndrome, psychogenic polydipsia/potomania, and others. It is critical to identify the mechanisms of hyponatremia before selecting the treatment of hyponatremia.

Hypernatremia

Hypernatremia is defined as serum sodium concentration greater than 145mEq/L. Mild hypernatremia is fairly common in children, especially among infants with gastroenteritis (Table 4). Hypernatremia in hospitalized patients is frequently iatrogenic, caused by inadequate water administration or excessive sodium administration. Moderate or severe hypernatremia has significant morbidity, the result of underlying disease, the effects of hypernatremia on the brain, and the risks of overly rapid correction.

An increase in the serum Na can result from an increase in the total body solutes, a decrease in body water, or a reduction of body water relatively greater than a concurrent reduction in total body solutes. Protective mechanisms to prevent the development of hypernatremia include the stimulation of thirst and the ability to excrete concentrated urine, thereby minimizing free water loss. For these mechanisms to be effective there must be adequate access to and the ability to retain free water. Given the potential for limited access to water, infants and the elderly are predisposed to hypernatremic dehydration. Hypernatremia

due to isolated water deficit is termed dehydration. If both salt and water deficits are present, this condition is termed hypovolemia.

Diarrhea is a common cause of hypernatremia in the urgent or emergent care setting.⁷ Though the degree of Na deficit may vary, generally children who present for care have true hypovolemia. Though hypernatremia due to salt excess is rare, this can occur with the improper mixing of infant formulas or iatrogenic administration of a salt load. The latter can result after sodium bicarbonate infusion during cardiopulmonary resuscitation or during therapy of refractory metabolic acidosis. Hypernatremia secondary to nearly pure water loss may develop if replacement of insensible water loss from the skin and respiratory tract is inadequate.

Central diabetes insipidus is due to insufficient release of ADH from the hypothalamic nuclei, and nephrogenic diabetes insipidus is due to a renal resistance to the effect of ADH. Most children affected with these disorders have normal thirst and free access to water and are able to maintain acceptable water balance. However, infants who do not have free access to water and children with intercurrent illness precluding adequate intake of free water are at risk for the development of hypernatremic dehydration.

The cause of hypernatremia is usually evident from the presenting history. In formula fed infants, an accurate account of formula preparation should be pursued to evaluate for inappropriate mixing, which would result in increased renal osmotic load. Inquiries of urine volume should also be made, as the production of significant urine in a child who presents with apparent hypernatraemic dehydration would be suggestive of diabetes insipidus.

Clinical Manifestations¹

The brain is particularly susceptible to the effects of hypernatremia. The clinical signs and symptoms result from the physiologic response to serum hypertonicity. Most conscious patients will exhibit a voracious thirst and if given the opportunity, will drink water. If ADH and oral intake do not compensate, the acute increase in extracellular tonicity as a result of the hypernatremia results in intracellular dehydration as water moves across the cell membrane to maintain osmotic equilibrium. The net result is a loss of brain volume, which in turn places mechanical stress on cerebral vessels. This mechanical stress can result in bleeding. Lethargy, alternating with irritability, and a high-pitched cry (infants) occur early and are followed by tremors and ataxia, then muscle twitching, tonic spasms, seizures (both focal and generalized), and ultimately coma. Physical signs may include altered mental status, hypertonia, hyper-reflexia, and nuchal rigidity (secondary to hypertonia). Since intracellular fluid shifts extracellularly, the intravascular volume is maintained, so that signs of

Table 4: Causes of hypernatremia based upon total body sodium content

<i>Low total body sodium</i>	<i>Normal total body sodium</i>	<i>High total body sodium</i>
Diarrhea	Increased insensible losses	Salt poisoning
Vomiting	Fever	Inappropriately mixed formula
Ostomy losses	Prematurity	Salt water drowning
Osmotic diuresis	Phototherapy	NaHCO ₃ given with CPR
Immature renal Conservation (prematurity)	Radiant warmers Tachypnea Nephrogenic DI Central DI	

NaHCO₃, sodium bicarbonate; CPR, cardiopulmonary resuscitation; DI, diabetes insipidus.

intravascular volume depletion are late findings. Chvostek's sign may be elicited occasionally, and a smooth, velvety, or doughy feel to the skin may be noted. Localizing neurologic findings suggest the possibility of CNS hemorrhage as a sequel of brain shrinkage. In a patient with DI, signs of intravascular depletion and dehydration may be absent if the thirst mechanism and access to water are preserved. Salt poisoning may cause pulmonary edema (tachypnea, hepatomegaly, rales) and acute CNS pathology without signs of intravascular depletion. An infant exposed to extreme heat and humidity is at risk for hypernatremic dehydration; consider child abuse or neglect in such cases.

Diagnosis⁸

Hypernatremia is usually discovered incidentally when electrolytes are obtained because of gastroenteritis, fever, altered mental status, seizures, polyuria, or polydipsia. In general, since the presentation of hypernatremia is non-specific, early diagnosis requires a high index of suspicion. Consider hypernatremia if the skin has a velvety, doughy feel or if the clinical history fits the common etiologies. If increased total body sodium from improper feeding technique is suspected, obtain some of the infant formula from the home and send it to the company and/or laboratory for evaluation. Also, watch how the caregiver prepares powdered formula and/or dilutes concentrated formula. Once hypernatremia is documented, use the urine osmolality and urine sodium to categorize the patient.

Management⁸

Be judicious in the fluid management of any patient with an electrolyte abnormality, as rapid correction carries its own risks, such as cerebral edema. If there are signs of intravascular depletion (resting tachycardia, orthostatic vital sign changes, weak peripheral pulses, poor capillary refill), give repeated boluses of 20 ml/kg of isotonic crystalloid (normal saline, Ringer's lactate) until perfusion is normalized. Hypernatremia is not a contraindication to using isotonic fluids, as these are hypotonic relative to the patient's serum; the hypernatremia will not be exacerbated. Hyperglycemia and hypocalcemia often accompany hypernatremia. Once the intravascular volume has been restored, obtain a CBC, electrolytes, Dextrostix®, calcium, creatinine, urinalysis, urine sodium and osmolality, and any other laboratory tests pertinent to the patient's presentation.

TBNa Depletion⁹

In hypernatremic dehydration, the key to therapy is restoration of isotonicity without causing rapid fluid shifts into the brain cells. Otherwise, cerebral edema can ensue. First, give normal saline boluses until perfusion is normalized (as above). Estimate the free water deficit using the formula:

Water deficit = $[0.6 \times \text{total body weight}] \times [(\text{serum sodium concentration}/140) - 1]$.

Replace the deficit over 48 hours, using D5½NS with one ampule of 10 percent calcium gluconate added per 500 ml of replacement fluid. Also add 40mEq/L of potassium acetate after adequate urinary output is established. Replace ongoing losses simultaneously while closely monitoring the clinical status and serum electrolytes. The goal is a slow fall in the serum sodium of 0.5 to 1.0 mEq/hour. Measure the sodium and glucose hourly to document the rate of sodium correction, and follow the calcium and potassium every 2 to 4 hours until normal levels are documented or the replacement is nearly complete. If hyperglycemia occurs, do not use insulin unless there are signs of glucose intolerance (glycosuria), as the glucose will generally correct with hydration alone. Increase the calcium infusion if hypocalcemia occurs.

TBNa Normal

Give maintenance fluids along with one-half of the excess urine output as D5W.

Treat central DI with vasopressin.

Increased TBNa/Salt Poisoning

Treat with peritoneal dialysis for serum sodium >200 mEq/L or if the patient has seizures or is comatose. Otherwise, give normal saline at a maintenance rate with furosemide (1 mg/kg) to achieve a net loss of sodium in excess of water. Manage a patient with adipsic hypernatremia by limiting the daily fluid intake along with closely monitoring the body weight, urine output, clinical symptoms, and serum sodium level. Hypertension may be the presenting sign of a patient with hyperaldosteronism, although malignant hypertension is rare. Consult a pediatric endocrinologist.

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Disorders of Magnesium and Phosphate Homeostasis

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Magnesium is the 4th most common cation in the body and the 3rd most common intracellular cation. Infants have slightly higher plasma magnesium concentrations than older children and adults. Only one percent of body magnesium is extracellular (60% ionized; 15% complexed; 25% protein bound). Because cells with higher metabolic rates have higher magnesium concentrations, most intracellular magnesium is present in muscle and liver. The normal plasma magnesium concentration is 1.5 to 2.3 mg/dL (1.2–1.9 mEq/L; 0.62–0.94 mmol/L), with some variation between clinical laboratories.¹ Magnesium is a necessary cofactor for hundreds of enzymes. It is important for membrane stabilization and nerve conduction. Adenosine triphosphate (ATP) and guanosine triphosphate need associated magnesium when they are used by ATPases, cyclases, and kinases.^{1,2}

HYPOMAGNESEMIA

Causes

Gastrointestinal or renal losses are the major causes of hypomagnesemia. Diarrheal stool has up to 200 mg/L of magnesium; gastric contents have only approximately 15 mg/L, but high losses can cause depletion. Steatorrhea causes magnesium loss as a result of the formation of magnesium-lipid salts; restriction of dietary fat can decrease losses.

The most common causes of hypomagnesemia are:^{1,3}

GIT Disorders

- Diarrhea
- Nasogastric suction or emesis
- Inflammatory bowel disease
- Celiac disease
- Cystic fibrosis
- Intestinal lymphangiectasia

- Small bowel resection or bypass
- Pancreatitis
- Protein-calorie malnutrition
- Hypomagnesemia with secondary hypocalcemia.

Renal Disorders

- Medications: Amphotericin, cisplatin, cyclosporin, loop diuretics, mannitol, pentamidine, aminoglycosides, thiazide diuretics
- Diabetes
- Acute tubular necrosis (recovery phase)
- Postobstructive nephropathy
- Chronic kidney diseases: Interstitial nephritis, glomerulonephritis, postrenal transplant
- Hypercalcemia
- Intravenous fluids
- Primary aldosteronism
- Genetic diseases
 - Gitelman syndrome
 - Bartter syndrome
 - Familial hypomagnesemia with hypercalciuria and nephrocalcinosis
 - Autosomal recessive renal magnesium wasting
 - Autosomal dominant renal magnesium wasting
 - Autosomal dominant hypoparathyroidism
 - Mitochondrial disorders.

Miscellaneous

- Poor intake
- Hungry bone syndrome
- Insulin administration
- Pancreatitis
- Intrauterine growth retardation
- Infants of diabetic mothers
- Exchange transfusion.

Clinical Manifestations^{4,5}

Hypomagnesemia causes secondary hypocalcemia by impairing the release of PTH by the parathyroid gland and through blunting the tissue response to PTH. This usually occurs only at magnesium levels <0.7 mg/dl. The dominant manifestations of hypomagnesemia are due to hypocalcemia: tetany, positive Chvostek and Trousseau signs, and seizures. However, with severe hypomagnesemia, these same signs and symptoms may be present despite normocalcemia. Many causes of hypomagnesemia also result in hypokalemia. Hypomagnesemia may produce renal potassium wasting and hypokalemia that corrects only with magnesium therapy. ECG changes with hypomagnesemia include flattening of the T wave and lengthening of the ST segment. Arrhythmias may occur, almost always in the setting of underlying heart disease.

Treatment

Severe hypomagnesemia is treated with parenteral magnesium. Magnesium sulfate, given at a dose of 25 to 50 mg/kg (0.05–0.1 ml/kg of a 50 percent solution; 2.5–5.0 mg/kg of elemental magnesium). This is administered as a slow intravenous infusion, although it may be given intramuscularly in neonates. The rate of intravenous infusion should be slowed if a patient experiences diaphoresis, flushing, or a warm sensation. The dose is often repeated every 6 hr (every 8–12 hr in neonates), for a total of 2 to 3 doses, before the plasma magnesium concentration is rechecked. Lower doses are used in children with renal insufficiency.^{2,4}

Long-term therapy is usually given orally. Preparations include magnesium gluconate (5.4 mg elemental magnesium/100 mg), magnesium oxide (60 mg elemental magnesium/100 mg), and magnesium sulfate (10 mg elemental magnesium/100 mg). There are sustained-released preparations, such as Slow-Mag (60 mg elemental magnesium/tablet) and Mag-Tab SR (84 mg elemental magnesium/tablet). Oral magnesium dosing should be divided to decrease cathartic side effects. Alternatives to oral magnesium are intramuscular injections and night time nasogastric infusion, both designed to minimize diarrhea. Magnesium supplementation must be used cautiously in the context of renal insufficiency.

HYPERMAGNESEMIA

Clinically significant hypermagnesemia is almost always secondary to excessive intake. Rare in the PICU except in children with renal failure or iatrogenic. May be found in neonates born to mothers who are receiving intravenous magnesium for preeclampsia or eclampsia.^{1,2}

Clinical Manifestations

Symptoms usually do not appear until the plasma magnesium level is >4.5 mg/dl. Hypermagnesemia inhibits acetylcholine release at the neuromuscular junction,

producing hypotonia, hyporeflexia, and weakness; paralysis occurs at high concentrations. The neuromuscular effects may be exacerbated by amino glycoside antibiotics. Direct central nervous system depression causes lethargy and sleepiness; infants have a poor suck. Elevated magnesium levels are associated with hypotension because of vascular dilation, which also causes flushing. Hypotension can be profound at higher concentrations due to a direct effect on cardiac function. ECG changes include prolonged P-R, QRS, and Q-T intervals. Severe hypermagnesemia (>15 mg/dl) causes complete heart block and cardiac arrest. Other manifestations of hypermagnesemia include nausea, vomiting, and hypocalcemia.^{3,5}

Treatment

Most patients with normal renal function rapidly clear excessive magnesium. Intravenous hydration and loop diuretics can accelerate this process. In severe cases, especially with underlying renal insufficiency, dialysis may be necessary. Hemodialysis works faster than peritoneal dialysis. Exchange transfusion is another option in newborn infants. Supportive care includes monitoring of cardiorespiratory status, provision of fluids, monitoring of electrolyte levels, and the use of pressors for hypotension. In acute emergencies, especially in the context of severe neurologic or cardiac manifestations, 100 mg/kg of intravenous calcium gluconate is transiently effective.^{1,5}

DISORDERS OF PHOSPHORUS HOMEOSTASIS

Derangements in the metabolism of phosphate are common in the intensive care unit and can be clinically significant. Serum phosphate measurements may not reflect total body phosphorus stores because the vast majority of total body phosphorus is found in the bones; the majority of phosphate is intracellular, and extracellular phosphate accounts for only a small fraction of total body phosphorus stores. There is no common laboratory test to accurately measure total body phosphate stores. Low serum phosphate concentration is referred to as hypophosphatemia, whereas a state of low total body phosphorus stores is referred to as phosphate depletion.^{2,6,7}

Phosphate serves a number of crucial functions. It is an essential component of the main energy “currency” of the cell adenosine triphosphate. Phosphate is also a component of phospholipids in cell membranes and of hydroxyapatite, the structural matrix of bone. Phosphate also serves as a buffer against acid-base derangements.^{5,8}

HYPOPHOSPHATEMIA

Hypophosphatemia⁷ is typically classified as mild (serum phosphate concentration 2.5 to 3 mg/dl), moderate (1 to 2.5 mg/dl), or severe (<1 mg/dl). Although mild-to-moderate hypophosphatemia may be subclinical, severe hypophosphatemia may be associated with significant

morbidity. As this metabolic complication hampers cellular energy production, it can affect several organ systems. Symptoms tend to be nonspecific in majority of cases and include fatigue and irritability. However, severe hypophosphatemia may lead to more serious problems, such as reduced diaphragmatic contractility, ventricular tachycardia and neuromuscular disturbances.^{6,8}

Causes^{5,7}

Transcellular shift

- Refeeding syndrome
- Respiratory alkalosis
- Insulin administration

Renal losses

- Diuretic therapy
- Osmotic diuresis
- Hyperparathyroidism (primary or secondary)
- Proximal renal tubular dysfunction
- Fanconi's syndrome

Extreme catabolic states

- Burns
- Trauma
- Sepsis

Insufficient intestinal absorption

- Malnutrition
- Phosphate-binding antacids
- Vitamin D deficiency
- Chronic diarrhea
- Nasogastric suctioning
- Malabsorption syndromes.

Clinical Manifestations^{2,7}

Clinical manifestations due to hypophosphatemia are rare unless the serum phosphate concentration is less than 1 mg/dL. Diffuse skeletal muscle weakness may be profound. Respiratory failure secondary to diaphragmatic weakness may occur. Respiratory failure may be primary, or it may manifest as an inability to wean from mechanical ventilation. Central nervous system dysfunction may include confusion, lethargy, and gait disturbance. Hematologic manifestations, including acute hemolytic anemia and leukocyte dysfunction (impaired phagocytosis and chemotaxis), have been reported. Cardiovascular manifestations may include acute left ventricular dysfunction and a reversible dilated cardiomyopathy that typically responds only to phosphate repletion. Rhabdomyolysis also may occur.

Treatment^{7,8}

Mild hypophosphatemia does not require treatment unless the clinical situation suggests that chronic phosphorus depletion is present or that ongoing losses are occurring. Oral phosphorus can cause diarrhea, so the doses should be divided.

Intravenous therapy is effective in patients who have severe deficiency or who cannot tolerate oral medications. Intravenous phosphorus is available as either sodium phosphate or potassium phosphate, with the choice usually based on the patient's plasma potassium level. Starting doses are 0.08 to 0.16 mmol/kg over 6 hr.

The oral preparations of phosphorus are available with various ratios of sodium and potassium. This is an important consideration because some patients may not tolerate the potassium load, whereas supplemental potassium may be helpful in some diseases, such as Fanconi syndrome or malnutrition. Oral maintenance doses are 2 to 3 mmol/kg/day in divided doses. Increasing dietary phosphorus is the only intervention needed in infants with inadequate intake. Other patients may also benefit from increased dietary phosphorus, usually dairy products. Phosphorus-binding antacids should be discontinued in patients with hypophosphatemia. Certain diseases require specific therapy. Vitamin D supplementation, not phosphorus, is the principal therapy in nutritional vitamin D deficiency. X-linked hypophosphatemic rickets is usually treated with a combination of 1, 25-dihydroxyvitamin D and oral phosphorus.

HYPERPHOSPHATEMIA

Hyperphosphatemia is defined as a serum phosphate level greater than 4.5 mg/dl; it may be clinically significant at levels greater than 5 mg/dl. The most common cause of hyperphosphatemia is renal failure. Renal insufficiency causes hyperphosphatemia because phosphate excretion by the kidneys is impaired. The serum phosphate level is usually normal until the creatinine clearance falls below 30 mL/min. Other causes of hyperphosphatemia include rhabdomyolysis, hemolysis, and tumor lysis syndrome. Any insult causing extensive cell damage releases phosphorus into the extracellular space.

Causes⁷

Transcellular Shifts

- Tumor lysis syndrome
- Rhabdomyolysis
- Acute hemolysis
- Diabetic ketoacidosis and lactic acidosis

Increased Intake

- Enemas and laxatives
- Cow's milk in infants
- Treatment of hypophosphatemia
- Vitamin D intoxication

Decreased Excretion

- Renal failure
- Hypoparathyroidism
- Acromegaly

- Hyperthyroidism
- Tumoral calcinosis with hyperphosphatemia.

Clinical Manifestations²

The principal clinical consequences of hyperphosphatemia are hypocalcemia and systemic calcification. Symptomatic hypocalcemia is most likely to occur when the phosphorus increases rapidly or when diseases predisposing to hypocalcemia are present (chronic renal failure, rhabdomyolysis).

Systemic calcification occurs because the solubility of phosphorus and calcium in the plasma is exceeded. This is believed to happen when plasma calcium \times plasma phosphorus, both measured in mg/dl, is more than 70. Clinically, this is often apparent in the conjunctiva, where it manifests as a foreign body feeling, erythema, and injection. More ominous manifestations are hypoxia from pulmonary calcification and renal failure from nephrocalcinosis.

Treatment^{7,8}

The treatment of acute hyperphosphatemia depends on its severity and etiology. Mild hyperphosphatemia in a patient with reasonable renal function spontaneously resolves; this can be accelerated by dietary phosphorus restriction. If kidney function is not impaired, then intravenous fluids can enhance renal phosphorus excretion.

For more significant hyperphosphatemia or a situation such as tumor lysis or rhabdomyolysis, in which endogenous phosphorus generation is likely to continue, addition of an oral phosphorus binder prevents absorption of dietary phosphorus and can remove phosphorus from the body by binding what is normally secreted and absorbed by the gastrointestinal tract.

Phosphorus binders are most effective when given with food. Binders containing aluminum hydroxide are especially efficient, but calcium carbonate is an effective

alternative and may be preferred if there is a need to treat concomitant hypocalcemia.

If the hyperphosphatemia is not responding to conservative management, especially if renal insufficiency is supervening, then dialysis may be necessary to increase phosphorus removal.

Dietary phosphorus restriction is necessary for diseases causing chronic hyperphosphatemia. However, such diets are often difficult to follow, given the abundance of phosphorus in a variety of foods. Dietary restriction is often sufficient in conditions such as hypoparathyroidism or mild renal insufficiency.

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Disorders of Potassium Homeostasis

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INTRODUCTION

Potassium is the most abundant intracellular cation in the body with only approximately 2 percent of total body stores present in the extracellular space. Among a variety of vital cellular functions, high cytosolic potassium concentration is required for growth, metabolism, cell division, and protein synthesis. Maintenance of the cytosolic potassium concentration and transcellular gradient is dependent on the function of the basolateral cell membrane enzyme, Na^+/K^+ -ATPase. This enzyme is physiologically regulated by insulin, thyroid hormone, catecholamines, aldosterone, and plasma potassium concentration. Hormonal and metabolic dysregulation may result from conditions present in ill children and result in abnormalities of potassium homeostasis.^{1,2}

Hyperkalemia and hypokalemia are the common electrolyte abnormalities found in hospitalized patients. The high incidence of abnormalities in serum potassium concentration reflects both physiologic abnormalities that are common in ICU patients and the effects of therapeutic interventions that are used in the care of critically ill patients. Because of comorbid conditions, critically ill patients are also at a higher risk of developing complications from altered serum potassium levels. Timely recognition and intervention are essential for minimizing morbidity and mortality due to abnormal serum potassium levels.^{3,4}

HYPOKALEMIA

Hypokalemia is defined as a measured serum potassium concentration below 3.5 mEq/L. Hypokalemia may result from total body deficit, transcellular shift of potassium to the intracellular space, or a combination of both processes. There are numerous causes of hypokalemia including renal loss, extrarenal loss, and increased cellular uptake. The common causes of hypokalemia seen in pediatric emergency departments are due to gastrointestinal loss, diuretic use, and diabetic ketoacidosis (DKA).¹

Loss of gastric or intestinal secretions from any cause will predispose a child to the development of hypokalemia by both direct and indirect mechanisms. The potassium concentration of lower intestinal fluids is relatively high, ranging from 20 to 50 mEq/L, and diarrhea may result in significant potassium loss. The potassium content of gastric fluid is lower at approximately 5 to 10 mEq/L, and hypokalemia associated with vomiting is not primarily due to enteral loss but increased renal excretion of potassium. Gastrointestinal losses resulting in volume contraction will stimulate the secretion of aldosterone which promotes sodium conservation and increased potassium excretion in the distal nephron. Gastric losses associated with metabolic alkalosis will increase the delivery of sodium and water to the aldosterone-sensitive site and facilitate this exchange. Metabolic alkalosis will also promote transcellular shift of potassium to the intracellular space to maintain electroneutrality.^{2,3}

Causes⁴

Decreased Potassium Intake

Increased renal excretion:

- Diuretics
- Metabolic alkalosis (chloride deficient)
- Diabetic ketoacidosis
- Increased mineralocorticoid effect
- Renal tubular acidosis (type 1 and type 2)
- Bartter's syndrome
- Gitelman's syndrome
- Magnesium depletion.

Increased Gastrointestinal Losses

- Diarrhea
- Laxatives
- Ostomy losses

Increased Cellular Uptake (Redistributive)

- Acute alkalosis
- Insulin therapy
- Elevated β -adrenergic activity
- Increase in bone marrow cell production.

Clinical Manifestations

The consequences of changes in serum $[K^+]$ occur as a result of alterations in the resting membrane potential, making cardiac and neuromuscular cells the most susceptible targets. The most serious and potentially fatal effects of hypokalemia are related to disturbances in cardiac electrical activity. When serum $[K^+]$ is less than 3.0 mEq/L, generalized weakness can develop. When serum $[K^+]$ decreases to less than 2.5 mEq/L, muscle necrosis and rhabdomyolysis can occur. With progression of hypokalemia, an ascending muscle paralysis develops, leading to respiratory failure.⁴

Management

In general, potassium replacement is indicated when there has been potassium loss. In clinical scenarios when potassium loss is accompanied by acid-base disturbance, a redistribution effect should be factored when losses are estimated. Magnesium supplementation is indicated in hypokalemia associated with hypomagnesemia. In all cases of significant hypokalemia, monitoring for EKG changes and muscle strength is imperative, and if abnormalities are present, immediate replacement is warranted.

The choice of oral or intravenous replacement will depend on the severity of the disorder and the ability to tolerate enteral salts. If the child is clinically well, oral therapy is preferable and can be provided two to four times per day as potassium chloride. Dosing may start at 2 to 5 mEq/kg per day and be adjusted on the basis of serial laboratory assessment. If there is concurrent metabolic acidosis, potassium citrate or bicarbonate can be provided.^{4,5}

If the child is unable to take oral medications or is symptomatic, intravenous potassium should be provided. If the child is not symptomatic, potassium can be added to the maintenance fluids. If intermittent infusion is indicated, this can begin with an intravenous dose of 0.5 to 1 mEq/kg (typical maximum 30 to 40 mEq/dose). The infusion rate for clinically stable patients should provide 0.25 mEq/kg per hour, though emergent conditions may warrant the maximal rate of 0.5 to 1 mEq/kg per hour (maximum 15 to 40 mEq/hour) with continuous EKG monitoring.⁵

HYPERKALEMIA

Hyperkalemia is defined as a serum potassium concentration (serum $[K^+]$) greater than 5.5 mEq/L. Hyperkalemia

is less frequent than hypokalemia but is more likely to cause serious complications in critically ill patients. Severe hyperkalemia requires rapid correction to prevent serious cardiovascular complications. The measured value for serum $[K^+]$ can be elevated as a result of *in vitro* phenomena, usually the release of K^+ from cells during the clotting process.^{1,2}

Pseudohyperkalemia should be recognized and considered in patients with marked elevations of white blood cells or platelets.² Simultaneous measurements of plasma (unclothed) and serum (clotted) $[K^+]$ should identify this problem. A serum $[K^+]$ that is 0.2 to 0.3 mEq/L greater than plasma $[K^+]$ is indicative of pseudohyperkalemia. Pseudohyperkalemia may also result from hemolysis of a blood specimen after collection; this event is usually identified in the laboratory and reported.³

Causes^{3,4}

Impaired K^+ Excretion

- Renal failure
- Mineralocorticoid deficiency
- Addison's disease
- Renal tubular acidosis (type 4)
- Heparin-induced inhibition of aldosterone synthesis
- Hereditary enzyme deficiencies
- Pseudohypoaldosteronism
- Drugs:* Potassium-sparing diuretics, angiotensin-converting enzyme inhibitors, nonsteroidal anti-inflammatory drugs, trimethaphan, cyclosporine, tacrolimus, pentamidine.

Shifts of K^+ Out of Cells

- Hypertonicity
- Tissue breakdown: Rhabdomyolysis, burns, trauma
- Drugs:* Beta blockers, digoxin, succinylcholine, arginine, lysine
- Familial hyperkalemic periodic paralysis
- Insulin deficiency or resistance.

Medications Associated with Hyperkalemia⁴

- NSAIDs
- ACE inhibitors
- Angiotensin II receptor blockers
- Amiloride
- Spironolactone
- Cyclosporine
- Propranolol
- Digitalis

Clinical Manifestations

The clinical features associated with hyperkalemia are a consequence of altered cellular transmembrane potassium gradient, which reduces the resting membrane potential.

Initially this increases membrane excitability, which is followed by a sustained reduction in excitability. Unless the rise is rapid, symptoms or signs generally do not become apparent until the serum potassium concentration exceeds 7.0 mEq/L. Clinical features predominantly involve cardiac conduction and neuromuscular disturbance. Cardiac dysrhythmias are the most serious consequence, and toxicity is exacerbated by a rapid rise in potassium concentration, acidosis, hyponatremia, and hypocalcemia. Early EKG changes include narrow peak T waves with shortened QT interval, which is followed by progressive lengthening of the PR interval and widening of the QRS complex. There may be loss of P-wave amplitude and eventual “sine wave” pattern when the QRS merges with the T wave. This is typically followed by ventricular fibrillation or standstill. Neuromuscular effects are rarely evident at potassium concentrations less than 8 mEq/L and include paresthesias, skeletal muscle weakness, and ascending flaccid paralysis. Respiratory muscles are typically spared.⁴

Diagnosis

If the potassium is >6.0 mEq/L, immediately obtain an EKG to identify cardiac conduction abnormalities such as peaked T waves (T wave >one-half the R or S wave) and a shortened QT interval. Later changes (K^+ >6.5–7.0) may include flattening of the P wave, lengthening of the PR interval, and widening of the QRS complex.⁵

Management

The treatment of hyperkalemia primarily directed towards enhancing potassium excretion or increasing the movement of potassium into cells as a temporary measure, as well as minimizing cardiac effects. Aggressive IV therapy is necessary for patients who are symptomatic (muscle weakness, cramps, etc.) or have EKG changes.

To shift potassium intracellularly, give 0.5 to 1 g/kg of glucose (2–4 mL/kg of a 25% dextrose solution) over 30 minutes concurrently with regular insulin (1 unit/5 g of glucose given). The potassium-lowering effect occurs in 10 to 20 minutes, but carefully monitor the serum glucose for both hyper- and hypoglycemia. Nebulized β_2 agonists,

such as salbutamol, are also effective at shifting potassium into the cells, but are less predictable than other therapies. The peak effect is 40 to 80 minutes after administration. Give 10 to 20 mg in 4 ml normal saline (4–8 times the dose used for the treatment of asthma). If there are associated peaked T waves, QRS widening, PR lengthening, or severe hyperkalemia (K^+ >7.0) give calcium chloride (20 mg/kg IV over 3–5 min) to stabilize the cardiac membrane potential. Protecting the myocardium early in the treatment course is crucial, as the potassium-lowering effects of the other therapies may not be effective for 30–60 minutes.⁵

To promote potassium excretion in the absence of peaked T waves, treat with polystyrene sulfonate (Kayexalate®), 1 g/kg dissolved in 4 ml of water, with sorbitol (PO or PR). This dose lowers the serum potassium by 0.5 to 1 mEq/L by enhancing GI excretion, but the onset is slow and duration is variable. For a patient who is not anuric, also give furosemide (1–2 mg/kg). The onset of action is within one hour, and the dose may be repeated every 6 hours. In patients with acute kidney injury, life-threatening hyperkalemia (serum potassium >7 mEq/L) is an indication for dialysis.⁶

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Intravenous Fluids in Pediatric Intensive Care Units

Vikas Bansal

INTRODUCTION

Intravenous fluids form an integral part of care of a sick child in intensive care unit. IVF therapy needs to be carefully prescribed and dose adjusted for each disease state in order to prevent or correct a disorder in serum sodium or volume status. It should also fulfill replacement of preexisting fluid deficit and ongoing fluid losses.

The most commonly used maintenance fluid, used to replace normal expected fluid losses in situations such as fasting, is hypotonic saline with dextrose. Volumes are typically calculated using a weight-based infusion rate: for the first 10 kg, 4 ml/kg/h, for the next 10 kg, 2 ml/kg/h and 1ml/kg/h for each kilogram thereafter.^{1,2} However, it may be inappropriate for those children who have non-osmotic production of antidiuretic hormone (ADH). The syndrome of inappropriate ADH⁷ occurs in meningitis, encephalitis, pneumonia, bronchiolitis and after surgery. Any consequent hyponatremia may be exacerbated by hypotonic IV fluids.

REASONS FOR INTRAVENOUS FLUID ADMINISTRATION

There are five common reasons to infuse intravenous fluids

- Defend normal blood pressure
- Return the ICF volume to normal
- Replacing ongoing renal losses
- Giving maintenance fluids to match insensible losses
- The need for glucose as a fuel for the brain.

DANGERS OF HOSPITAL-ACQUIRED HYPONATREMIA

Hyponatremia, serum sodium less than 135 mEq/L, is the most common electrolyte abnormality, affecting approximately 25 percent of hospitalized children.³ The majority of hyponatremia occur in children receiving hypotonic fluids in the hospital setting and can, therefore, be viewed

as an iatrogenic complication of inappropriate fluid therapy. The most serious complication of hospital-acquired hyponatremia is hyponatremic encephalopathy, for which children are particularly at high-risk as they have a larger brain-to-intracranial volume ratio than adults, which allows less room for brain expansion. There are many documented cases of permanent neurologic impairment and death from hyponatremic encephalopathy in otherwise, healthy children receiving hypotonic fluids.⁴

The issue of preventing hospital-acquired hyponatremia has now achieved greater prominence as it has become increasingly clear in the adult population that any degree of hyponatremia can have dangerous consequences and is associated with increased morbidity and mortality.⁵ It is now known that mild chronic hyponatremia (sodium <130 mEq/L) in adults can produce subtle neurological impairment affecting both gait and attention, similar to that of moderate alcohol intake.⁶ It is now well-established in adults that hospital-associated hyponatremia is an independent risk factor for all-cause mortality, with studies documenting an association in the ambulatory setting⁷ and general medical wards,⁸ as well as in patients with community acquired pneumonia⁹ congestive heart failure,¹⁰ and end-stage liver disease.¹¹ Hyponatremia is also recognized as an independent predictor of increased medical costs in adults.¹² Although similar studies are lacking in pediatrics, it has been recently demonstrated in preterm neonates (<33 weeks gestation) that hyponatremia is the most predictive risk factor for poor neuromotor outcome.¹³

PREVENTION OF HOSPITAL-ACQUIRED HYPONATREMIA

Calculating maintenance IV fluids on the basis of daily urine output and insensible fluid losses at the rate of 1500 ml/m²/day (assigning 1 ml of water for each kcal utilized), with a sodium composition of IVF of 30 mEq/L may be appropriate for a stable patient requiring long-term tube

feeds or total parenteral nutrition, it does not answer the fluid needs of the acutely ill child. A variety of common disorders encountered in hospitalized children are associated with arginine vasopressin (AVP) excess, which places children at risk for the development of hyponatremia when hypotonic fluids are administered. Recent studies have revealed that the historic approach of prescribing hypotonic fluids in children results in an unacceptably high incidence of hyponatremia.¹⁴

Different fluid regimes proposed to prevent hospital acquired hyponatremia include continued use of hypotonic solutions with fluid restriction¹⁵ isotonic solutions with fluid restriction¹⁶ and the use of isotonic solution.¹⁷

Previous studies demonstrated that the magnitude of EFW intake is not sufficient to explain the fall in serum sodium in all the cases of hospital acquired hyponatremia.¹⁸ The recent randomized studies confirmed that the incidence of hyponatremia is significantly less in isotonic fluid group in comparison to hypotonic fluid group and the fluid type, but not the rate of maintenance fluid administered, is a significant risk factor for hospital acquired hyponatremia.^{19,20}

Indication of 0.9 Percent Normal Saline as a Maintenance Fluid

The administration of 0.9 percent NaCl is primarily indicated for disease states that are associated with AVP excess. As can be seen from Table 1, these disorders encompass the vast majority of hospitalized children requiring maintenance parenteral fluids. For these conditions 0.9 percent NaCl would be administered in 5 percent dextrose in water at a rate of approximately 1500 ml/m² per day.²¹ It should be noted that even normal saline could result in a fall in serum sodium in a patient with a fixed inability to excrete free water and a urine osmolality exceeding 530 mOsm/kg H₂O.²² One exception where the use of 0.9 percent NaCl may be ineffective in adequately preventing hospital-acquired hyponatremia is in neurosurgical patients, where cerebral salt wasting can develop. Below is a discussion of the fluid management strategies of common childhood disorders associated with AVP excess, where hypotonic fluids should be avoided and 0.9 percent NaCl administered.

Hypovolemic States

Volume depletion (dehydration) is a frequent reason that children require IVFs in the acute care setting. Numerous conditions can lead to volume depletion, the most common being gastroenteritis. Volume depletion can be isonatremic, hyponatremic, or hypernatremic. Regardless of the type, the volume deficit is primarily extracellular, and fluid resuscitation should be with an isotonic fluid. Children with moderate to severe volume depletion should receive rapid administration of isotonic fluids in doses ranging from 20 to 60 ml/kg in order to reestablish

Table 1: Indication of 0.9% normal saline as a maintenance fluid

Effective circulating volume depletion

Dehydration
Salt wasting nephropathy
Bartter syndrome
Adrenal insufficiency

Decreased peripheral vascular resistance

Sepsis
Hypothyroid

Euvolemic states of antidiuretic hormone (ADH) excess Central nervous system disturbances

Meningitis
Encephalitis
Brain tumors
Head injury

Pulmonary disease

Pneumonia
Asthma
Bronchiolitis
Cancer

Medications

Cytoxan
Vincristine
Narcotics
Carbamazepine
Selective serotonin reuptake inhibitors

Nausea, emesis, pain, stress

Postoperative state

Glucocorticoid deficiency

tissue and organ perfusion. Hypovolemia is a potent stimulus for vasopressin production, and the administration of hypotonic fluid will predictably result in hyponatremia from water retention. Unfortunately, a common practice in pediatrics is to either treat volume depletion with hypotonic fluids, use hypotonic fluids following acute volume expansion, or increase the maintenance fluid rate 50 to 100 percent with a hypotonic fluid in order to correct volume depletion. Recent data have revealed that all of these approaches result in hyponatremia,²³ with an almost 20 percent incidence of hospital-acquired hyponatremia (sodium <135 mEq/L) in children receiving hypotonic maintenance fluids following bolus therapy with 0.9 percent NaCl for gastroenteritis. Children with volume depletion should receive 0.9 percent NaCl at a rate of 1500 ml/m² per day, following initial bolus therapy. This not only serves as prophylaxis against hyponatremia, but also will expand the extracellular volume more rapidly, correcting the volume depletion faster. If the child is assessed to have ongoing signs of volume depletion following the initial fluid bolus, it would be safer to give an additional fluid

bolus rather than to increase the rate of IVF to greater than 1500 ml/m² per day. Once the child is deemed volume replete as evidenced by good urine output and peripheral perfusion, 0.9 percent NaCl could be discontinued in favor of hypotonic solutions or IVF discontinued altogether if oral intake is deemed adequate. It must be emphasized that patients with gastroenteritis with large ongoing gastrointestinal free water losses or high insensible losses from fever could develop hypernatremia from 0.9 percent NaCl. In these patients, and in patients with hypernatremic dehydration, 0.9 percent NaCl should only be used until the patient is deemed volume replete, after which hypotonic fluids should be used to keep up with ongoing losses and to treat hypernatremia (sodium >144 mEq/L). Close monitoring of serum sodium will be needed in these high-risk patients.

Euvolemic states of arginine vasopressin excess: syndrome of inappropriate secretion of antidiuretic hormone

There are many common childhood disorders that place hospitalized children at risk for developing hyponatremia due to nonosmotic and nonhemodynamic stimuli for AVP release, such as pneumonia, bronchiolitis, asthma, positive pressure ventilation, central nervous system (CNS) infections, and head trauma. Any euvolemic child who develops hyponatremia in the absence of renal insufficiency, congestive heart failure, nephrosis, cirrhosis, or adrenal insufficiency most likely has 'the syndrome of inappropriate secretion of antidiuretic hormone' (SIADH). SIADH is a disorder that can lead to hyponatremia due to the nonphysiologic secretion of ADH, which leads to free water retention followed by a natriuresis that maintains fluid balance at the expense of serum osmolality. SIADH is one of the most common causes of hyponatremia in both children and adults in a hospital setting. It has been reported in numerous conditions, but primarily occurs in children with central nervous system and pulmonary disorders and as a side effect of medications. Other common physiologic stimuli for AVP release that can lead to euvolemic hyponatremia indistinguishable from SIADH are nausea, vomiting, pain, stress, and hypoxia. Virtually every hospitalized child should be considered at risk for the development of hyponatremia, and if IVF are needed 0.9 percent NaCl would be the most effective prophylaxis.

Postoperative Setting

The need to administer IVFs is particularly important in the postoperative setting. Postoperative patients are at particular risk for developing both hospital-acquired hyponatremia and hyponatremic encephalopathy. The incidence of hospital-acquired hyponatremia is almost 30 percent in postoperative children, and almost half of the reported cases of hyponatremic encephalopathy in children have occurred in postoperative children,⁴ most of whom underwent minor surgical procedures. Postoperative patients

are at risk for developing euvolemic hyponatremia, which is similar to that seen with SIADH, due to numerous physiologic stimuli for AVP production, such as pain, stress, nausea, vomiting, narcotics, and volume depletion. Even a minor surgical procedure, such as a percutaneous renal biopsy, is associated with elevated AVP levels in 30 percent of patients.

The main factor contributing to hyponatremia in the postoperative setting is the administration of hypotonic fluids. Many recent surveys and audits of fluid-prescribing practices reveal that hypotonic fluids are primarily being used in the postoperative setting.

Indication for Fluid and Sodium Restriction

There are certain disease states where the ability to excrete both salt and water is severely impaired and both fluid and sodium restriction is necessary to prevent fluid overload. Disease states where both sodium and water restriction is indicated can be broadly classified as either edematous states or oliguric states. Below is a discussion of fluid management strategies in both conditions.

Edema-forming States

The most common conditions that lead to edema are congestive heart failure, hepatic cirrhosis, and nephrotic syndrome. The mechanism of edema formation and its treatment are different in each of these conditions. What they all have in common is an impaired ability to excrete free water due to decreased effective circulating volume, which makes hyponatremia a common associated complication. In edema-forming states it is best to avoid IVF use altogether and manage the patient with oral sodium restriction and therapy directed to the underlying disease, including loop diuretics and albumin infusion when indicated. If IVFs are needed, fluid should be restricted to approximately 600 ml/m² per day, which would be equivalent to 1000 ml/day in an adult patient. Also, mild hyponatremia is a common finding in these patients and the administration of hypotonic fluids, even at a restricted rate, could perpetuate or aggravate the hyponatremia. Hyponatremia is an independent risk factor for mortality in both congestive heart failure and cirrhosis in adults, so in these patients fluid restriction with 0.9 percent NaCl may be the best choice.

Oliguric States

Oliguric acute kidney injury can result from decreased renal perfusion; ischemic, toxic, or obstructive insults; or glomerular or tubulointerstitial inflammatory processes. In prerenal states of acute kidney injury, such as sepsis or hypovolemic shock, fluid resuscitation is essential and life saving. An evolving literature suggests that fluid overload in children with hemodynamic instability and

acute kidney injury is associated with increased mortality.²⁴ Excess fluid administration in children with oliguric acute kidney injury such as acute glomerulonephritis can result in complications such as congestive heart failure, pulmonary edema and severe hypertension. In these disease states fluid management must be carefully balanced between giving sufficient volume to reverse renal hypoperfusion and avoiding excess fluid overload and its resulting complications.²⁵ Fluid management in these patients is complicated and may include the use of diuretics and renal replacement therapies. In general a patient who is oligoanuric following the correction of any volume depletion should have his fluids restricted to approximately 400 to 600 mL/ m²/day, which is roughly equal to insensible losses, unless he is receiving a renal replacement therapy or responding to diuretics. With this degree of fluid restriction it is unlikely that significant fluid overload or hyponatremia will develop, and a hypotonic fluid may be appropriate to replace insensible free water losses. Close monitoring of the patient's volume and electrolyte status will be needed and IVFs adjusted accordingly.

Indications for Hypotonic Fluid Administration

Children with ongoing urinary or extrarenal free water losses will need to be provided with an adequate volume of electrolyte free water to prevent or correct hypernatremia and dehydration. The administration of 0.9 percent NaCl could result in hypernatremic dehydration

Renal Concentrating Defects

Children with renal concentration defects will usually need hypotonic fluids at a rate of administration equal to or greater than 1500 mL/m² per day. The composition and rate are largely determined by the severity of the renal concentrating defect. The most severe renal concentrating defects are seen with congenital nephrogenic diabetes insipidus, a rare hereditary disorder where there is varying resistance to AVP. These children can have severe polyuria and will typically require IVFs with approximately 0.1 percent NaCl at rates anywhere between 3000 and 6000 mL/m² per day to prevent or correct hypernatremia. If at all possible, their fluid needs are best met orally. A variety of conditions in children are associated with an acquired nephrogenic diabetes insipidus, where there may be only a partial concentrating defect. These children can be either asymptomatic or severely polyuric. If IVFs are required they should usually be hypotonic, but there are exceptions. In some forms of acquired nephrogenic diabetes insipidus, such as those due to a tubulopathy such as Bartter's syndrome or Fanconi syndrome, there is renal salt wasting that will require that fluids be administered at above-standard maintenance with significant sodium supplementation. Similarly, in polyuric states such as in the recovery phase of acute tubular necrosis, urinary electrolyte losses can be

substantial and excessively hypotonic fluids could produce hyponatremia. In conditions of high-output chronic kidney disease, such as renal dysplasia, if the glomerular filtration rate (GFR) is greatly reduced there will be a relative inability to excrete free water, and the administration of excessive hypotonic fluids can also result in hyponatremia. In these disorders, the measurement of the urine sodium concentration can help aid in choosing the appropriate sodium concentration of IVF.

Patients with central diabetes insipidus (CDI) are best treated with Desmopressin (DDAVP). In patients with acute CNS injury, such as head trauma, the development of CDI can be abrupt, and severe hypernatremia can develop if they are receiving 0.9 percent NaCl. Urine output and serum sodium must be monitored closely in cases of acute CNS injury in order to detect central diabetes insipidus early and to administer hypotonic fluids until DDAVP is started. Once DDAVP is used, hypotonic fluids are no longer indicated and could result in dangerous hyponatremia.

Extrarenal Free Water Losses

There are a variety of conditions where acutely ill, hospitalized children will have large extrarenal free water losses. The preterm neonate will have proportionally higher dermal insensible water losses than the older child and will need to be supplemented with free water. At the same time, preterm neonates have obligatory urinary sodium losses and reduced GFR, which puts them at risk for hyponatremia. Therefore, careful electrolyte monitoring is essential. Febrile patients will also have higher insensible losses, but if renal function is normal they should be able to generate free water by excreting hypertonic urine and should not be at substantial risk for hypernatremia. Patients with large gastrointestinal free water losses from voluminous diarrhea, emesis, or intestinal drains are at risk for both hypernatremia and hyponatremia, depending on the composition of fluids they are receiving. Ongoing losses will need to be replaced with a composition of fluids that approximates gastrointestinal losses, usually 0.45 percent NaCl.

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Head Trauma in Pediatrics: Role of Intensivist

Dhiren Gupta, MA Sheikh

MANAGEMENT GOALS

The management goals are:¹

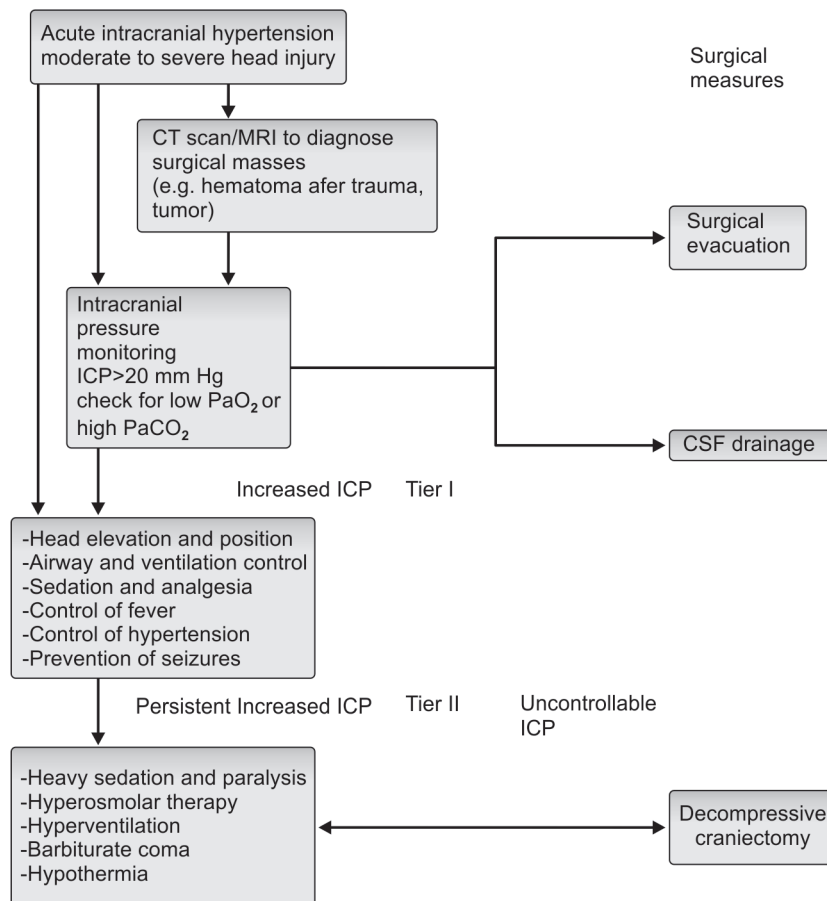
- Maintenance of adequate cerebral perfusion with well oxygenated blood
- Control of increased intracranial pressure (ICP) by reducing the volume of cranial vault contents

- Early recognition of, and when possible, prevention of events known to contribute to secondary brain injury. They are hypotension, hypoxemia, hypercarbia, acidosis, hyperthermia and seizures.

MANAGEMENT OVERVIEW

Do not use mannitol if patient is hypotensive.

Flow chart 1: AIH and head trauma—management algorithm



Recognition of Increased Intracranial Pressure² (Flow chart 1)

- *Raised ICP alone:* headache, emesis, papilledema
- *Local brain distortion:* headache, emesis, drowsiness, decerebrate rigidity, third nerve palsy, bradycardia, hypertension, abnormal respiration, impaired brain stem reflexes
- *Changes due to ischemia:* altered sensorium, fixed dilated pupil, hypertension, apnea, and absent brain stem reflexes.

Immediate Neurovitals Assessment

- Glasgow coma scale
- Pupillary size and reaction
- Airway maintenance
- Respiration (rhythm and symmetry)
- Pulse—rate, rhythm, volume
- Capillary refill time.

Inform neurosurgeon while stabilizing the patient. Imaging to be done only after initial stabilization.

A. Intubation¹

Indications

- Flaccid or extensor (decerebrate) or flexor (decorticate) posturing
- Glasgow coma scale ≤ 9 or deteriorating conscious state
- Ventilatory insufficiency ($\text{PaO}_2 < 60$ mm Hg in room air, or a $\text{PaCO}_2 > 45$ mm Hg).
- Loss of airway reflexes (pooling of secretions in throat)
- Severe facial injuries (La Forte fracture, mandibular fracture).

Care during Intubation

Give 100 percent FiO_2 via non-breathing mask and give IV lidocaine 1 mg/kg—wait for 3 to 5 minutes before laryngeal manipulation.

Use RSI technique unless hypoxic, apneic.

Use etomidate or propofol for sedation and, vecuronium or rocuronium as neuromuscular agent if required. (avoid succinylcholine as it can worsen the ICP).

B. Ventilation

Keep PaCO_2 between 35 and 40 mm Hg (in absence of arterial sampling target ETCO_2 35).

PEEP – 3 to 5, up to maximum 10 cm if required (e.g. coexisting ARDS or lung collapse).

Use lidocaine before endotracheal suctioning.

Short-term use of hyperventilation via hand bagging for no longer than two minutes only if there is impending cerebral herniation.

C. Circulation

If patient presents in shock insert minimum two large bore cannulae in upper limbs (preferably). IV saline bolus dose of 10 to 20 ml/kg (up to 2-3 boluses) till intravascular volume is restored. After a maximum of 40 to 60 ml/kg resuscitation fluid, packed cells should be used for further fluid resuscitation. Three percent saline IV bolus (2-6 ml/kg) can be used in patients with increased intracranial pressure and shock.

If cardiovascularly unstable despite fluid resuscitation, it is important to consider bleeding from other sites, especially femur, abdomen, chest, pelvis, and in infants the scalp.

After restoration of intravascular volume provide maintenance fluid.

Holliday-Segar formula for maintenance fluid requirements by weight		
Wt (kg)	ml/day	Water ml/h
0-10 kg	100/kg	4/kg
11-20 kg	1000 + 50/kg for each kg >10	40 + 2/kg for each kg >10
> 20 kg	1500 + 20/kg for each kg >20	60 + 1/kg for each kg >20

Give 2/3 of maintenance fluid calculated by Holliday-Segar formula.

<10 kg – add dextrose to normal saline or N/2 with dextrose

>10 kg – NS unless low sugar

Add KCL 2 ml/100 ml to maintenance fluid

Guide for type of fluid—If serum Na <145 mmol/L, use 0.9 percent saline, otherwise use 0.45 percent saline.

Inotrope Selection^{2,3}

- Commence dopamine at 5 to 10 mcg/kg/min IV if hypotensive.
- Add noradrenaline 0.05 to 1 mcg/kg/min IV if required. Target cerebral perfusion pressure (CPP = MAP – ICP):

Newborn >30 mm Hg, 1 month to 1 year >40 mm Hg, 1 to 10 years >50 mm Hg and 10 to 15 years >60 mm Hg.

Other targets - Central venous pressure - ≥ 8 mm Hg in ventilated, ≥ 6 in non-ventilated patients), urine output – 1 ml/kg/hour.

Target of various blood pressure (in absence of intracranial pressure monitoring):

Systolic blood pressure - 90 mm Hg + (2 × age in years) in children 1 to 10 years.

It is essential to keep the systolic blood pressure above the 95th centile for age.

Maintain age appropriate MAP 55 + age × 2 or CPP + 20 mm.

D. General Management^{1,4,5}

When to Notify Neurosurgeon?

- Moderate to severe head injury
- Deteriorating level of consciousness as measured by GCS (decrease >1 point) in any admitted patient
- Onset of focal signs:
 - Pupillary inequality
 - Hemiparesis
- Clinical signs consistent with herniation
- Clinical signs suggestive of seizure activity
- Raised ICP or low CPP
- The intensivist in consultation with the neurosurgeon will determine at what level and how the ICP or CPP should be treated, and this will be individualized for each patient.

Sedation and Analgesia

Patient on ventilator support

Morphine 40 to 100 µg/kg/hr or Fentanyl – 2 to 10 µg/kg/hr

Midazolam 0.1 mg/kg stat, continuous infusion 0.05 mg/kg/hr – 0.2 mg/kg/hr

Diazepam 0.1 to 0.5 mg/kg/dose every 6-hourly.

Propofol Intermittent boluses (1-2.5 mg/kg can be used for brief procedures, spikes of increased ICP. Continuous infusion (1.5-4.5 mg/kg/hr)

Monitoring Use Bispectral Index or continuous EEG if available.

Preferred combination: Combination of Morphine 50 µg/kg/hr + 0.1 mg/kg/hour

Patient not on ventilator: Do not use sedative agents, use intravenous intermittent analgesic agents like fentanyl (1 µg/kg) or NSAID – Diclofenac Na (1 mg/kg) so as not to disturb the level of consciousness which is an important sign to monitor the patient's condition.

Paralysis

Do not paralyze except for during intubation or patient having refractory and or sustained ICP after sedation and analgesia.

Agents – Do not use Pancuronium in presence of tachycardia.

Vecuronium - 0.1 mg/kg stat dose, Continuous infusion 0.05 mg – 0.1 mg/kg/hr

Position

Keep head in midline and raise head end to 15 to 30 degrees (avoid in presence of hypotension)

Avoid Trendelenberg position (head down)

Use appropriate hard cervical collar in suspected cervical trauma.

Use sand bags for maintenance of position. Pressure area care (to prevent decubitus ulceration) will be required every 2 hours. The child should be turned 1/4 supine, side to side, maintaining neutral alignment of the head. The occiput, heels and other bony prominences are important areas to observe. A pressure-relieving device (e.g. rubber gloves filled with air) should be used to reduce the likelihood of occipital pressure areas. If a spinal cord injury is suspected, the patient should be routinely log rolled.

Temperature Control

Maintain temperature 36.5 to 37.5°C. Aggressively control fever by using paracetamol orally or per rectally. Do not induce hypothermia unless specifically indicated (mentioned as 2nd or 3rd tier therapy).

Imaging

X-ray cervical spine AP and lateral view is—indicated in all patients with head trauma with loss of consciousness, pain in neck, intoxicated patient and with distracting painful injuries (e.g. femur fracture).

CT scan of the head performed after initial stabilization at the time of admission, upon subsequent deterioration in neurological condition and at the discretion of the intensivist or neurosurgeon.

Anticonvulsants

*Prophylactic anticonvulsants*²—Drug of choice is Phenytoin or Fosphenytoin (if hemodynamically unstable). Do not use phenobarbitone. Prophylactic use is indicated in severe head trauma (GCS ≤9), space occupying lesion (contusion, hemorrhage, depressed fracture, midline shift). Duration – 1 week (after consciousness is regained).

Seizures occurring at any time after head trauma, should be managed in accordance with standard approaches to patients with new-onset seizures. Use benzodiazepines (midazolam 0.1 mg/kg IV and repeat dose after 5 minutes if seizures are not controlled) as intermittent doses or continuous infusion.

Prophylactic Antibiotics

Antibiotics (Ceftriaxone) indicated for patients who present with the compound skull fracture and externally draining intraventricular catheter.

Indications and Contraindications of ICP Monitoring (Preferably via Intraventricular Catheter)

Indications: Severe TBI (Glasgow Coma Scale <9), Mild to moderate TBI with abnormal admission head CT scan.

Contraindications: Central nervous system infection, coagulation defects, anticoagulant therapy, scalp infection, severe midline shift resulting in ventricular displacement, cerebral edema resulting in ventricular collapse.

Nutrition, Metabolic Requirements and Stress ulcer Prophylaxis

Despite decreased cerebral metabolic rate for oxygen (CMRO₂) post head injury, resting energy expenditure is significantly increased. Patients who are not on neuromuscular blockers should be provided with 140 to 150 percent of the normal resting energy expenditure. For those patients on neuromuscular blockers, intake should be 100 to 120 percent of the normal resting energy expenditure.

If the patient is constipated, consider the administration of stool softeners. This may help to prevent the Valsalva maneuvers (which will increase ICP).

E. Treatment of Raised Intracranial Pressure^{5,6,7,8}

The primary objective is the maintenance of an adequate cerebral perfusion pressure. If there is sustained intracranial hypertension clinically or on measurement (ICP 20-24 mm Hg for 30 minutes, or ICP 25-29 mm Hg for 10 minutes, or ICP 30 mm Hg or more for 1 min) following interventions can be done as per the facilities and expertise available.

(In absence of ICP monitoring we will consider as increased ICP if patient shows following sign and symptoms—Hypertension, bradycardia, irregular respiration (Cushing triad) asymmetrical pupil, non-reacting pupil, sluggishly reacting pupils: caution – Above signs are late manifestations of ICP).

- i. Forced hyperventilation targeting PaCO₂ 26 to 30 mm Hg via hand bagging for no longer than two minutes (only if there is cerebral herniation or an ICP > 40 mm Hg)
- ii. Ensure adequate sedation and analgesia.
- iii. Mannitol 0.25 to 0.5g/kg/dose IV (1.25-2.5 ml/kg of 20 percent) Up to 4 doses in 24 hours.

Precautions: Ensure serum osmolality is no greater than 320 mOsm or osmolal gap not more than 10 (difference between calculated and measured osmolality)

- iv. Hypertonic saline 3 percent can be used as alternative. Bolus dose of 2 to 6 ml/kg followed by infusion of 0.1 ml to 1 ml/kg/hr.

Aim of sodium should be 145 to 155 mEq. (335–345 mOsm/kg, max 360 mOsm/kg with BUN and glucose within physiologic ranges).

Osmotic therapy must be tapered after 24 to 48 hours of continued use to avoid rebound.

Both mannitol and hypertonic saline can be used sequentially.

Intermittently or continuously drain CSF (if ventricular drain in place or lumbar drains can be inserted). (Lumbar drain can be used if there is no mass lesion and cisterns are open).

- v. Thiopentone. Avoid hypotension. Slow bolus dose of 1 to 5 mg/kg IV (Maximum of 1 mg/kg/min with not more than 5 doses recommended depending upon blood pressure response)

- vi. Paralyze and cool to 33°C. Cooling to be done maximum up to 72 hours. The patient's core temperature should be allowed to rise 1 degree every three hours up to 37 degrees. Cooling and rewarming should be achieved by servo-controlled warming/cooling blanket.

- vii. When to operate –

Decompressive craniectomy, evacuation of mass lesion with or without duraplasty

Severe TBI, no mass lesion, refractory ICP

Any TBI, mass lesion causing significant tissue shift

External ventricular drains—can monitor ICP and also drain cerebrospinal fluid. Controlled lumbar drain can also be inserted in presence of discernible basilar cisterns (on CT scan).

Treatment to Reduce Intracranial Pressure Based on Response of Treatment

Stage Ia (mandatory to all): 15 to 30° head end of bed up, maintaining temperature 36.5 to 37.5°C, analgesia, comfort, maintaining arterial oxygen saturation (SaO₂) > 97 percent, maintaining arterial oxygen pressure (PaO₂) > 75 to 80 mm Hg, maintaining arterial carbon dioxide pressure (PaCO₂) at 35 to 40 mm Hg (4.5 kPa), (Optional - maintaining jugular venous oxygen saturation (SjvO₂) > 55%)

Stage Ib: Commencing mannitol/Hypertonic saline.

Stage II: Reducing PaCO₂ to 30 mm Hg (4.0 kPa), temperature 33°C, application of thiopentone (maintaining SjvO₂ > 55%).

Stage III: Decompressive Craniectomy

When to Switch from Stage I to Stage II or Stage III

First Stage to Second Stage

Failure to reduce ICP below 20 mm Hg within 2 hours of sequential mannitol/hypertonic saline infusion. Development of adverse effect (renal failure, congestive heart failure, rebound phenomenon, severe hyponatremia) barring continuation of osmotic agents.

Return of ICP to pretreatment value within 4 hours of osmotic agent bolus, i.e. before next dose of osmotic agent is due is a relative indication for switching to next tier, unless CPP can be maintained more than the desired lower limits.

Second Stage to Third Stage

Failure to reduce ICP by 25 percent of pretreatment value
Persistent ICP elevation >20 to 25 mm Hg during metabolic suppression therapy (thiopentone) despite burst suppression EEG pattern at 1 to 2 burst per minute for >2 hours

Persistent ICP elevation >20 to 25 mm Hg during induced hypothermia with target temperature of 32° to 34° for >2 hours. Development of adverse effect (marked

hypotension requiring >1 vasopressor to keep adequate CPP and MAP; coagulation abnormality with increased bleeding risk; presence or development of severe infection/sepsis) barring use/continuation of hypometabolic agents.

Weaning from ICP Therapy

Once stability of ICP has been maintained for 24 to 48 hours, therapies can be gradually withdrawn in the reverse manner to which they were commenced. The order of weaning is usually:

- Normalize PaCO₂ and Osmotherapy
- Cease paralysis
- Reduce sedation
- Remove ICP monitor
- Extubation

MANAGEMENT PHYSIOLOGICAL BASIS

Do not use mannitol if patient is hypotensive:

Acute intracranial hypertension (AIH) is a clinical condition defined as the persistent elevation of intracranial pressure (ICP) above 20 mm Hg for greater than 5 minutes in a patient who is not being stimulated. AIH occurs commonly in acute brain injury related to trauma, ischemia, or hemorrhage, and is associated with poor outcome regardless of cause. It is a neurologic emergency that requires prompt diagnosis and treatment. Normal ICP in children varies with age (newborn 1.5-6, infants 2-6, toddler 5-6, and older children 6-13 mm Hg), during day, coughing and body position. While managing patient with acute intracranial hypertension maintain ICP <20 mm Hg between 8 yrs to adult, <18 mm Hg between 1 and 8 years and <15 mm Hg in infants).

Intracranial pressure (ICP) is defined as pressure within vault that results due to interaction between brain parenchyma ($\approx 80\%$), cerebrospinal fluid ($\approx 10\%$), and cerebral blood volume ($\approx 10\%$). Monroe and Kellie doctrine states that the alteration in one compartment must be compensated by opposite change in other compartment or with increase in ICP. Normally ICP is kept within normal limits. Initially with increase in contents of the vault, the CSF is pushed to spinal canal and further increase in volume pushes blood into jugular vein and decrease CSF production. At some point the compensation fails and ICP rises suddenly. Intracranial dynamics also depend on autoregulation, compliance, CBF, cerebral perfusion pressure, and cerebral metabolic rate. Autoregulation helps in maintaining the CBF and CBV within limits with change in systemic pressure. Failure of autoregulation will result in changes in CBF and CBV with change in systemic pressure. Change in brain compliance will result in sudden rise in ICP. CBF is regulated by pCO₂, pH, arterial oxygen, CPP, fever, seizure and cerebral metabolic rate. Fever and seizure will increase the cerebral metabolic rate.

CPP: It is an indirect indicator of CBF and is the pressure at which cells are perfused. CPP is calculated by measuring mean arterial pressure minus ICP (CPP adults >70 mm Hg, child >50 -60 mm Hg, infants and toddler 40-50 mm Hg). CPP <30 mm Hg is associated with universal mortality.

Causes of Intracranial Hypertension

Intracranial (primary)

- Brain tumor
- Trauma (epidural and subdural hematoma, cerebral contusions)
- Nontraumatic intracerebral hemorrhage
- Ischemic stroke
- Hydrocephalus
- Idiopathic or benign intracranial hypertension
- Other (e.g. pseudotumor cerebri, pneumoencephalus, abscesses, cysts)

Extracranial (secondary)

- Airway obstruction
 - Hypoxia or hypercarbia (hypoventilation)
 - Hypertension (pain/cough) or hypotension (hypovolemia/sedation)
 - Posture (head rotation)
- Hyperpyrexia
- Seizures
- Drug and metabolic (e.g. tetracycline, rofecoxib, lead intoxication)
- Others (e.g. high-altitude cerebral edema, hepatic failure)

Postoperative

- Mass lesion (hematoma)
 - Edema
 - Increased cerebral blood volume (vasodilation)

Neurological injury and possible mechanism of raised ICP

<i>Neurological injury</i>	<i>Possible mechanism of raised ICP</i>
Intraparenchymal bleed	Cerebral edema and mass effect
CNS infections (bacterial/viral)	Inflammatory response, cerebral edema, hydrocephalus, cerebral hyperemia
Traumatic brain injury (TBI)	Mass effect, edema, ischemia, intraventricular and intracerebral bleed
Intraventricular bleed	Hydrocephalus
Hydrocephalus	Impaired CSF absorption, edema
Brain tumor	Mass effect, edema, hydrocephalus

Goal directed management of raised intracranial pressure (ICP) is to maintain physiological end points within normal range and prevent secondary brain injury (ischemia, edema, and neurochemical alteration). Various factors which worsen secondary brain injury are hypoxia, hypoperfusion, free radicals, release of excitatory neurotransmitters, increase in intracellular calcium and potassium.

Treatment of Systemic Hypertension

It is unwise to reduce systemic blood pressure in patients with hypertension associated with untreated intracranial mass lesions because cerebral perfusion is being maintained by the higher blood pressure. In the absence of an intracranial mass lesion, the decision to treat systemic hypertension is more controversial and may need to be individualized for each patient. When pressure autoregulation is impaired, which is common after TBI, systemic hypertension may increase CBF and ICP.

In addition, elevated blood pressure may exacerbate cerebral edema and increase the risk of postoperative intracranial hemorrhage.

Systemic hypertension may resolve with sedation. If the decision is made to treat systemic hypertension, the choice of antihypertensive agent is important. Vasodilating drugs, such as nitroprusside, nitroglycerin, and nifedipine, can be expected to increase ICP and may reflexively increase plasma catecholamines, which may be deleterious to the marginally perfused injured brain. Sympathomimetic-blocking antihypertensive drugs, such as β -blocking drugs (labetalol, esmolol) or central acting α -receptor agonists (clonidine), are preferred because they reduce blood pressure without affecting the ICP. Agents with a short half-life have an advantage when the blood pressure is labile.

Sedation in Traumatic Brain Injury and AIH

Benzodiazepines are particularly suitable in the neuro-intensive care unit, but due to their plateau effect, cannot depress brain electrical activity even at high doses. A further disadvantage is that they present a long duration of action. Combination of midazolam and morphine gives good analgesia and sedation. It is also cost effective when given as infusion.

Propofol administration has been proposed as an alternative in TBI patients. Propofol decreases ICP through a reduction in brain metabolism, which explains its potential neuroprotective effect. The combination midazolam-propofol allows control of intracranial hypertension with the possibility of obtaining burst-suppression at high doses. Such a combined strategy reduces the use of barbiturates. The 'propofol infusion syndrome' must be a constant fear when using propofol. This syndrome, characterized by multiorgan failure, has a high incidence in sepsis or septic shock, which are therefore contraindications to propofol administration. It is mandatory to

stop propofol in the event of metabolic acidosis (with or without lactates), hyperkalemia, renal insufficiency, rhabdomyolysis or triglycerides level above 4 mmol/L. Hypertriglyceridemia is a warning symptom in this context. Due to mentioned problems with propofol infusion syndrome continuous infusion especially >24 hours is not recommended therapy in pediatric age group.

Ventilation in Neurological Cases

Once the airway has been secured, ventilator settings should be adjusted to the optimal setting required to maintain an oxygen saturation above 97 percent, a PaO_2 between 80 and 120 mm Hg and a PaCO_2 within 35 to 40 mm Hg range. The mode of ventilation should be selected based on patient response and comfort. Prophylactic hyperventilation is not advocated. Hypocapnia is induced to lower ICP by decreasing the cerebral blood volume (CBV) via cerebral arterial vasoconstriction. Cerebral blood flow (CBF) decreases by approximately 3 percent per mm Hg change in PaCO_2 (range, 60-20 mm Hg PCO_2) in patients with traumatic brain injury.

Classification of severity of Hypocapnia

Target PaCO_2	Range
26 mm Hg (<3.5 kPa)	Intensified forced hyperventilation
26 to 30 mm Hg (3.5 to 3.9 kPa)	Forced hyperventilation
31 to 35 mm Hg (4.0 to 4.7 kPa)	Moderate hyperventilation
36 to 45 mm Hg (4.8 to 6.0 kPa)	Normoventilation

Current Role for Hypocapnia in Acute Brain Injury

There are only two proven indications of forced hyperventilation (which should be done for <2 minutes)

Imminent Brain Herniation

There is a strong physiologic (and empirical) rationale for brief use of hypocapnia to acutely reduce ICP. Although the evidence is limited, the rapidity of induction and its immediate effect on CBF make it a useful strategy while definitive measures are being instituted.

Intraoperative use During Neurosurgery

Hypocapnia is used successfully during neurosurgery to facilitate access or to acutely reduce brain bulk.

Moderate hypoventilation (31-35 mm Hg) can be used as last medical measure in cases of refractory ICP.

Precautions

It is important to remember that when acute hypocapnia (forced hyperventilation) is used in these settings,

normocapnea should be restored as soon as is feasible, because hypocapnia becomes ineffective within hours. If moderate hypoventilation is used for 24 hours (maximum permissive time) then it should be withdrawn gradually (not >5 mm/hour) to prevent rebound intracranial hypertension.

Limitations of Hypocapnia

Hypocapnia may worsen neuronal ischemia and reperfusion injury. Hypocapnia during resuscitation after cardiac arrest is associated with worsened brain injury and it aggravates hypoxic-ischemic central nervous system damage especially in the immature brain (<2 year). After 60 hrs of continuous hyperventilation, hypocapnia becomes ineffective or counterproductive in controlling ICP over time.

Osmotherapy

Physiological principles of osmotic agents are same. Osmotic gradient is necessary to draw water from cells. Minimum 10 percent change in osmolality is required to decrease or increase water from brain tissue. The efficacy of osmotherapy in reducing the ICP depends upon the presence of an osmotic gradient between blood, CSF and brain. Once the osmotic gradient has been obliterated by the entry of the solute into the CSF and brain compartments, and by the transient appearance of idiogenic osmoles, the therapeutic efficacy of osmotherapy is lost and rebound rise in ICP may develop. Two osmotic agents are currently in use in most neurocritical care units: mannitol and hypertonic saline. Both are highly effective in reducing acutely elevated ICP in various clinical conditions, with almost immediate effect lasting for several hours. It is essential that autoregulation should be intact in children where osmotherapy is being used.

Mannitol[®]

Mannitol is the preferred osmotic agent due to its availability and physician's familiarity of use. It has several mechanisms of action. Intravenous bolus administration of mannitol lowers the ICP in 1 to 5 minutes with a peak effect at 20 to 60 minutes. An immediate effect from bolus administration results from plasma expansion with reduction of blood viscosity, improvement in microvascular cerebral blood flow, cerebral oxygenation, and CPP with reduction in cerebral blood volume, and ultimately lowering of ICP. A slightly delayed effect occurring within 15 to 30 minutes and lasting for up to 6 hours, results from a direct osmotic effect on neural cells with reduction in total brain water. Additional possible mannitol effects include reduced CSF production, free radical scavenging, and inhibition of apoptosis. Repeated doses of mannitol require ICP monitoring since the effect diminishes over

time and a rebound phenomenon has been noted after prolonged use in experimental models although clinical studies have shown variable results. The osmolar gap (mentioned below) correlates better with the mannitol level and is the preferred monitoring parameter to prevent mannitol-induced renal failure.

Dose

Mannitol in the dose of 0.25 to 0.5 gm/kg (1.25 to 2.5ml/kg of 20%) as bolus and can be given 6 hourly will result mean reduction of ICP by 34 to 52 percent.

Monitor

Euvolemia must be established prior to instituting mannitol therapy to avoid further reduction in cerebral perfusion. A measured serum osmolality >320 mOsm/L, osmolar gap >10 or change in osmolar gap from baseline >10 correlates with poor mannitol clearance, and increased risk of renal toxicity.

Hypertonic Saline[®] (HTS)

Hypertonic saline refers to any saline solution with a concentration of sodium chloride greater than physiologic saline (0.9%), and it can be used as a continuous infusion or in bolus form to prevent and/or treat intracranial hypertension is effective for control of increased ICP by reducing CBV especially after severe head injury.

Dose

Three percent saline 0.1 to 1.0 ml/kg/hr as continuous infusion may be preceded by bolus (2-6 ml/kg). Hypertonic saline has similar efficacy with mannitol and may be used interchangeably, especially in patients with a high osmolar gap.

Monitor

Serum osmolality, serum sodium, renal function and neurological status.

Target Na and Osmolality

Worsened outcome was not encountered until sodium values exceeded 155 mEq/L. This would correspond approximately to a serum osmolality of 335 to 345 mOsm/kg (BUN and glucose within physiologic ranges). Maximum osmolality allowed is 360 mOsm/kg. Once clinical parameters achieved HTS should be tapered 25 percent every 6 hourly.

Precaution

Do not raise serum Na >0.5 mEq/L/hr in patients with chronic hyponatremia. (central pontine myelinosis). Preferably use central venous line for infusion.

Mechanism of Action

Dehydration of cerebrovascular endothelial cells and erythrocytes (making them more deformable). Increases plasma volume expansion, reverses vasospasm and also decreases endothelial cell edema. Though not well understood tempers the inflammation and acts as immunomodulator, thereby reducing secondary brain injury. Hypertonic saline may help in re-establishing the electrochemical gradients, resting membrane potential. HTS may interrupt the process of cell hyperstimulation and death.

Side Effects

Rebound elevation in ICP, central pontine myelinosis, hematologic abnormalities like bleeding and dyselectrolytemia like hypokalemia and hyperchloremic acidosis.

The risks of bleeding complications are greatest when 10 percent or more of the normal plasma volume is replaced with HTS.

Comparison between Mannitol and Hypertonic Saline

Although there are only a small number of comparative trials evaluating mannitol against hypertonic saline in the treatment of intracranial hypertension, it has become popular to view hypertonic saline as having at least some advantages over mannitol. This is mainly due to the theoretical advantage that sodium chloride (1.0 compared with 0.9 mannitol) has a higher osmotic reflection coefficient across an intact blood-brain barrier (BBB). Less sodium permeability may evoke a greater increase in serum osmolality. The creation of a higher transendothelial osmotic gradient in the vascular compartment may lead to more interstitial and intracellular brain and body water extraction into the intravascular space. Improved brain edema reduction, better ICP decrease and perfusion increase are considered mainly to then attenuate secondary brain injury progression. Another reason for superiority of hypertonic saline over mannitol is augmentation of intravascular volume and cardiovascular performance. Therefore it can be used in presence of hypotension.

Theoretical osmolalities of solutions employed to treat intracranial hypertension.⁹

0.9% Saline	308 mOsm/kg
3% Saline	1026 mOsm/kg
7.5% Saline	2567 mOsm/kg
20% Saline	6844 mOsm/kg
23.4% Saline	8008 mOsm/kg
30% Saline	10267 mOsm/kg
7.5% Saline/6% dextran	2568 mOsm/kg
7.2% Saline/6% HAES (200/0.6)	2464 mOsm/kg
10% Mannitol	550 mOsm/kg
15% Mannitol	825 mOsm/kg
20% Mannitol	1100 mOsm/kg
25% Mannitol	1375 mOsm/kg

Suggested laboratory monitoring with hyperosmolar therapy

Every 2 to 4 hours	Serum sodium, serum osmolality
Every 4 to 6 hours	Blood gas analysis
Every 6 to 12 hours	Hb, PT/APTT, Platelets

Drainage of Cerebrospinal Fluid

Drainage of CSF is frequently performed in TBI patients. External strain gauge allows the continuous measurement of ICP and the calculation of CPP (when the drainage line is externally clamped), or withdrawal of CSF (when the drainage line is open). In case of low cerebral compliance due to cerebral edema, the evacuation of a few milliliters of CSF may be sufficient to decrease ICP dramatically. It has been shown that a 3 ml withdrawal of CSF resulted in a mean 10 percent decrease in ICP and a mean 2 percent increase in CPP, which were sustained for 10 min. This therapy is simple, cost-effective and overrides the often serious systemic complications related to drug or physical therapies, especially those induced by barbiturates and hypothermia. Drain placement might be technically difficult, and can be complicated by cerebral contusion or ventriculitis.

In absence of intraventricular drains lumbar drains can be placed at the level of the L3 or L4 vertebrae for CSF withdrawal in presence of refractory ICP. Before performing this procedure one should ascertain that basal cisterns should be open (CT scan).

Steroids in AIH^{8,9}

Steroids are particularly effective for treating intracranial hypertension secondary to cerebral tumoral process and bacterial meningitis. The majority of available evidence indicates that steroids do not improve outcome or decrease ICP in TBI patients.

The most commonly used regimen is intravenous dexamethasone, 4 mg every 6 hours. For other neurosurgical disorders, such as TBI or spontaneous intracerebral hemorrhage, steroids have not been shown to have a benefit and in some studies have had a detrimental effect. The CRASH trial is a recently completed, large, placebo-controlled randomized clinical trial of methylprednisolone for 48 hours in patients with TBI. Administration of methylprednisolone resulted in a significant increase in the risk of death from 22.3 to 25.7 percent (relative risk 1.15, 95% confidence interval 1.07-1.24). This trial confirmed previous studies and guidelines that routine administration of steroids is not indicated for patients with TBI.

SUMMARY

Effective treatment of intracranial hypertension involves meticulous avoidance of factors that precipitate or aggravate increased ICP. When ICP becomes elevated, it is

important to rule out new mass lesions that should be surgically evacuated. Medical management of increased ICP should include sedation and paralysis, drainage of CSF, and osmotherapy with either mannitol or hypertonic saline. One of the key issues is to consider that TBI is more likely a syndrome than a disease. After trauma, the traumatized brain is characterized by a huge pathophysiological heterogeneity. A single, unique therapy cannot be efficient for all the different types of brain trauma. This could partly explain why systematic use of an increased CPP approach, hypothermia, corticosteroids and albumin all failed to demonstrate any positive effect in large multicenter trials. For intracranial hypertension refractory to initial medical management, barbiturate coma, hypothermia, or decompressive craniotomy should be considered.

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Newer Antiepileptic Drugs in the ICU

RK Sabharwal

Abstract

A recent study in the *Journal of the American Medical Association* found over 40 percent of the best designed, peer-reviewed scientific papers published in the world's top medical journals misrepresented the actual findings of the research.¹ Physicians are far more likely to report favorable results of treatment than they are to publish insignificant or unfavorable results. The “spin doctors” writing the papers found a way to show treatments worked, when in fact, they didn't. If the conclusions in 40 percent of the papers published in medical journals are being spun toward independent interests, how can we consider the medicine we are practicing “evidence based?”

Scientific Medical Journal publication is rapidly increasing in volume. It has become the most explosive field of journal publications worldwide. New medical articles are appearing at a rate of at least one every 26 seconds. Peer-review is the process that decides whether your work gets published in an academic journal. It doesn't work very well any more, mainly as a result of the enormous number of papers that are being published (an estimated 1.3 million papers in 23,750 journals in 2006). There simply aren't enough competent people to do the job. The overwhelming effect of the huge (and unpaid) effort that is put into reviewing papers is to maintain a status hierarchy of journals. *Any paper, however bad, can now get published in a journal that claims to be peer-reviewed.*

INTRODUCTION

The incidence of seizures in children is significantly higher than adults with the highest incidence occurring during the first year of life. With more than 20 antiepileptic drugs (AEDs) currently available to treat epilepsy optimum use of such a complex armamentarium is a challenge even for the epilepsy specialist. Although many, but not all, new AEDs have comparable efficacy to old standard drugs in well-controlled trials, *none of the new AEDs is superior to old drugs in terms of seizure remission.*² Although many believe that some modern AEDs are better tolerated than older ones, the authors of the ILAE treatment guidelines have suggested that statistically this has been very hard to show. One area in the field of epilepsy, where benefit of newer AEDs may be discernible is in the drug treatment of status epilepticus (SE), although the ultimate prognosis of SE rests predominantly on the etiology.

Seizures and status epilepticus (SE) in the intensive care setting can be seen in two main groups of patients: patients admitted to the intensive care unit (ICU) because of continuous or repetitive seizures requiring aggressive

treatment, and patients admitted for medical or surgical reasons that develop seizures during the course of their ICU stay. The intensive care unit (ICU) presents a challenge to the intensivist, the pediatrician, and the neurologist with regards to the diagnosis of seizures. Patients in the ICU may be comatose, sedated, or paralyzed, obscuring typical signs. An increased likelihood of non-convulsive status epilepticus (NCSE) is prevalent in such patients.

Changing Definition of Status Epilepticus

The highest SE incidence figures are found in the less than 2 age group, where the rate is over 10 times greater than in adults.^{3,4} Twenty-four percent of SE occurs in the first year of life and up to 64 percent occurs in the first 5 years of life. In up to 12 percent of cases of children with a first seizure attack, the event acts like an authentic SE. Only 25 to 28 percent of cases of SE in children have a prior history of epilepsy. Up to 17 percent of cases of SE in children are recurrent, 11 percent in the first 12 months, 18 percent in 24 months, and 20 percent from 36 to 48

months, with the first and second SE episode an average of 10 months apart.⁵

Status epilepticus (SE): It was initially defined as “an enduring epileptic condition”, without specifying exact durations. Since then, the definition has undergone multiple revisions to include and then modify the required duration, shortening the required seizure duration from 30 minutes to 5 minutes.⁶ From a clinician’s standpoint, it is in good practice to consider that all patients arriving at the emergency room suffering from an epileptic seizure could have SE and should be treated accordingly. This shortening of time was based largely on data demonstrating that seizures that do not cease in 5 to 7 minutes are less likely to terminate without intervention. It has also been shown that there is a 15-minute “therapeutic interval” after which it is very difficult to control epileptic activity. The potential for neuronal injury is positively correlated with the duration of the seizure, while pharmacoresistance increases with time and is reflected in the number of drugs administered. The various forms of SE include partial SE, nonconvulsive status SE, absence status SE, myoclonic SE, etc. The prognosis for SE is strongly related to etiology.

Febrile status epilepticus (FSE): It occurs in approximately 5 percent of febrile convulsions and accounts for about 25 percent of all childhood cases of status epilepticus. The treatment of FSE is similar to the treatment of other forms of SE. Although by definition, FSE is a febrile seizure lasting 30 minutes, treatment should be initiated with benzodiazepines 5 minutes into the seizure. A number of studies have shown that in FSE, as with nonfebrile seizures, a seizure that has not resolved by 5 minutes is less likely to stop spontaneously.

Refractory Status Epilepticus

The exact definition is still unclear, with different studies defining refractory status epilepticus (RSE) with varying durations, and a lack of response to different numbers (two or three) and types of medications. Literature reports that many authors consider refractory SE as persistence of status beyond 60 minutes. However, this is a regressive approach, as it implies that the SE that has not lasted 60 min is not “alarming”. Most authors consider RSE as “*generalized convulsive or nonconvulsive SE that continues clinically or electrographically despite 1st- and 2nd-line therapy*”.^{7,8} In the few available retrospective studies, estimated RSE frequency is between 31 and 43 percent of patients presenting as SE; almost all seem to require a coma induction for treatment. The failure to treat aggressively early on increases the likelihood of developing RSE. Factors found to be predictive of RSE for patients in SE include encephalitic etiology, severe impairment of consciousness at presentation, absence of a history of epilepsy (*de novo* SE), and low anticonvulsant levels (in patients with known epilepsy).

Super-refractory Status Epilepticus

In a subgroup of patients, refractory status epilepticus may last for days, weeks or months, despite treatment with multiple AEDs and coma-inducing medications. This lengthy course was reported in 20 percent of adults with refractory status epilepticus, and was referred to as malignant, refractory status epilepticus.⁹ A new term “*super-refractory status epilepticus*” was very recently used to describe such patients. Super-refractory status epilepticus is defined as status epilepticus that continues or recurs 24 h or more after the onset of anesthetic therapy, including those cases that recur on the reduction or withdrawal of anesthesia.¹⁰ Super-refractory status epilepticus is not uncommonly encountered in neurointensive care, but its exact frequency is not known. It is often associated with an encephalitic etiology, younger age, and previous good health, failure to respond to multiple drugs including coma inducing medications, and high morbidity and mortality. The status persists for days, weeks and even more than a month and poses an exhausting challenge to the treating staff and parents alike. A rare syndrome of sudden onset SE in developmentally normal children with devastating consequences has been reported in literature, and seen by a number of US. These cases often are initially regarded as viral encephalitides; the clinical features are of acute onset of an intractable convulsive status epilepticus following a brief fever that is refractory to all treatment interventions. Often these children are treated in the intensive care setting for weeks to months with high dose suppressive therapy in a state of therapeutic coma. Mortality is high and survivors are left with severe cognitive and neurological deficits, and chronic epilepsy. No infectious agents are isolated and neuropathology shows no evidence of inflammation.^{11,12} It is possible that some of these cases may be due to influenza or other viral encephalopathy, metabolic, mitochondrial, or an autoimmune disorder. This condition may be under-recognized and under reported.

Subtle Status Epilepticus

It is important to remember that even if the patient stops seizing clinically but does not wake up promptly; there is a high probability of ongoing subclinical seizures or electrographic SE. This is not uncommon and EEG monitoring remains supreme in determining that a nonconvulsive status is not persisting. True subclinical SE (i.e. no physical manifestations) is quite uncommon, but it can occur in comatose patients. Still, even patients in coma often have subtle physical manifestations of SE, such as rhythmic nystagmoid eye movements or very low amplitude twitches of one or more fingers. Eye open coma should also raise suspicion for SE and prompt an EEG.

PATHOPHYSIOLOGY

Most seizures terminate spontaneously within several minutes, possibly due to a GABA mediated recurrent inhibition that occurs in response to seizures. However, with continuing seizures, inhibitory GABA receptors are internalized in clathrin coated vesicles, some of which are recycled to the cellular membrane, and some of which are destroyed in lysosomes. As GABA is the principle inhibitory transmitter, this reduction in GABAergic activity may be an important reason for seizures to become persistent, and this decrease in GABA-mediated inhibition *would be responsible for the BZD resistance detected during continuing status, and to some extent that of phenobarbital*. It has also been repeatedly shown that the extracellular ionic environment, which can change in SE, may be an important factor in perpetuating seizures, and the normally inhibitory GABA (A)-mediated currents may become excitatory with changes in extracellular chloride concentrations. At the same time, excitatory N-methyl-d-aspartate (NMDA) receptors may be mobilized to the membrane. This receptor trafficking results in a decreased inhibitory control, and increased excitation that may lead to continuing status epilepticus and refractory states. In addition, the activation of the NMDA receptor by the excitatory neurotransmitter glutamate may be required for the propagation of seizure activity. This may suggest a role for NMDA-modulating medications such as ketamine and topiramate.⁷

GENERAL MEASURES IN THE MANAGEMENT OF STATUS EPILEPTICUS

All patients in whom there is a possibility of refractory, ongoing seizure activity (manifesting clinically or confirmed electrographically) need to be cared for in an ICU by staff proficient in the management of SE.¹³ A recent report by Tripathi et al.¹⁴ that majority of patients of RSE did not require ICU care raises some doubts, and sets dangerous precedents and potential medicolegal implications in the management of a potentially disabling and life-threatening disorder.

The main aims of treatment are (a) to support vital functions, (b) to identify and treat causal or precipitating factors and (c) to terminate ictal activity.

General Principles

“Rapidity and aggressiveness of treatment” is of paramount importance in the treatment of SE. There is animal and human data supporting the concept that therapeutic interventions are most effective when initiated early. Efficacy of benzodiazepines, phenytoin and barbiturates decrease significantly with increasing seizure duration in controlled animal experiments. In humans, first line medications control SE in 65 to 80 percent when initiated

within 30 minutes, but only in 40 percent if started after 2 hours of onset.

All contemporary protocols take a staged approach to treatment.¹⁰ Typically, in Stage 1 (early status epilepticus), therapy is with benzodiazepines. If seizures continue despite this therapy, the patient is said to be in Stage 2 (established status epilepticus) and therapy is with intravenous antiepileptic drugs such as phenytoin, LVA or valproate. If seizures continue despite this treatment, the patient is said to be in Stage 3 (refractory status epilepticus) and general anesthesia is usually recommended, at a dose that results in EEG burst suppression (a level of anesthesia at which all seizure activity is usually controlled).

FIRST LINE DRUGS

They are fast-acting drugs with a short half-life, and are the first to be administered in the event of a seizure.

Benzodiazepines

Benzodiazepines (BZDs) remain the most important agents in the management of epilepsy. Benzodiazepines, which work through the GABA inhibition of repetitive firing, are easy to use, rapid acting, with efficacy of at least 65 to 75 percent in the treatment of SE. They are drugs of first choice for SE and seizures associated with post-anoxic insult, and are also frequently used in the treatment of febrile, drug-induced, acute repetitive and alcohol withdrawal seizures. Among the approximately 35 BZDs available, a select few are used for the management of seizures and epilepsy: clobazam, clonazepam, clorazepate, diazepam, lorazepam and midazolam.

Lorazepam

Lorazepam (LRZ) is generally given as an IV bolus at doses of 0.05 to 0.1 mg/kg over 2 mt and the dose may be repeated after waiting for 5 minutes. Clinical studies in children have been mostly unblinded and have included retrospective and prospective designs. In a prospective open-label study, Appleton et al¹⁵ compared IV or rectal lorazepam and diazepam treatments in 86 children. A single dose terminated seizures in 76 percent of patients treated with lorazepam and in 51 percent of patients treated with diazepam. The advantage of LZP over DZP or midazolam (MDZ) is its long-lasting clinical effect, which is determined by the pharmacologic properties of the drug. DZP is more lipophilic and is subject to extensive redistribution, thereby decreasing the concentration of DZP in the brain.

Advantages of LRZ over DZP are its duration of action against SE (4-14 hours as opposed to 20 minutes) and its higher initial response rate. One group reported that children receiving DZ for SE more often required intubation and mechanical ventilation than comparable children receiving LRZ.¹⁶

Midazolam

In the treatment of status epilepticus, midazolam (MDZ) can be administered by IV bolus, continuous IV infusion or IM injection. It can also be administered buccally or nasally. Rectal administration is not recommended because of poor bioavailability. Midazolam is the most reliably absorbed intramuscular (IM) benzodiazepine for use in seizures and SE. Midazolam administered IM has been consistently shown to produce serum levels at 80 percent of peak levels within 5 minutes of administration. When administered intramuscularly, MDZ only takes 116 seconds to terminate seizures, as compared to 34 seconds when given by the intravenous (IV) route. Results from a randomized controlled trial that compared buccal MDZ with rectal DZP for emergency treatment of seizures in children suggested that MDZ was more effective than diazepam. Therapeutic success (defined as cessation of visible signs of seizure activity within 10 min of drug administration, lack of respiratory depression and no further seizures within 1 h) was noted in 56 percent of MDZ-treated patients.¹⁷ In controlled clinical trials, the efficacy of intranasal MDZ was similar to or better than that of IV or rectal DZP. Midazolam has also been found to be safe and effective when administered as a continuous infusion to treat refractory generalized convulsive SE. In 2008, a Cochrane review¹⁸ concluded on the basis of published trials that the 'evidence supports the use of buccal midazolam as the first-line treatment of acute tonic-clonic seizures in childhood including convulsive status epilepticus in which intravenous access is unavailable'.

Midazolam as a continuous IV infusion (CIV) is a treatment option for RSE. The recommended loading dose is 0.2 mg/kg, and boluses should be repeated every 5 minutes until seizures stop, up to a maximum total loading dose of about 2 mg/kg. The initial rate is 0.1 mg/kg per hour with a continuous dose range: 0.05 mg/kg to 4 mg/kg per hour (this is higher than in older literature, and even higher doses are occasionally used). The elimination half-life is 1.5 to 3.5 hours initially; with prolonged use, there may be tolerance, tachyphylaxis, and significant prolongation of half-life, up to days. Thus delayed recovery following weaning of therapy can occur. The drug can be tapered slowly over 24 hr or more. Rapid weaning is fraught with relapse of seizures. The main advantage of its use is its strong antiepileptic action. Its disadvantages include a purported strong tendency for rapid and acute tolerance to develop (sometimes after only 1 day of use) and thus the risk of seizure relapse. Midazolam is a strong respiratory depressant, and has cardiodepressant effects also, but these are generally less marked than those of barbiturate anesthesia.

It is essential that the cessation of SE be confirmed by an EEG. *If one particular infusion regimen fails, as evidenced by a return of clinical or electrographic seizures on discontinuation or reduction of the infusion, then that particular regimen should*

be abandoned, although the agent may be used in a combination regimen thereafter.

SECOND LINE DRUGS

The onset of action of these drugs is slower than that of BZDs, but they last longer and are therefore very useful as maintenance therapy. High response rates are seen if they are used early in the course of SE.

Fosphenytoin/Phenytoin

The phenytoins work through membrane Na^+ and Ca^{2+} channel stabilization, reducing the likelihood of repetitive neuronal firing. Phenytoin (PHT) is an effective anti-SE agent, but cannot be delivered rapidly enough to be considered a first-line agent. It has a long duration of action when an adequate dose is given (e.g. a 20 mg/kg loading dose yields a plasma concentration above 20 $\mu\text{g/ml}$ for 24 hours). Fosphenytoin is a water-soluble prodrug of phenytoin that is completely converted to phenytoin following parenteral administration. Thus, adverse events related to propylene glycol do not occur. The IV fosphenytoin preparation is buffered to a pH of 8.6 to 9.0, which makes it less likely to cause vascular complications. It is converted to phenytoin in 8 to 15 minutes. It is metabolized by the liver and has a half-life of 14 hours. Since 1.5 mg of fosphenytoin is equivalent to 1 mg of phenytoin, the dose, concentration, and infusion rate of IV fosphenytoin are expressed as phenytoin equivalents (PEs). The initial dose of fosphenytoin is 20 mg PE/kg, and it can be infused three times faster than IV phenytoin. Some experts feel that the therapeutic effect of these agents is maximal at the end of an infusion. Thus, there is no need to "wait for the drug to work" before proceeding to other treatment options.

IV fosphenytoin is preferred to IV phenytoin due to its water solubility and normal pH, thus allowing more rapid administration with less irritation of veins, no risk of necrosis with extravasation, less hypotension during administration, and compatibility with all IV fluids. It is rapidly dephosphorylated in the bloodstream to phenytoin, with a half-life of 10 to 15 minutes. Useful serum levels can be obtained within 1 to 2 hours after completion of the IV load. It can be given intramuscularly, but levels will not be therapeutic for 30 minutes.

Cardiac complications can still occur with fosphenytoin (due to phenytoin), and one must remember that phenytoin is effectively still being loaded. Free phenytoin levels can become very high in patients with low albumin or who are on other highly protein bound drugs such as benzodiazepines and valproate, and this can cause impaired mental status, occasional myoclonus, and possible seizure exacerbation for more than 15 minutes after the end of the infusion. Adverse effects unique to fosphenytoin include perineal paresthesias and pruritis; however both are related to rate of administration. Fosphenytoin is

not associated with local irritation as is phenytoin. Cardiac arrhythmias and hypotension have not been significant problems with intramuscular dosing, but intravenous dosing has been associated with hypotension.

IV Levetiracetam

Levetiracetam binds to the synaptic vesicle protein SV2A, decreasing calcium influx into the presynaptic terminal. It is unclear how levetiracetam (LVA) suppresses seizures, perhaps related to decreased release of excitatory neurotransmitters. Adding to its multifunctional effects, LVA also blocks high voltage activated (HVA) calcium channels and alters GABA function. The pharmacokinetic profile of single-dose LVA in children aged 2 to 46 months is similar to that reported in children aged 4 years and above, and is characterized by rapid absorption, resulting in peak plasma concentrations within 1.4 h of dosing and a half-life of approximately 5 to 7 hours. LVA plasma clearance in infants aged less than 6 months is slower compared to that in children aged 6 months to 4 years. LVA is a broad spectrum anticonvulsant and can be administered rapidly as a loading dose over 15 minutes, although adult studies suggest infusion times of 5 minutes is well tolerated.

It has shown good results in controlling neonatal seizures. Khan et al¹⁹ in a retrospectively analysis noted that 22 patients received a LVA load of 10 to 50 mg/kg for neonatal seizures. Nineteen of 22 patients (86%) demonstrated immediate seizure cessation at 1 hour. Seven of twenty-two patients (32%) achieved complete seizure cessation after administration of the loading dose, 14 (64%) achieved seizure cessation by 24 hours, 19 (86%) by 48 hours, and all 22 (100%) by 72 hours. In comparison with other IV anticonvulsants, LVA has few known adverse effects, including a low risk of sedation, cardiorespiratory depression, or coagulopathy, and thus is potentially useful in critically ill pediatric patients. In children with repetitive seizures; Abend et al²⁰ found that LVA terminated SE in 5/10 children at a loading of 20 to 30 m/kg. In these LVA was used as first line drug. In others who had received drugs earlier LVA reduced the number of seizures but did not terminate SE.¹⁹ In a similar trend, Gallentine et al²¹ noted that in the treatment of RSE in children, LVA was felt to be of benefit in 45 percent (5/11) of cases, resulting in either resolution of RSE or successful weaning of patients off continuous infusions of other anticonvulsants. In 27 percent (3/11), response to LEV was unclear as other medications were either added or increased concomitantly with LEV use. The median latency to cessation of RSE following LEV initiation was 1.5 days (range = 1-8 days). All responding patients were on LEV doses \geq 30 mg/kg/day (median 40 mg/kg/day).

Although intravenous LEV is an interesting alternative for the treatment of SE due to the lack of significant

centrally depressive effects and low potential of drug interactions, one has to be aware of the nonrandomized retrospective study design, the heterogeneous patient population and treatment protocols, as well as the publication bias inherent in these types of studies. Only a large randomized control trial with an adequate comparator will reveal the efficacy and effectiveness of this unique drug.²²

LVA can be administered as a 30 mg/kg loading dose administered at a rate of 5 mg/kg/minute. Maintenance doses of 30 to 60 mg/kg/day in t.i.d schedule can continue. Pharmacokinetically, LVA completely avoids hepatic metabolism, which may prove beneficial in complex patients with liver dysfunction or metabolic disorders or those patients at risk for major drug interactions. In comparison with other IV anticonvulsants, LVA has few known adverse effects, including a low risk of sedation, cardiorespiratory depression, or coagulopathy, and thus is potentially useful in critically ill pediatric patients. Rare reports of thrombocytopenia and altered liver functions have been described. Therapy with long-term LVA, however, is associated with variable sedation, significant behavioral, mood and memory changes. Triggering of myoclonic SE in a patient with myoclonic-astatic epilepsy was also reported, suggesting that not all myoclonic SE responds well to levetiracetam. Status gelasticus may also have been triggered by levetiracetam.

IV Sodium Valproate

IV valproate (VPA) was recently approved for the treatment of SE in Norway (in 2004) for SE, in adults and Germany (in 2007) as third choice drug for generalized convulsive SE, as second choice for simple and complex partial SE and as a first choice in absence SE.²³ A number of studies on intravenous VPA used to control various types of SE (GCSE, partial NCSE, status myoclonus, and absence status) in a variety of patient populations, ranging from children to elderly patients with cardiovascular instability, showed a low incidence of adverse events, in particular, no hemodynamic adverse effects, even when VPA was administered at higher than recommended infusion rates.

The benefits of VPA is that it has a broad-spectrum of action, ease of administration, solution compatibility, intermediate to long duration of action, rapid onset of action, and can be used as maintenance therapy. It has been consistently shown to be as or more effective than PHT in the control of seizures. It is a good alternative as a second-line AED when compared with PHT and fosphenytoin, with global responses in 66 to 100 percent of cases (mean, 81%). Its benefit lies in a relatively low risk for hypotension and sedation that is of significant benefit in the monitoring and management of patients with SE. This attribute affords a choice of a good AED in lieu of PHT in the management of SE, in hospitals with limited ICU facilities, particularly after a benzodiazepine has failed.

VPA should not be used if liver dysfunction, coagulopathy, thrombocytopenia, mitochondrial disease, or an underlying metabolic disorder exists. It differs from older generation AEDs in being an enzyme inhibitor, rather than inducer; one must be vigilant for increased levels or effect of concomitant P-450-metabolized medications. There is a dramatic fall of its level after addition of antibiotics, such as meropenem or amikacin, possibly owing to accelerated renal excretion. Hypotension has been reported in rapid infusions. Further, valproic acid may induce encephalopathy, with or without elevated ammonia levels and this possibility must be considered in patients with persisting encephalopathy.²⁴

A rapidly growing body of literature reports the use of LVA and VPA in SE. These studies are largely favorable, and describe impressive efficacy at the price of only a few, generally mild side effects. However, one has to beware of publication bias: Physicians are far more likely to report favorable results of treatment than they are to publish insignificant or unfavorable results.²⁵ A number of studies have been recently published from India, but have been criticized on bias and methodological issues.^{22,26}

The initial bolus may be 30 mg/kg administered at 5 mg/kg. If seizures are terminated, then a continuation of periodic (twice per day) dosing may be appropriate. If seizures recur, a continuous infusion of 1 to 5 mg/kg/hr may be tried.

THIRD LINE DRUGS

These drugs should be reserved for when the above medications fail. When used, it is always essential to consider the potential risk of respiratory depression and the need for assisted respiration, and therefore admitting the patient to the ICU for monitoring including continuous EEG monitoring. Phenobarbital, thiopentone, lignocaine, chloral hydrate, etc. are outside the scope of discussion in this review.

Propofol

Propofol (2, 6-di-isopropylphenol) is a potent intravenous hypnotic agent that is widely used in adults and children for sedation and the induction and maintenance of anesthesia. Propofol has gained popularity for its rapid onset and rapid recovery even after prolonged use. The principal antiseizure mechanism of action is as an agonist on GABA-A receptors, but modulation of Ca- and Na- channels has also been described. Propofol is hydrophobic and is prepared as a milky white emulsion containing soybean oil, egg lecithin, and glycerol. It is highly lipophilic. Because of its short half-life of 3 minutes, it must be used in a continuous IV infusion for long duration. The recommended dose is a bolus of 1 to 2 mg/kg, followed by a continuous infusion of 1 mg/kg to 15 mg/kg per hour with a recommended maximum dosage of 5 mg/kg per hour if maintained for days.

There is no consensus regarding total duration of induced coma when seizures are controlled, but 12 to 24 hours seems to be the most commonly used duration. It is prudent to avoid prolonged use of propofol (>48 hours) at higher doses (>5 mg/kg per hour), and once used creatine kinase and lactic acid should be followed closely. A retrospective study of 33 children (aged 4 months to 15 years) with RSE indicated that propofol was more effective than thiopental in terminating seizures (64% versus 55%). The mean treatment duration with propofol was 57 hours (range, 10-264 hours). Propofol was initiated with a bolus of 1 to 2 mg/kg followed by an infusion of 1 to 2 mg/kg/hr, which was increased as needed to a maximum of 5 mg/kg/hr. Complications, including rhabdomyolysis and hypertriglyceridemia, prompted discontinuation in 18 percent of patients.²⁷ Propofol induces burst suppression within 35 minutes of initiation,²⁸ but maintenance of burst suppression requires frequent titration. Hypotension requiring vasopressor administration occurs in 50 to 70 percent of patients.²⁸

Some evidence suggests that propofol may not be as safe as midazolam in very ill patients.²⁹ One study found that propofol was associated with a 56 percent mortality rate in patients with Acute Physiology and Chronic Health Evaluation (APACHE) scores exceeding 20, whereas patients treated with midazolam had a 17 percent mortality rate.²⁹ A review of the literature reveals multiple instances in which prolonged propofol administration (>48 hours) at high doses (>4 mg/kg/h) may cause a rare, but frequently fatal complication known as propofol infusion syndrome (PRIS). PRIS is characterized by metabolic acidosis, rhabdomyolysis of both skeletal and cardiac muscle, arrhythmias, myocardial failure, renal failure, hepatomegaly and death. PRIS has been described as an 'all or none' syndrome with sudden onset and probable death. Common laboratory and instrumental findings in PRIS are myoglobinuria, downsloping ST-segment elevation, an increase in plasma creatine kinase, troponin I, potassium, creatinine, azotemia. Propofol should be used with caution for sedation in critically ill children and adults, as well as for long-term anesthesia in otherwise healthy patients, and doses exceeding 4 to 5 mg/kg/h for long periods (>48 h) should be avoided. If PRIS is suspected, propofol must be stopped immediately and cardiocirculatory stabilization and correction of metabolic acidosis initiated. A rebound increase in seizures can occur if propofol is withdrawn too rapidly a characteristic that is common amongst short-acting GABAergic AED's. The dose of propofol can be reduced by 5 percent every hour, so that weaning is over within 24 hours. Propofol is associated with abnormal motor events resembling seizures the exact nature of these events remains to be elucidated. There is a risk of misinterpreting common drug-induced involuntary movements as seizures. These involuntary movements can have a myoclonic appearance, or mimic convulsive seizures. Differentiation

from epilepsy can be difficult and is not helped by the EEG, which is often obscured by the movement artifact. It has been suggested that the propofol-induced movements are of peripheral origin or due to the lack of cortical inhibition, and a small dose of a nondepolarizing muscle relaxant such as vecuronium, may help distinguish myoclonus of peripheral and central origin.¹⁰

Topiramate

TPM achieves 90 percent of peak plasma concentration (C_{max}) in <2 hours after oral administration. The basic mechanisms of action of topiramate include enhancement of the inhibitory function of GABA_A receptors, inhibition of excitatory AMPA receptors, blockage of sodium and L-type calcium channels, and inhibition of carbonic anhydrase isoenzymes. The efficacy of topiramate in aborting refractory SE might be attributed to a combination of mechanisms. However, the delayed effect, the lack of IV formulation and the lack of controlled clinical trials relegate topiramate to a secondary role in the treatment of refractory SE.

Patients in RSE were given TPM by an oral or enteral route as 10 mg/kg divided into two daily doses for 2 days, followed by 5 mg/kg divided into two daily doses thereafter.³⁰ The RSE was controlled in 21 hrs. Some protocols slowly titrated the medication, resulting in control in 3-6 days, whereas others started at a higher dose and produced a response within 1 day. In a retrospective cohort study of clinical topiramate use in newborns with acute symptomatic seizures that were refractory to standard agents, Glass et al³¹ achieved apparent reduction or no further seizures in 4 of 6 neonates. However, a recent randomized, controlled trial suggested that topiramate in doses up to 25 mg/kg/day may not be an efficacious add-on agent for infants aged 1 month to 2 years with refractory epilepsy.³²

Because it exhibits mechanisms independent of GABA-receptors, topiramate *may be effective later in refractory status epilepticus*, after GABA-receptors have been targeted by other agents. Studies suggest that rapid titration is safe, but one should be vigilant of topiramate induced acidosis, particularly if the patient is on propofol or zonisamide. Nevertheless, topiramate has shown efficacy in management of RSE or super-refractory SE in sporadic case reports, and deserves more attention in well controlled trials.

Ketamine: New Use of an Old Drug!

Ketamine is a noncompetitive *N*-methyl-D-aspartate-glutamate receptor antagonist that may be effective in later stages of RSE, because it acts independently of GABA-related mechanisms. As SE progresses the inhibitory GABA-receptors are internalized and are partly destroyed in the lysosomes. At the same time excitatory NMDA receptors are externalized to the membrane surface. This receptor trafficking results in increased excitation

and marks the setting of RSE. Ketamine, being a NMDA receptor antagonist acts best at this stage. Experiments in rats showed that ketamine had no effect at 15 min into the seizures, but terminated the status at 1 hour, emphasizing that ketamine will show benefit in the stage of RSE. As activation of NMDA receptors induces cerebral ischemic damage, ketamine clearly has a neuroprotective potential. Indeed, experimental reports suggest neuroprotective effects of ketamine.

Five children aged 4 to 7 years and with known severe epilepsy and nonconvulsive SE were given the parenteral preparation (50 mg/ml, Ketalar, Pfizer) orally in a dose of 1.5 mg/kg/day in two divided doses. Ketamine was administered for 5 days in addition to maintenance antiepileptic treatment and then stopped without weaning. All demonstrated a response within 48 hours, as measured by reduced seizures on EEG, and improved mental status.³³ However, these children had epileptic encephalopathies like Lennox-Gastaut syndrome, etc. and not true convulsive SE. Another report concerned a 13-year-old girl with RSE of 4 weeks duration, who received an intravenous bolus of 2 µg/kg of ketamine, followed by an infusion (maximum dose, 7.5 µg/kg/hr) and within 90 seconds, clinical and electrographic seizures terminated. She was then treated for 2 weeks with intravenous ketamine which improved seizure control such that she had only several seizures per day.³⁴ Ketamine may be associated with improved cerebral perfusion, and *there is hardly any evidence that ketamine raised intracranial pressure*.²⁴ There are many case reports of ketamine use in RSE in adults, and ketamine has been found to have lesser suppressing effects in respiration and anesthesia. However, to avoid possible neurotoxicity, it appears safer to combine ketamine with GABAergic compounds, also because of a likely synergistic effect.

IV Lacosamide (LCM)

LCM is a functionalized amino acid with anticonvulsant properties. It acts by enhancing the slow inactivation of sodium channels. It is a newer anticonvulsant FDA approved in 2009. An intravenous preparation was recently approved for use, and a number of reports of its use in SE and seizures have appeared in literature. Hofler et al³⁵ reviewed past studies of 63 adults treated for SE with IV LCM with a success rate of 32 percent. In their own study of 48 patients published in 2011, 86 percent of patients with SE and all patients with seizure clusters (SC) were controlled with IV LCM.³⁵ There was a clear order effect of the drug, with 100 percent response rate in all 10 patients in which LCM was used as the first drug and 87 percent response (in 26 of 30 patients) in which LCM was used as the second or the third drug. Median initial bolus dose was 200 mg (range 200-400 mg) in patients with SE and 200 mg in patients with SC. Maximum infusion rate was 60 mg/min. These data support use of IV LCM as a potential alternative to

standard antiepileptic drugs for acute treatment of seizure emergency situations, although randomized controlled studies in children are needed. Sleepiness, dizziness, headache, diplopia and perioral hypoesthesia were the most common adverse events.

Carisbamate: Shows broad-spectrum activity in animal models of seizures and epilepsy through an as yet unidentified mechanism which, however, does not seem to replicate the modes of action of established anticonvulsants.

Brivaracetam: It is a synaptic vesicle protein 2A (SV2A) ligand, with much higher affinity than levetiracetam for this target. It shows broad-spectrum anticonvulsant activity in preclinical models and, in particular, reduces markedly cumulative seizure duration in the rat model of self-sustained status epilepticus. Brivaracetam shows marked synergism with diazepam.

Because the mechanisms of action of carisbamate, brivaracetam, and topiramate differ fully or partly from those of benzodiazepines, phenytoin, barbiturates, and valproic acid, it is possible that at least some of these agents will prove to be of value in the management of status epilepticus refractory to currently used drugs.

Immunological Treatment

It has also become apparent that a number of cases of 'cryptogenic' refractory status SE are immunologically mediated. A range of new antibodies have been uncovered, including antibodies against the NMDA receptor, which seems a cause of some cases of unexplained status epilepticus. It is now a common practice to attempt immunological therapy in patients with refractory SE or malignant RSE of uncertain origin, or that associated with a variety of antibodies. Emergency treatment is usually attempted with either several courses of IV immunoglobulin and/or high-dose methylprednisolone, and may be continued with repeated course of IV immunoglobulin, steroids, and other immunomodulatory agents such as cyclophosphamide or rituximab. There are only anecdotal case reports of results of such therapy.

Verapamil, a calcium-channel blocker, also inhibits P-glycoprotein, a multidrug transporter that may diminish AED availability in the brain. Few case reports on its use in humans are available; this medication nevertheless appears relatively safe (under cardiac monitoring) up to dosages of 360 mg/day in adults.³⁶

Anesthetic agents (other than thiopental and pentobarbital): There have been several case reports of successful use of inhalation anesthetics in the setting of RSE. These include isoflurane and desflurane. These agents have not been rigorously tested in a clinical trial.

Isoflurane

It is an inhaled anesthetic agent. A beneficial effect has been described in SE resistant to all kinds of AED's. It also

has a possible seizure inducing effect. Less information is available about the use of other inhaled anesthetics such as enflurane and halothane. All these agents can increase intracranial pressure, so they should only be used in SE refractory to all other treatments and under close monitoring. Isoflurane may be neurotoxic for the developing brain, and there is concern about the possibility that it could also produce neurotoxicity in adults with SE when used for prolonged periods of time.

Etomidate

Cases have been described in which seizures have been controlled after evolving to refractory SE, but the number of references is small. It has a high risk of adrenal insufficiency due to acute hemorrhage of the adrenal glands. It can cause myoclonus and spike and wave discharges on the EEG.

Magnesium

Is life saving in the very rare congenital magnesium deficiencies, and in status due to acquired hypomagnesemia. It was also frequently used to control status epilepticus in porphyria (especially acute intermittent porphyria). There is a body of experimental evidence demonstrating its anti-epileptic action; and its effect in blocking the N-methyl-D-aspartate receptor may be the basis of this action.

Magnesium infusion has been used to increase serum level to 3.5 mmol/L in the treatment SE refractory to other treatments.

MANAGEMENT OF STATUS EPILEPTICUS

Out-of-hospital or No IV Access Available

Buccal midazolam (0.2 mg/kg), intranasal midazolam (0.2 mg/kg) or rectal diazepam (0.3-0.5 mg/kg).

Impending SE: Emergency Room

Lorazepam 0.1 mg/kg IV (max. 5 mg) over 1 to 2 min.

Allow 5 minutes to determine whether seizure terminates.

Repeat benzodiazepine administration if patient has not received 2 doses of benzodiazepines. (Be sure to consider prehospital dosing).

Established SE: Administer 2nd Anticonvulsant

Fosphenytoin 20 to 30 mg PE/kg IV at 3 mg PE/kg/min (max 150 mg PE/min) (PE = phenytoin equivalents)

Phenytoin 20 to 30 mg/kg IV at 1 mg/kg/min (max 50 mg/min).

The infusions should begin at 50 percent of the maximum infusion rate (e.g. 25 mg/min phenytoin), followed by gradual titration of infusion rate upward according to the blood pressure response.

Testing to be Considered

Bedside glucose, basic metabolic panel, magnesium, phosphate, calcium, creatine kinase, complete blood count, liver function tests, coagulation tests, anticonvulsant levels, toxicology, cultures, head CT, EEG. Draw phenytoin level (10 min after infusion completed).

Refractory SE

If seizure continues after fosphenytoin/phenytoin infusion then patient has refractory SE regardless of time elapsed. *Shift to ICU.* The management of RSE is less well established and largely operator dependent.

Option A

Administer 3rd anticonvulsant:

- Levetiracetam 30 mg/kg IV at 5 mg/kg/min.
- Consider in patients with hemodynamic instability or possible metabolic/liver disease. *or*
- Valproate Sodium 30 mg/kg at 5 mg/kg/min.
- Contraindicated if liver disease, thrombocytopenia, or possible metabolic disease. *or*

Option B

The traditional approach is to proceed to a third agent, usually a loading dose of IV phenobarbital. Alternatively, a loading dose of IV valproate or IV levetiracetam may be administered. Experts believe that only a small percentage of patients who have failed treatment with two antiseizure drugs will respond to a third conventional agent. They are usually choosing to go directly to rapid acting drugs (midazolam, thiopentone or propofol) once a patient has failed 1st and 2nd line drugs rather than to use phenobarbital.

Coma-induction

However, only 7 to 10 percent of patients who have not responded to timely and appropriate doses of first and second-line AED therapy will then respond to any third-line IV AED^{22,37} and at least an additional 20 minutes are required to terminate SE in the few patients who do respond. Use of a third-line AED may be justifiable if one is trying to avoid intubation, although many authors favor proceeding directly to continuous infusion therapy at this point.

Initiate coma with midazolam 0.2 mg/kg bolus (maximum 10 mg) over 2 min, and then initiate infusion at 0.1 mg/kg/hr. If clinical seizures persist 5 min after initial midazolam bolus, then administer additional midazolam bolus of 0.2 mg/kg bolus.²⁴

Continue infusion. If clinical seizures persist after another 5 min, then administer another midazolam bolus of 0.2 mg/kg, and increase infusion to 0.2 mg/kg/hr. Continue pharmacologic coma for 24 hr after last seizure, with

EEG goal of burst suppression. Continue EEG monitoring with at least tid reviews. Continue initial medications.

Coma Phase

Continue pharmacologic coma for 24 hr after last seizure, with EEG goal of burst suppression. Continue EEG monitoring with at least tid reviews. Continue initial medications and optimize their blood levels.

Weaning Phase

Reduce midazolam by 0.05 mg/kg/hr every 3 hr, with frequent EEG review. If no clinical or electrographic seizures, then wean until off. Continue EEG for at least 24 hr after end of infusion, to evaluate for recurrent electrographic seizures.

Repeat Coma Phase

If clinical or subclinical seizures occur, reinstitute coma with midazolam for 24 hr. Start midazolam at infusion rate that achieved burst suppression and increase according to suggested midazolam titration algorithm.

Initiate topiramate 10 mg/kg NG loading dose followed by 5 mg/kg NG divided b.i.d.

Super-refractory se

If seizures persist at maximum midazolam (generally 2 mg/kg/hr.) or midazolam infusion is not tolerated, consider transition to thiopentone, pentobarbital. Also consider topiramate, ketamine, high dose phenobarbital, valproic acid or levetiracetam (if not already used) or propofol.²³ Maximize the maintenance doses of ongoing medications. Re-evaluate to search for a treatable cause. ACTH, ketogenic diet, etc. should be used if all fails.

Multiple Continuous Infusion Therapy

In general, if a single-agent infusion therapy is not effective on the first trial, it generally remains ineffective thereafter. It is not known whether combinations of these infusions are more effective or safer. If hypotension is a major problem, then the infusion rate of thiopentone can be lessened if midazolam is commenced. Moreover, the different modes of action may enhance the chance of terminating SE. It is worth re-emphasizing that continuous infusion therapy simply provides temporary abolition of SE. Optimization of maintenance AED therapy is at least as important as the choice of infusion therapy.

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Acute Heart Failure: Is Digoxin Outdated?

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INTRODUCTION

Cardiac glycosides have played an important role in treatment of heart failure since the time it was first codified by William Withering. However, its use throughout the last 200 years has not been free of controversies which were predicted by William Withering in his famous quote “After all, in spite of opinion, prejudice or error, time will fix the real value upon this discovery”.¹ The most commonly prescribed cardiac glycoside all over the world has been digoxin. Here we will go into a brief discussion on the pathophysiology of acute heart failure, management goals in acute heart failure, examine the results of trial which have studied the usage of digoxin patients with heart failure and finally the current place of digoxin in management of acute heart failure in contemporary practice.

Acute Heart Failure

Acute heart failure (AHF) is a clinical syndrome that reflects the inability of myocardium to meet the metabolic requirements of the body including the growth process.

Factors Affecting Cardiac Output

The cardiac output (CO) is dependent on stroke volume (SV) and heart rate (HR). The SV further depends on the preload, myocardial contractility and afterload.² The HR and rhythm are also important contributors to AHF. It may be worth noting that arrhythmia may be an important cause or precipitator of AHF.

Factors affecting Myocardial Performance

Under most circumstances, the CO is directly proportional to the amount of blood coming into it. This is a direct effect of the muscle stretch which results in muscle to contract with a greater force. This is the Frank-Starling principle. This mechanism operates in AHF, but

as ventricular function may be abnormal, the response is inadequate. If the Frank-Starling curve is depressed, fluid retention, vasoconstriction, and a cascade of neurohumoral responses lead to the syndrome of AHF. Over time, LV remodeling with dilatation and hypertrophy further compromises cardiac performance, especially during physical stress (Fig. 1).³

Etiology of Acute Heart Failure

On the basis of pathophysiology, the etiology of AHF may be classified into:

Increased preload may stretch the muscle fiber beyond physiologic states resulting in an effective decrease in cardiac function. This is seen in volume loading conditions like L – R shunts, mitral regurgitation, aortic regurgitation and complete heart block (unusually increased end diastolic volume due to a highly prolonged diastole).

Impaired myocardial contractility results in a decreased myocardial function as in myocarditis (viral or metabolic),

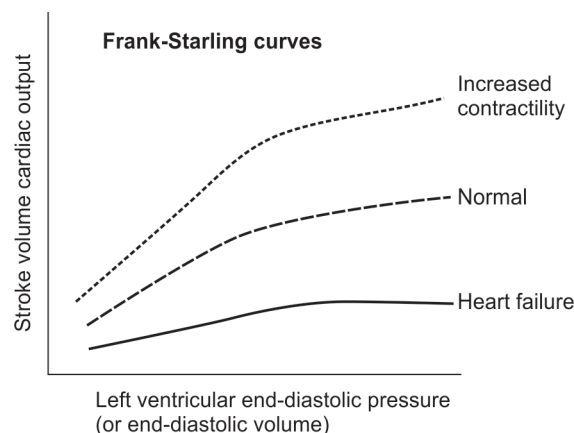


Fig. 1: Frank-Starling curve

cardiomyopathy and anomalous left coronary artery from pulmonary artery (ALCAPA).

Increased afterload: When ventricles work against abnormally high afterload that results in myocardial failure, e.g. coarctation of aorta (CoA), aortic stenosis, interrupted aortic arch.

Inadequate diastolic filling would result in a low cardiac output due to decreased filling. This would typically be seen in tachyarrhythmias, constrictive pericarditis and severe ventricular hypertrophy.

Under these conditions, various compensatory mechanisms are activated which initially have beneficial effects but if they persist for long they cause non-salutary effects and potentiate heart failure.^{4,5}

MANAGEMENT

The goal in management of AHF is to optimize the CO so as to meet the metabolic demands adequately.⁶ The goals include:

- Preload optimization
- Improving myocardial performance
- Optimizing the afterload
- Controlling heart rate
- Optimizing the oxygen carrying capacity of the blood
- Removing the underlying cause.

Digoxin in Acute Heart Failure

Looking at the management goals in a patient with acute heart failure digoxin may be useful in increasing the myocardial performance, optimizing the heart rate, induction of diuresis and providing relief from the neurohormonal symptoms related to heart failure. We now look at how digoxin fulfils these roles in a patient with heart failure.

Mechanisms of Action

Digoxin is a potent inhibitor of the intrinsic membrane protein $\text{Na}^+ \text{K}^+ \text{ATPase}$. Thereby causing the upward and leftward shift of the ventricular Frank-Starling curve, which relates cardiac performance to the ventricular filling and increases the ejection fraction.^{7,8}

In addition to this in heart failure patients, digoxin slows the ventricular rate in sinus rhythm by sympathetic stimulation withdrawal. In patients with atrial fibrillation it helps in control of ventricular rate by increase in parasympathetic tone.

It also causes an increase in blood flow, a reduction in vascular resistance, venodilation and a reduction in heart rate thereby increasing the cardiac output. Digoxin also causes a reduction in the norepinephrine levels, serum aldosterone and plasma renin activity.

Diuresis is induced by an increase in the cardiac output, inhibition of the tubular reabsorption of sodium and increasing the atrial natriuretic peptide levels.

Pharmacokinetics

Digoxin undergoes an exponential renal excretion, with an elimination half-life of 36 to 48 hours in patients with normal kidney functions.⁷ In preterm neonates the elimination half-life may be as high as 60 to 170 hours.⁹ Initiation of therapy at maintenance dosage cause the steady state plateau concentration to be achieved after 7 to 10 days in patients with normal kidney functions.⁷ Dosage reduction is needed in patients with renal failure as the volume of distribution is decreased in these patients.¹⁰ Digoxin crosses the placenta. Levels in the umbilical cord are similar to blood levels in the mother. Nearly 30 per cent drug is excreted via the fecal route.¹¹

Clinical Benefits

Benefit on digoxin in heart failure has been shown in various clinical trials. These have mainly showed improvement in the symptomatology. They have also been shown to increase the exercise capacity and the oxygen consumption, improved hemodynamics at rest and on exercise, improved left ventricular function (LVEF) at rest and on exercise and reduction in the heart rate. Digoxin has been shown to improve the heart failure scores. These benefits are not related to the heart rhythm or the etiology of the heart failure.¹²⁻¹⁴

These beneficial effects were shown by the PROVED (Prospective Randomized Study of Ventricular Failure and the Efficacy of Digoxin) and the RADIANCE (Randomized Assessment of Digoxin on Inhibitors of Angiotensin Converting Enzyme) trials.

The Digitalis Investigation Group (DIG) trial is the largest trial on digitalis. A total of 6800 patients with LVEF <0.45 were enrolled in the trial. This trial showed no effect of digoxin on mortality of patients with heart failure. But symptomatic improvement and reduction in the hospitalization rates were noted in patients receiving digoxin more so in patients with ejection fraction <0.25. The points highlighted by these trials were:

- No effect on mortality
- Symptomatic improvement and reduction in incidence of hospital admissions in patients receiving digoxin
- Benefits noted were incremental to use of diuretics and inhibitors of angiotensin converting enzyme
- Improvement in the ejection fraction
- Increase in the incidence of arrhythmia associated deaths.

Further, the data from spironolactone and carvedilol trials involving patients with heart failure have revealed that digoxin is effective in combination with these drugs.¹⁵

Current evidence from adult studies point to an increased incidence of toxicity, higher mortality and higher rate of hospitalization in patients with digoxin levels greater than 1.2 ng/ml.¹⁶

It is important to note that all the above trials have been conducted on adult patient population and there are

no randomized control trials detailing the use of digoxin in children with heart failure. Smaller uncontrolled studies evaluating the effect of digoxin in patients with large left to right shunts have shown contradictory results.^{17,18}

In a study of 21 infants with Ventricular Septal Defects and heart failure by Berman et al, symptomatic improvement was noted in 12 patients whereas contractility improved in six patients only.¹⁷ Kimball et al showed no improvements in sign and symptoms on infants receiving digoxin and diuretics in his study on 19 infants with ventricular septal defect.¹⁸ No credible data exists on the efficacy of digoxin in heart failure in children with LV systolic dysfunction or valvar regurgitations and on long-term survival in any of these trials. Despite the lack of data regarding its use in children, digoxin continues to be used by most clinicians in our country as detailed below in a survey by Jain S et al in the management of pediatric heart failure due to various causes.¹⁹

- Digoxin use is clearly indicated in children with primary myocardial disease with left and/or right ventricular dysfunction in children
- Digoxin use is also indicated in symptomatic patients with left to right shunts and those with valvar regurgitations
- In patients with heart failure due to myocarditis, the use of digoxin is mandated in the early stages, but caution needs to be exercised and lower dosage of digoxin are indicated in these patients
- Rapid digitalization may be needed in patients with heart failure due to tachyarrhythmias and those symptomatic patients in heart failure due to other causes, who have not received digoxin earlier
- Digoxin use does not improve long-term survival in pediatric patients with heart failure but helps in tiding over acute exacerbations of heart failure in these patients.

CONCLUSION

Digoxin continues to be used in a significant way in patients with acute heart failure and those with chronic heart failure primarily in symptomatic patients. Its easy availability, generations of use and low cost makes it an attractive choice in the management of patients in developing countries where there may be prolonged waiting period before a definitive treatment might be available. The clinical trials for digoxin use in adult population of patients have validated the beneficial effect of digoxin in this subclass of patient population. In absence of similar studies in children it seems fair to extrapolate this data for management of pediatric acute heart failure.

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The prevalence of tuberculosis (TB) is increasing in both the developing and the developed world and children, in particular, represent a high-risk group for acquiring the disease. Making a correct diagnosis of tuberculosis in children is extremely challenging because of non-specific symptoms, difficulties in specimen access and collection, low yield of gastric aspirate cultures (30–60%) and problems in the interpretation of tuberculin skin testing in young children. The diagnosis often relies on imaging. In children, the pathological changes associated with pulmonary TB are usually non-cavitary and paucibacillary. Hence, the correct interpretation of the chest radiograph is imperative for the diagnosis of pulmonary TB in childhood.¹ A thorough understanding of the pathogenesis of TB is a prerequisite to the interpretation of the clinical and radiological findings of the disease.

PATHOGENESIS OF PULMONARY TUBERCULOSIS

Pulmonary tuberculosis (PTB) can be classically divided into primary and post primary (or reactivation) TB, each with corresponding radiological patterns. Due to the changing epidemiology, considerable overlap in the radiological presentations of these entities may exist.

Primary Pulmonary Tuberculosis

Primary TB infections are of respiratory origin. The primary pulmonary parenchymal focus is known as the Ghon focus.² From the Ghon focus, bacilli usually drain via local lymphatics to the regional lymph nodes. The upper lobes drain to the ipsilateral-paratracheal nodes, while the rest of the lung drains to the perihilar nodes, with dominant lymph flow from left to right.³ The combination of the Ghon focus and the enlarged draining lymph nodes form the primary complex: the *Ranke or Ghon complex* (Fig. 1).⁴ The formation of the Ghon complex is often

subclinical and a random chest radiograph following primary infection is often normal or reveals only a single component (usually hilar adenopathy).^{2,3} In the immunocompetent patient, development of specific immunity is usually adequate to limit further multiplication of bacilli, the host remains asymptomatic, and lesions heal.⁵ This is seen in 95 percent of immunocompetent patients. In children, a clinical diagnosis of primary tuberculosis usually is made when an abnormal chest radiograph is coupled with clinical evidence of pulmonary disease and a documented conversion of the PPD TB skin test.

Healing of TB occurs with resorption of caseous necrosis, accompanied by deposition of collagen (fibrosis) and



Fig. 1: Chest X-ray PA view shows right hilar lymphadenopathy with associated lymphangitis and peripheral consolidation on the same side suggestive of primary complex (Ghon Complex)

calcification.⁶ This process takes place in the pulmonary foci, the affected locoregional lymph nodes, and extrapulmonary locations (kidneys, metaphyses of long bones, and brain) originating from minimal hematogenous dissemination. The radiological counter parts of these silent, healed lesions are a calcified pulmonary focus and/or mediastinal or hilar node. The evidence of hematogenous (minimal) dissemination can be calcifications in the lung apices *Simon's foci* and in peripheral organs. These healed pulmonary and extrapulmonary lesions harbor bacilli in dormant position, at low metabolic rate, but are a source of continuous antigenic stimulation for maintenance of hypersensitivity to tuberculous antigen.

In a proportion of primarily infected individuals the primary complex continues to progress spreading through the bronchogenic, lymphatic or hematogenous route giving rise to *progressive primary form of the TB*.

Postprimary Pulmonary Disease

Postprimary TB results from reactivation of dormant residual foci or reinfection, in a previously sensitized host. Rarely, it is due to an exogenous super infection on an inactive or even active original infection-true reinfection.⁷

It is characterized by the following:

1. Liquefaction of caseous necrosis.
2. Formation of cavities.
3. Progressive fibrosis and lung destruction.

Postprimary TB can develop through the following mechanisms:

- a. Postprimary TB can develop from reactivation of bacilli in the lung. Reactivation occurs preferentially in the apical, posterior segments of the upper lobes, and apical segment of the lower lobe, because the oxygen tension is highest in the upper lung zones. Another explanation for this anatomical distribution is that the lymph flow may be restricted in the upper lung zones of the erect lung. The early parenchymal infiltrate of postprimary tuberculosis results from the intensive inflammatory reaction in the hypersensitive host. After reactivation, these lesions reach confluence, liquefy, and slough into a bronchus leaving a cavity.
- b. Perforation of a lymph node into a bronchus or a tuberculous bronchitis can cause ulcerations of principal and/or segmental bronchi. Frequently, the anterior segment bronchus of the upper lobe and middle lobe bronchus are affected. Aspiration of bacilli in the bronchial lumina will cause bronchogenic dissemination.

After antituberculous therapy, radiographs show disappearance of infiltrates and development of fibrosis. Fibrosis can be stable or regress. If AFB staining and/or culture remain negative and the imaging features remain stable over a period of six months, the process can be considered as *inactive TB*.

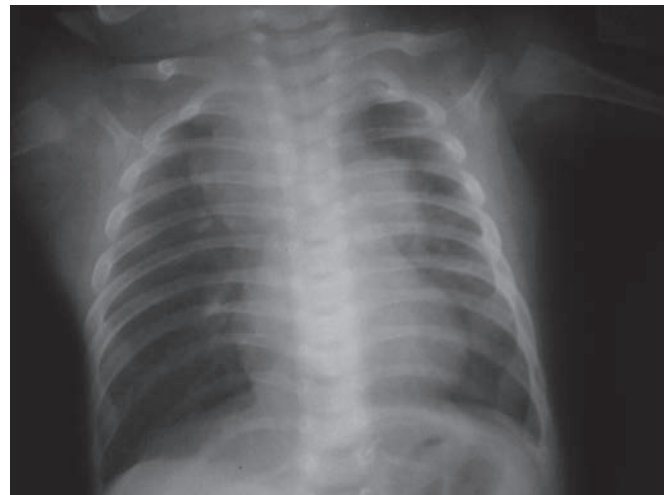


Fig. 2: Chest X-ray PA view shows bilateral paratracheal lymphadenopathy with compression of trachea in lower part

RADIOLOGICAL PATTERNS OF PULMONARY TUBERCULOSIS

Primary Pulmonary TB

The most common abnormality in primary TB in children is lymph node enlargement, seen as presence of hilar and/or mediastinal lymphadenopathy in 83 to 96 percent of cases.^{8,9,12} The lymphadenopathy is usually unilateral and commonly located in the hilum or the paratracheal region, although other combinations (bilateral hilar/mediastinal, isolated mediastinal, subcarinal and aortopulmonary window) have been described (Fig. 2).⁷⁻¹⁰ The prevalence of adenopathies decreases with age.¹³ Chest radiography remains the initial imaging technique for detecting lymphadenopathy, which is usually seen in association with parenchymal consolidation or atelectasis but can also be the sole radiographic manifestation of the disease especially in children. The position, contour and caliber of the airways are useful for determining the presence of mediastinal lymphadenopathy on the AP film. On plain chest X-ray, adenopathy is seen as discrete dense soft tissue shadow which is well circumscribed. It can, however, manifest as an ill-defined hilar prominence rather than distinct nodal enlargement which is often best detected on the lateral chest radiograph.^{2,11} Lateral view radiographs demonstrate lymphadenopathy as lobulated densities seen posterior to the bronchus intermedius where it completes the inferior portion of a doughnut-shaped density; the upper half is seen in normal individuals as an up-side-down 'horseshoe' made up of the right and left main pulmonary arteries and the aortic arch (Figs 3A and B).¹⁴ Occasionally, the chest radiograph may be normal and lymphadenopathy may be detected only on computed tomography (CT). However, in clinical practice in children, there is often overdiagnosis of hilar adenopathy with slightly rotated or expiratory films. Thymus, body of

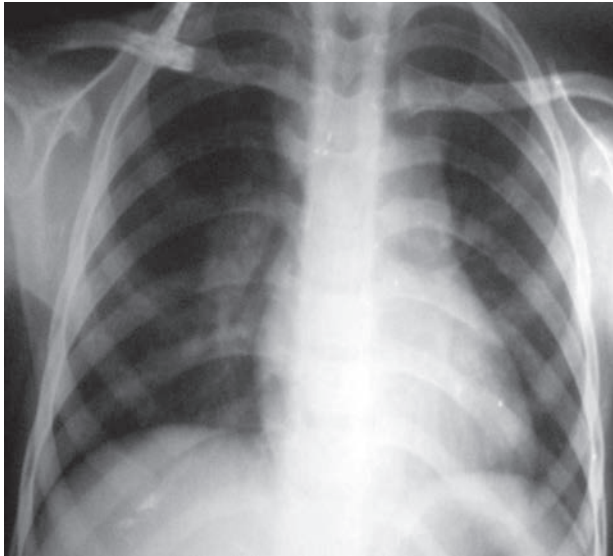


Fig. 3A: Chest X-ray PA view shows right hilar lymphadenopathy

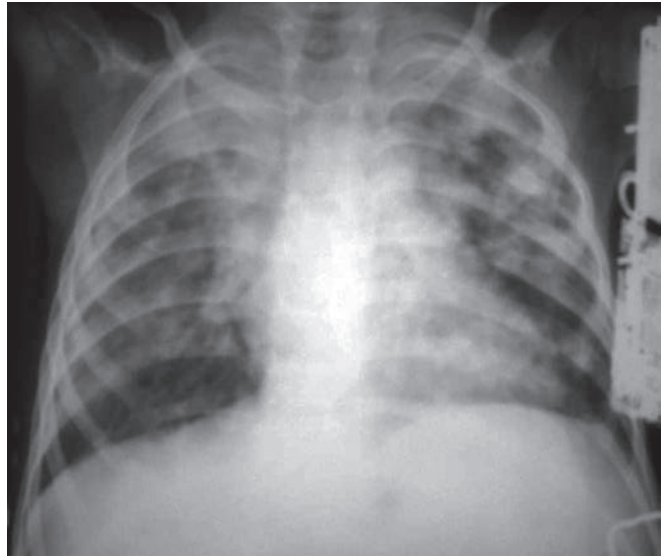


Fig. 4: Chest X-ray PA view shows inhomogeneous opacities in bilateral lung fields suggestive of progressive primary disease

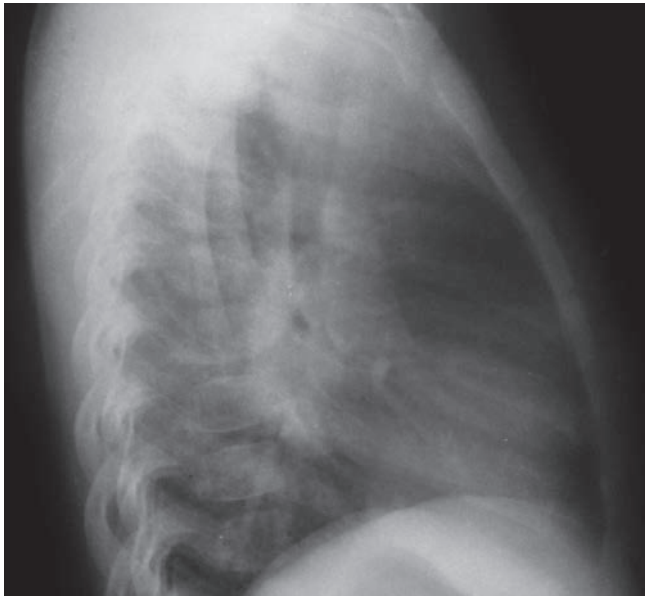


Fig. 3B: Chest X-ray Right lateral view shows a lymph node mass around carina (Doughnut sign)

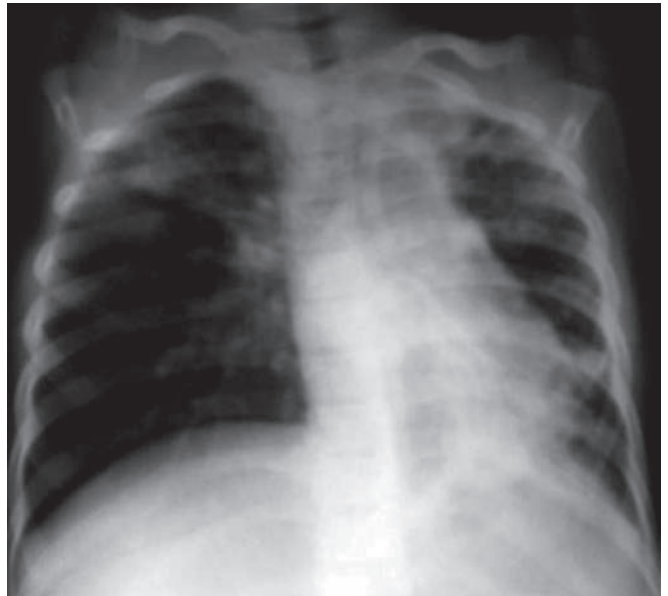


Fig. 5: Chest radiograph PA view shows left lower lobe collapse with compensatory hyperinflation of the right lung

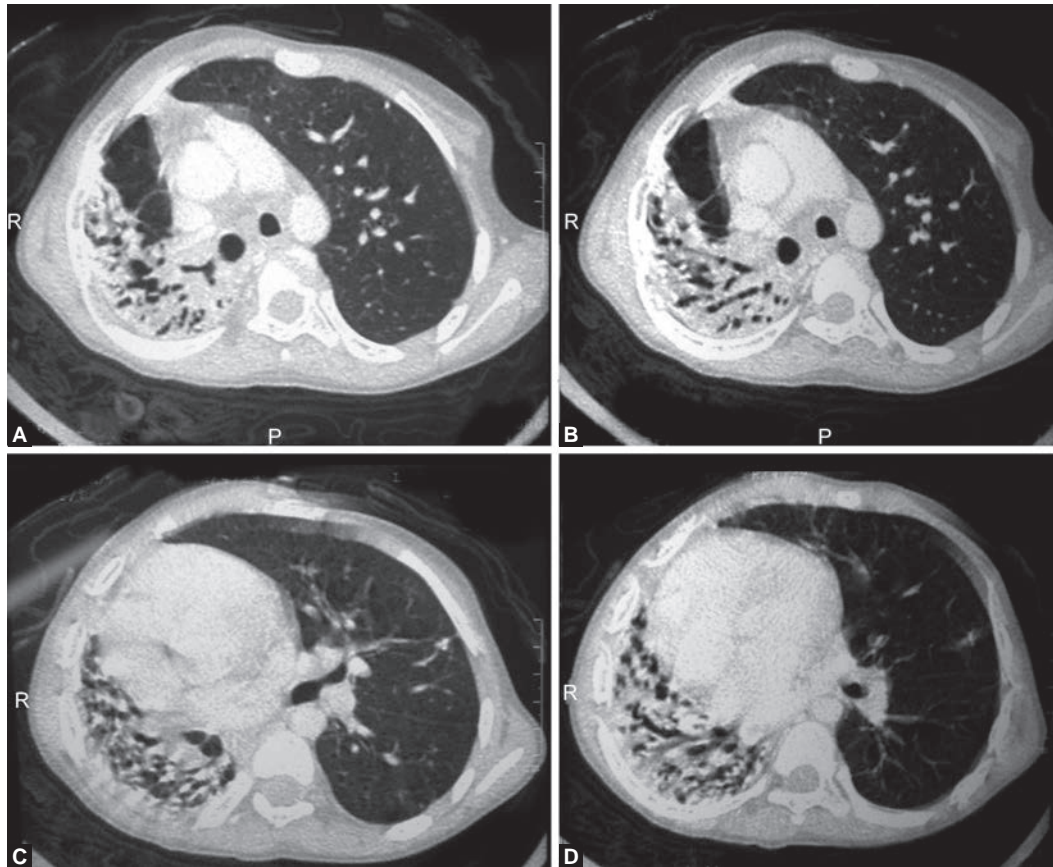
manubrium can also mimic paratracheal lymphadenopathy. There are significant inter- and intra-observer differences in the detection of lymphadenopathy by readers.¹⁵

Progressive Primary Pulmonary TB

Progressive primary TB manifests radiographically in four major ways: Parenchymal disease, Atelectasis, Pleural effusion, and Miliary disease.¹² Associated parenchymal infiltrates related to air space consolidation are encountered on the same side as nodal enlargement in approximately two-thirds of pediatric cases of primary PTB.¹³ The opacity is typically homogeneous, has ill-defined borders and may

contain an air bronchogram,^{16,17} although patchy, linear¹⁸ and nodular lesions have also been described (Fig. 4).³ Consolidation typically occurs in a segmental or lobar distribution, although multifocal involvement can be seen.¹³ Important clues to differentiate it from bacterial pneumonia include the presence of lymphadenopathy, lack of systemic toxicity, long duration of symptoms and finally the failure to respond to conventional antimicrobials.

Collapse or atelectasis is especially seen in children due to small caliber airways and a higher prevalence of lymphadenopathy (Fig. 5). It is caused by endobronchial disease or extrabronchial compression by enlarged hilar



Figs 6A to D: Contrast axial CT chest (Lung window) shows atelecto-bronchiectasis of the right middle and lower lobe (Right middle lobe syndrome)

lymph nodes.¹¹ Obstructive atelectasis and over inflation can occur. Atelectasis most often involves an anterior segment of an upper lobe or the medial segment of the middle lobe (right middle lobe syndrome) (Figs 6A to D).^{9,19} Pleural effusion and miliary disease will be covered later.

Role of CT Scan in Diagnosis of Primary TB

Computed tomography (CT) scan is more sensitive in detecting lymph node in the chest.^{14,20} However, it is still not preferred as a front line investigation due to its limited availability, cost, high radiation dose, the need for IV contrast medium and the need for sedation in certain cases. The risk of radiation exposure with CT in children is significant. Considerations unique to the pediatric population include increased radiosensitivity of certain tissues, particularly in infancy,²¹ a longer lifetime for radiation-related cancer to occur, and a lack of size-based adjustments in technique. In addition to increased organ sensitivity, small children also receive a greater radiation dose than larger children or adults from the same CT settings.²² In view of the above, this modality should be used judiciously and not blindly in all cases.

On contrast-enhanced CT scan, tuberculous adenopathies, when measuring more than 2 cm, show a very

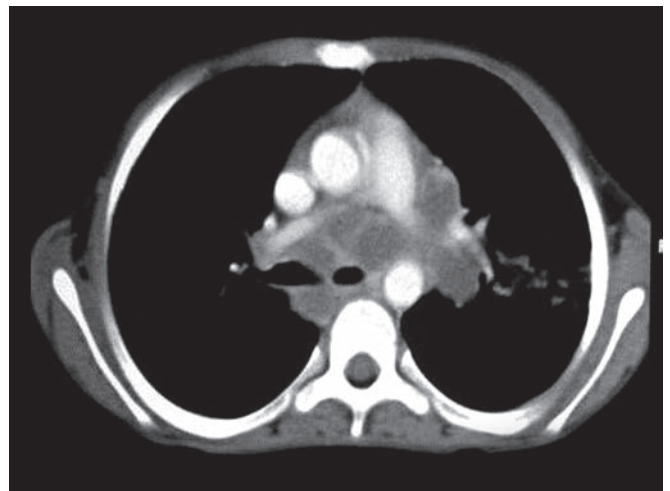


Fig. 7: Contrast axial CT chest (mediastinal window at the level of main pulmonary artery) shows sub carinal and right hilar lymphadenopathy with typical rim enhancement

characteristic, but not pathognomonic, *rim sign* consisting of a low-density center which shows caseous necrosis, surrounded by a peripheral rim enhancement, which represents the vascular rim of the granulomatous inflammatory tissue and obliteration of the perinodal fat (Fig. 7).¹⁰

Calcification as well as low-attenuation areas within the nodes is not a reliable marker for disease activity on CT as it may be seen in both active and inactive disease.²⁴ On CT, the parenchymal consolidation in primary TB is most commonly dense and homogeneous but may also be patchy, linear, nodular, or mass like.²³ CT may be useful in determining disease activity. A tentative diagnosis of active TB on CT in patients with mediastinal tuberculosis could be based on the pattern of parenchymal findings consistent with (but not exclusive to) active pulmonary tuberculosis, such as centrilobular nodules, branching linear opacities and cavities.²⁵ Some children can have no systemic symptoms despite active disease while others with inactive disease may have large calcified nodes and symptoms due to illness other than tuberculosis. Given this poor reliability of assessing activity through imaging, biopsy and culture of the diseased nodes may be considered for determination of disease activity in patients with mediastinal tuberculous lymphadenitis but these are invasive and time-consuming.^{18,26} The culture results are sometimes negative in patients with active nodal disease.²⁶

Postprimary Pulmonary TB

It results from the reactivation of dormant residual foci, spread at the time of the primary infection.

The radiographic findings of postprimary TB may overlap those of primary TB. Lesions are usually more focal and nodular than in primary infection, and in contrast to the fibrosis and healing seen in primary infection, the postprimary form more typically has a predilection for the upper lobes, displays inflammation and caseating necrosis, with destruction and cavitation of adjacent parenchymal tissue.

Postprimary TB Manifests Radiographically As

- a. Parenchymal disease and cavitation
- b. Endobronchial TB
- c. Pleural disease
- d. Other complications. Endobronchial and pleural disease will be dealt later in the chapter.

Radiographs in postprimary TB may show extensive abnormalities, such as apicoposterior infiltrates, cavities, pleural exudates, fibroproductive lesions causing distortion of lung parenchyma, elevation of fissures and hila, pleural adhesions, and formation of traction bronchiectasis (Fig. 8). The most common radiographic manifestation of reactivation pulmonary TB is focal or patchy heterogeneous consolidation involving the apical and posterior segments of the upper lobes and the superior segments of the lower lobes (Fig. 9).^{23,28} Another common finding is the presence of poorly defined inhomogeneous nodules and linear opacities, which are seen in approximately 25 percent of patients (Fig. 10).²⁸ Cavities, the radiologic hallmark of reactivation TB, are evident radiographically

in 20 to 45 percent of patients (Fig. 11).^{23,27,28} The cavity walls may range from thin and smooth to thick and nodular. Cavities are more frequently multiple than single and range from a few millimeters to a few centimeters in diameter and typically occur within areas of consolidation. With healing they can get progressively thin and balloon into large emphysematous spaces, although they usually resolve with or without scarring. It can be difficult to distinguish thin walled cavities from bullae, cysts, or pneumatocele. When multiple apical cavities are encountered, the possibility that cystic bronchiectasis are present in addition to necrotic cavities must be considered. Air-fluid levels in the cavity can occur.

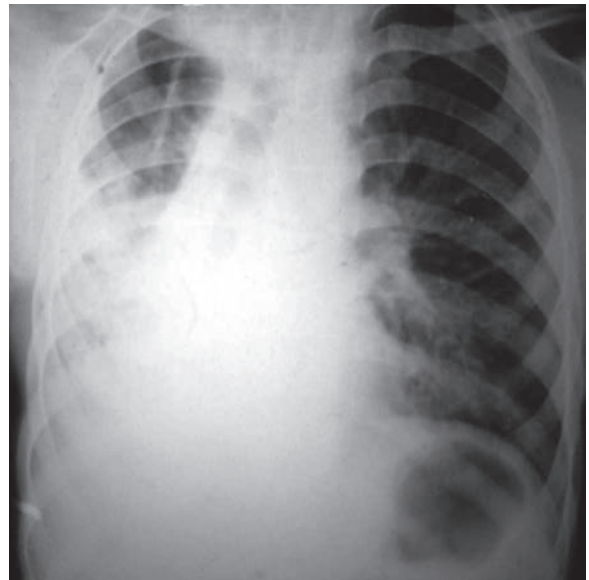


Fig. 8: Chest X-ray PA view shows right side collapse with areas of bronchiectasis

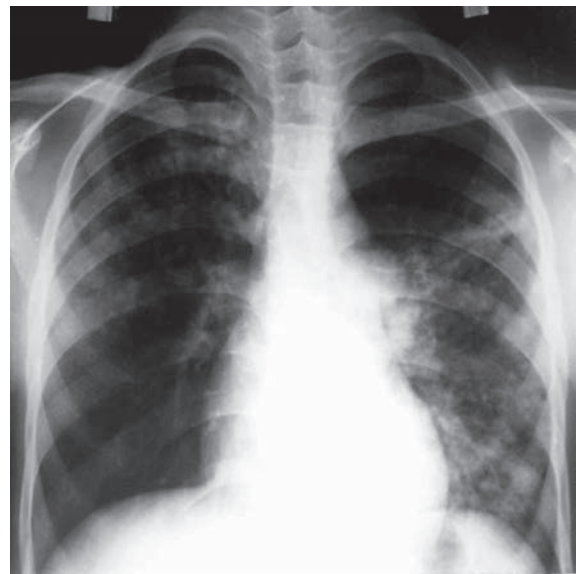


Fig. 9: Chest radiograph PA view shows infiltrates in the right upper lobe and bronchiectatic changes with volume loss in left lower lobe suggestive of Postprimary TB

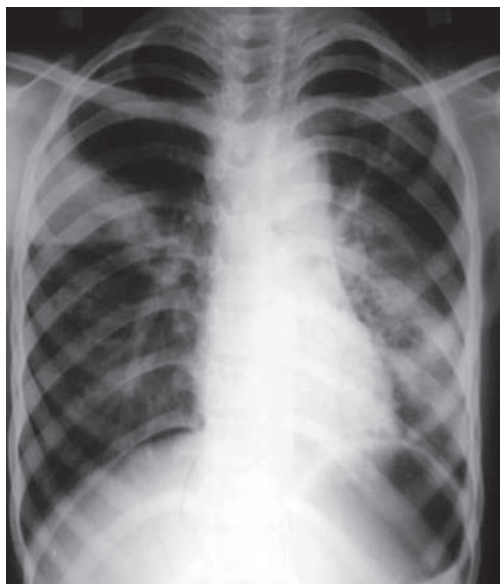


Fig. 10: Chest X-ray PA view shows nonhomogeneous opacities in left upper and right lower lobes. The right upper lobe shows cavitary pneumonia

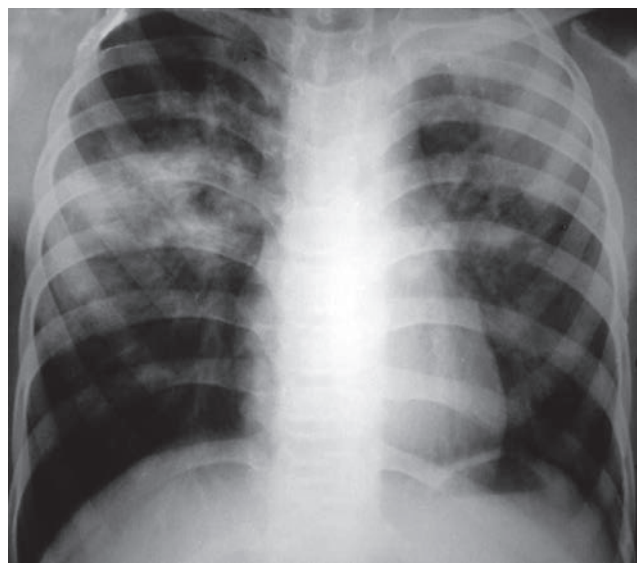


Fig. 11: Chest X-ray PA view shows cavity with thick, irregular walls, surrounded by clearly defined, nodular opacified areas (fibroproliferative disease)

Hilar or mediastinal lymphadenopathy is uncommon in reactivation TB, being seen in approximately 5 to 10 percent of patients.^{27,28} Pleural effusion, typically unilateral, occurs in 15 to 20 percent of patients.²⁹

Bronchogenic spread is radiographically identified in about 20 percent of cases of postprimary TB and manifests as multiple, ill-defined micronodules, distributed in a segmental more than lobar distribution, distant from the site of the cavity formation and typically involving the lower lung zones.³⁰ On CT scan, it is identified in almost 95 percent of cases.³¹ High-resolution (HR) CT is the imaging



Fig. 12: Contrast axial CT chest (Lung window at the level of ventricles) showing bilateral tree-in-bud opacities

technique of choice for these micronodular lesions (typically 2 to 4 mm centrilobular nodules) and sharply marginated linear branching opacities which represent caseous necrosis containing bacilli within and around terminal and respiratory bronchioles (tree-in-bud sign) (Fig. 12).²⁵ The centrilobular small nodules and tree-in-bud sign reflect the presence of endobronchial spread of disease and are a reliable marker of the disease activity. The most common CT findings of reactivation pulmonary TB are centrilobular small nodules, branching linear and nodular opacities (tree-in-bud sign), patchy or lobular areas of consolidation, and cavitation.³²

Radiological Patterns Encountered in Both Primary and/or Postprimary PTB

Several radiological patterns are not exclusively seen in either primary or postprimary TB.

Miliary Tuberculosis

Acute hematogenous widespread dissemination of TB bacilli in lungs and other organs, results in the development of miliary tuberculosis, where innumerable small tuberculous granulomas develop. It occurs in 2 to 6 percent of primary TB and also occurs somewhat more frequently in reactivation TB.³⁷ In the latter situation, miliary TB may be seen in association with typical parenchymal changes or may be the only pulmonary abnormality. It is seen classically in children (most commonly <2 years), within a few months (usually 6 months) after first contact. Each focus of miliary infection results in local granulomas that, when well developed, consist of a region of central necrosis surrounded by a relatively well-delimited rim of epithelioid histiocytes and fibrous tissue. Initially, standard radiographs

can be normal, as the resolution may not be good enough to pick fine miliary shadows.³³ Computed tomography can demonstrate miliary disease before it becomes radiographically apparent. After a few weeks, the classic miliary pattern on conventional radiographs is seen: innumerable (1-3 mm diameter) nodules, similar in appearance, diffusely distributed in both lungs, especially the lung apices (Fig. 13). Thickening of interlobular septa and fine intralobular networks are frequently evident. Diffuse or localized ground glass opacity is sometimes seen, which may herald acute respiratory distress syndrome.^{32,34,35} With therapy, the nodules usually resolve in 2 to 6 months.

Pleural Effusion

Pleural effusions most often are a manifestation of primary TB but can occur in 6 to 18 percent of patients with post-primary disease.²⁷ Exudative pleuritis is a late complication of primary TB seen most frequently in older children and adolescents. It occurs 3 to 6 months after initial infection due to a hypersensitivity response to tuberculo-protein released into the pleural space and is often asymptomatic. When it is a part of primary infection, pleural effusion is usually unilateral, large²⁷ and on the same side as the primary focus of TB (Fig. 14). It can occur without evidence of parenchymal disease on chest radiographs.²⁷ During reactivation process, pleural effusion is usually small and accompanied by parenchymal abnormalities.²⁷ Diagnosis of bronchopleural fistula is based on the presence of air in the pleural space and a changing air-fluid level.²⁷ Rarely, tuberculous pleurisy may become localized, causing a tuberculous empyema usually in association with extensive parenchymal disease and cavitation.³⁶ This empyema may break through the parietal pleura to form a subcutaneous abscess, called as empyema necessitatis.³⁷

Contrast-enhanced CT scan of patients with post-primary pleural effusion typically shows smooth thickening of visceral and parietal pleura ("split-pleura" sign).³⁸ In chronic tuberculous empyema, CT shows a focal fluid collection with pleural thickening and calcification and with or without extrapleural fat proliferation. Diffuse pleural thickening, but without pleural effusion on CT, suggests inactivity.³⁹

Resolution of effusion is prompt and complete with antituberculous therapy,¹² however residual pleural thickening or calcification can result. New subpleural lung nodules can develop during medication for TB pleural effusion. These paradoxical subpleural nodules should not be considered as treatment failure as they eventually resolve with continued medication.⁴⁰

Tracheobronchial Tuberculosis

Tracheobronchial TB has been reported in 10 to 20 percent of all patients with pulmonary TB.²⁴ It is usually seen as a complication of primary TB, as it frequently originates

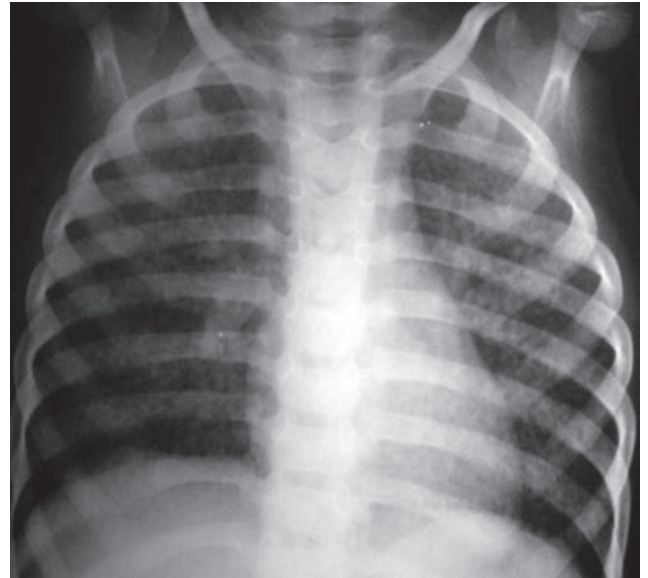


Fig. 13: Chest X-ray PA view shows miliary tuberculosis

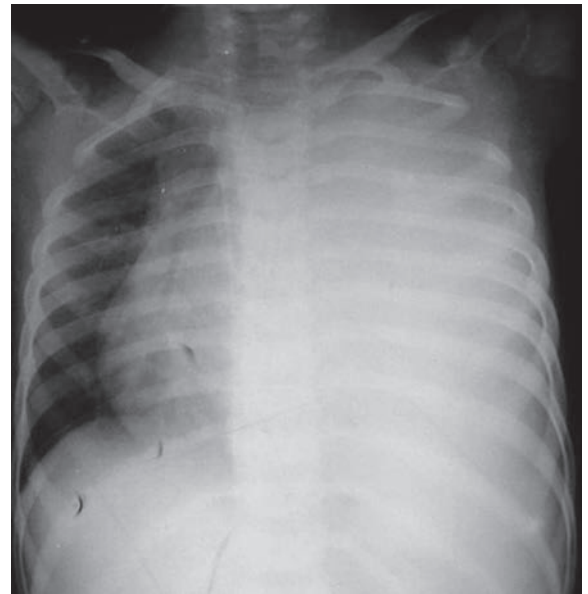


Fig. 14: Chest radiograph PA view shows massive left sided Pleural effusion with shift of the mediastinum

from perforation of an adenopathy into a bronchus,⁴¹ but it can also be caused by lymphogenic and hematogenous spread. Bronchoscopy will reveal presence of residual or active fistulas. These lesions produce fibrotic stenosis after healing, and post obstructive bronchiectasis. It is the most common cause of inflammatory stricture of the bronchus. Plain radiographs can be completely normal; however, associated parenchymal opacities predominating in the upper lobes and segmental or lobar atelectasis are radiographically apparent in 65 to 75 percent and 19 to 25 percent of cases, respectively.⁴² During active stage of the disease, the airway lumen show irregular narrowing with thickened walls, whereas in fibrotic stage, the airways

show smooth narrowing with thin walls.^{24,39} Both the main bronchi can be equally involved in active disease, while the left main bronchus is more commonly involved in fibrotic stage.²⁴

On HRCT scans, acute tracheobronchial TB typically manifests as irregular or smooth circumferential bronchial narrowing associated with wall thickening.²⁴ Enhancement and enlarged adjacent mediastinal nodes are also common findings in the active stage of stenosis. After healing of this focal infection of the bronchial wall, cicatricial bronchostenosis may occur.

Tuberculoma

Although, pulmonary tuberculomas are most often the result of healed primary TB, they are seen in 3 to 6 percent of cases of postprimary tuberculosis as the main or only abnormality on chest radiographs.⁴³ It is a round or oval granuloma measuring 0.4 to 5 cm in diameter with smooth or sharply defined margins, and are single or multiple. The possible mechanisms of tuberculoma formation are a healed, filled-in cavity or else a rounded-off, contracted healing tuberculous lesion.⁴³ The majority of lesions remain stable in size and may calcify. Calcification is found in 20 to 30 percent of tuberculomas and they are usually nodular or diffuse.⁴² Small round opacities (“satellite lesions”) are observed in the immediate vicinity of the main lesion in 80 percent of cases.

Tuberculomas show active glucose metabolism caused by active granulomatous inflammation. These lesions accumulate 18F-FDG and cause PET scans to be interpreted as false-positive for malignancy.⁴⁴ Unlike 18F-FDG PET scans, 11C-choline PET scans can help differentiate between lung cancer and tuberculoma.⁴⁵ The standard uptake value of tuberculoma is low in 11C-choline PET scans.

Radiological Changes in HIV and TB Coinfection

Recently, with the AIDS epidemic, there is increasing incidence of TB infection in HIV-infected patients. The AIDS patients can have massive hematogenous dissemination following primary infection, and thus have high risk of more fulminant course. During the first year after infection with TB, the risk of developing progressive primary disease is almost 30 percent, in contrast with the 3 percent risk of immunocompetent patients.⁴⁶ Because of deficient cellular immunity, they are also prone to reactivation TB. Most of the TB infections in HIV patients are postprimary TB. The radiographic appearance of HIV-associated PTB is dependent on the level of immunosuppression at the time of overt disease.⁴⁷

In patients with early stage HIV, where immune function is relatively intact, radiographic findings are similar to those of non HIV-infected individuals.⁴⁸ At severe levels of immunosuppression, there is a significantly higher prevalence of mediastinal and/or hilar lymphadenopathy and a

lower prevalence of cavitation.⁴⁹ A miliary pattern of disease and pleural effusions are also more commonly seen. Extrapulmonary localizations are frequent in HIV-infected patients and involve brain, pericardium, intestine, peritoneum, and spine. Furthermore, HAART may result in paradoxical worsening or TB manifestations in patients with immune reconstitution inflammatory syndrome.^{50,51}

Radiological Changes on Follow-up or Treatment

Radiological assessment may prove valuable in evaluating response to treatment, particularly in the absence of culture or sensitivities. The regression of imaging abnormalities following adequate treatment is often a slow process, and it is not unusual to find an initial deterioration before improvement.¹ In the majority of cases, localized areas of consolidation resolve within a month; more extensive disease may improve more gradually over a period of several months. Complete resolution may not occur, and residual areas of scarring, focal nodularity, and volume loss are the more commonly seen end points of treatment.

The volume of lymphadenopathy is a poor indicator of response to treatment as nodes often enlarge initially and may take a long time to show signs of resolution, even in the face of effective therapy. Nodal calcification usually develops six months or more after the initial infection and is more common than parenchymal calcification.^{9,11} In two-thirds of the cases, parenchymal focus resolves without radiological sequel.^{7,8} However, a radio-graphically visible scar persists in one-third of cases⁷ and a calcified scar is seen in 15 to 17 percent cases.⁹ Resolution is slow and it takes six months to two years for complete clearing.⁸ Miliary parenchymal disease is the exception to the rule and resolution is usually more rapid than in nonhematogenous disease, usually leaving no chronic sequel in the lungs. The response of active TB cavities to treatment is typically enlargement but with thinning of the cavity wall such that there is an overall reduction in the amount of abnormal soft tissue. On completion of treatment the cavity may persist or become contracted by fibrosis. The resolution of a tuberculous pleural effusion is readily achieved following effective therapy; however residual pleural thickening or calcification can result.

RADIOLOGICAL PATTERNS OF EXTRAPULMONARY TB

Central Nervous System Tuberculosis

Tuberculosis usually accesses the intracranial compartment via the hematogenous route from a primary focus usually the lungs; three to six months after the initial infection. It can also result from direct spread of calvarial or middle ear infection. Hematogenous spread leads to formation of small subpial and subependymal foci (Rich foci) in the brain and spinal cord. In some individuals foci rupture and release bacteria into the subarachnoid space

causing meningitis. In others, foci enlarge to form tuberculomas without meningitis. The timing and frequency of these events in relation to primary pulmonary infection is dependent upon age and immune status. In children, dissemination usually occurs early and the risk of CNS tuberculosis is highest in the first year following infection.⁵² In high prevalence countries, CNS tuberculosis predominantly affects very young children (<3 years).

Central nervous system (CNS) TB may be focal in the form of a tuberculoma or a tuberculous abscess, or may be more widespread, in the form of meningitis and arachnoiditis. The most common presentation of CNS TB is tuberculous meningitis followed by tuberculomas (20-37). Computed Tomography (with and without contrast) and magnetic resonance imaging form the main imaging modalities for CNS tuberculosis.

Tuberculoma

In developing countries intracranial tuberculomas are commonly seen in children and young adults. Tuberculomas may be single or more commonly, multiple. Infratentorial tuberculomas are more common.^{53,54}

Computed Tomography

Tuberculomas form 99 percent of all focal TB lesions and usually occur without tuberculous meningitis (TBM). These lesions are iso- or hyperdense to cortex before administration of IV contrast medium. This feature differentiates these lesions from abscesses, which are of low density and are usually larger than 2 cm.⁵⁵⁻⁵⁷ Tuberculomas may be ring enhancing or nodular/discoid enhancing after IV contrast, have irregular walls of varying thickness and show

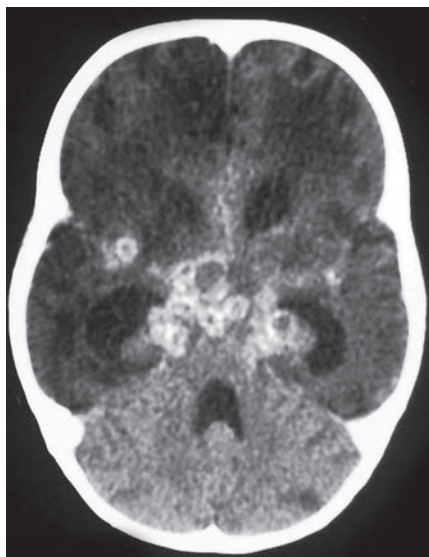


Fig. 15: CECT brain shows multiple conglomerate ring enhancing lesions suggestive of tuberculoma. Also there is dilatation of the fourth ventricle and temporal horns of bilateral lateral ventricle suggestive of communicating hydrocephalus

perilesional edema (Fig. 15). They are usually smaller than 2 cm in size and they rarely calcify.⁵⁵⁻⁵⁷ TB abscesses, which are larger and also rim-enhance, are of low density centrally. They are therefore indistinguishable from pyogenic abscesses and can also be confused with neoplasms.

Magnetic Resonance Imaging

Tuberculomas have a characteristic low signal on T2-weighted images and on T1-weighted images the signal is isointense to that of cortex.⁵⁸⁻⁶⁰ There is accompanying surrounding edema and ring enhancement occurs after IV gadolinium administration. Sometimes the center of a tuberculoma may show some hyperintensity as the gummatous necrosis gives way to caseous necrosis.^{58,59} TB abscesses, however, have features inseparable from pyogenic abscesses with T2 hyperintensity and T1 hypointensity, surrounding edema and ring enhancement.^{59,60}

Neither of these imaging modalities can reliably distinguish tuberculoma from other causes of ring enhancing lesions, in particular pyogenic bacterial abscess, neurocysticercosis (unless MRI reveals a parasitic scolex within the lesion), toxoplasmosis, or neoplasia.⁶¹

There is a promising role of magnetic resonance spectroscopy (MRS) in differentiating the causes of ring enhancing brain lesions: a large lipid CH₂ peak has been used to specifically identify tuberculomas.⁶² To differentiate it from neurocysticercosis choline/creatine ratio is useful. A ratio of >1 is seen in tuberculoma.⁶³

TB Meningitis

This is the most severe and life-threatening form of TB in children. Even though the CNS is involved in a more diffuse manner, TBM may be asymmetrical, unilateral and even focal. About 50 percent of patients with TBM have chest X-rays suggesting active or previous pulmonary tuberculosis;⁶³ ten percent have miliary disease, which strongly suggests CNS involvement.

Computed Tomography

Computed tomography (CT) scanning has become essential for rapid diagnosis and detection of the complications of TBM. The most common cerebral CT features of TBM are hydrocephalus and basal contrast enhancing exudates, found in 80 percent of children with TBM. Basal enhancement is the most sensitive and characteristic finding of TBM. It may be subtle on CT scanning and has variable appearances. Basal enhancement has ill-defined margins compared with normal vessel enhancement and the most common sites are suprasellar, middle cerebral artery and sylvian cisterns (Fig. 16).⁶⁴ The double-line sign represents meningeal enhancement of two adjacent lobes while visualization of the vessel between these, results in a triple-line sign. In about 50 percent of patients the meningeal exudates/granulation tissue produced can be identified on

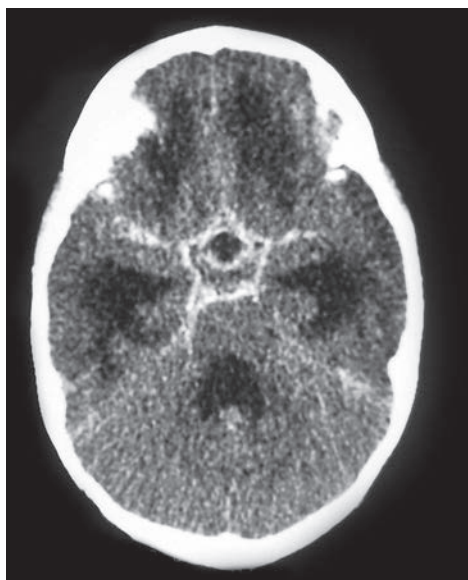


Fig. 16: CECT brain shows dilatation of fourth ventricle along with supratentorial ventricular cisterns suggestive of communicating hydrocephalus. Exudates are also seen in basal cisterns and bilaterally along the middle cerebral artery

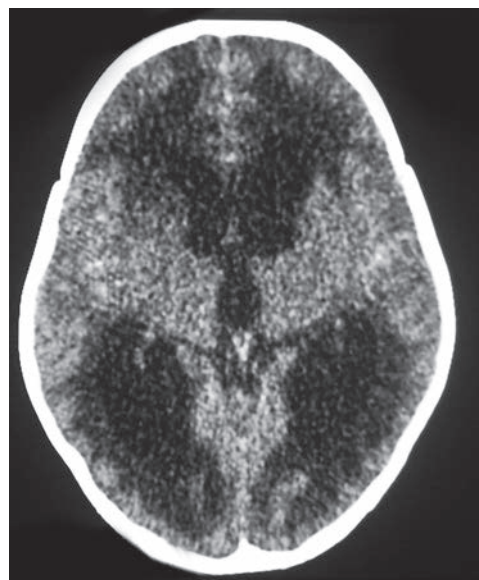


Fig. 18: CECT brain shows dilatation of bilateral lateral and third ventricle with periventricular ooze suggestive of communicating hydrocephalus and exudates in bilateral sylvian fissure

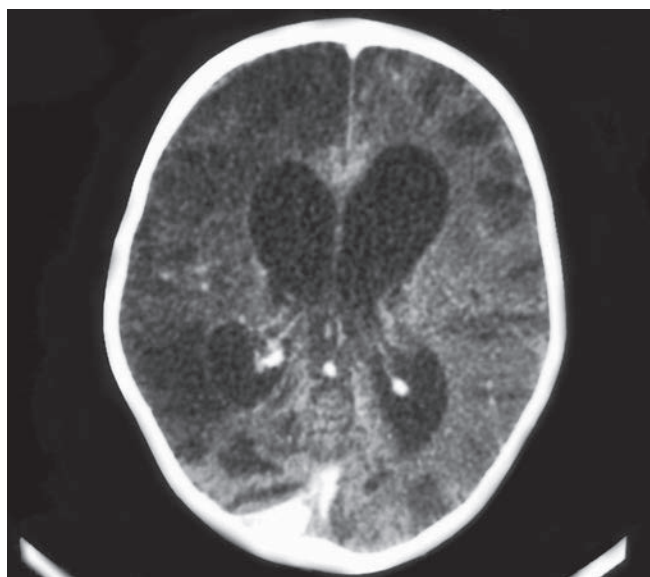


Fig. 17: CECT brain shows dilatation of bilateral lateral ventricle and large hypodense area in right cerebral hemisphere in middle cerebral artery territory suggestive of infarct

non-contrast scans as hyperdensity in the basal cisterns.⁶⁵ This is the most specific sign of TBM and similar appearances are seen in patients with subarachnoid hemorrhage or intrathecal contrast medium. An important complication of TBM is infarction as a result of vasculitis (Fig. 17). It is an important determinant of prognosis, as patients with bilateral basal ganglia infarcts have a poor prognosis.⁶⁶ Infarcts also occur adjacent to areas of severe meningeal

and cisternal inflammation due to direct extension of disease into the parenchyma, and are known as 'border-zone' infarction.

Hydrocephalus is the other major complication of TBM and is usually of the communicating type, which does not often require shunting (Fig. 18). True non-communicating hydrocephalus may result in markedly enlarged ventricles, periventricular lucency and features of raised intracranial pressure. The triad of basal enhancement, hydrocephalus and infarct has the same specificity as cisternal hyperdensity prior to contrast medium administration.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is an excellent tool for the detection of infarction; and, basal enhancement—which stands out against the flow voids in the vessels of the circle of Willis. Spinal arachnoiditis is relatively uncommon, and MRI detects it more often. MRI with IV gadolinium is the modality of choice for making the diagnosis and this demonstrates enhancement of the dura-arachnoid complex around the cord, enhancing nodules and even segmental signal abnormality and enhancement of the cord itself.⁶⁷

Sequel of TBM includes meningeal or ependymal calcifications, focal areas of atrophy secondary to infarcts and hydrocephalus and rarely syringomyelia or syringobulbia.⁶⁸ Except for calcifications which are better evaluated by CT than by MR imaging,⁶⁹ in general all other kinds of lesions associated with TBM are demonstrated better on MR images than on CT scans.⁷⁰

TB Spine

TB of the spine (Pott's Spine) is the most common site of osseous involvement. The thoracic spine is most commonly affected; the radiological features include bone marrow edema and enhancement, posterior element involvement, canal stenosis, and spinal cord or nerve root compression.⁷¹ Inter-vertebral disk enhancement, vertebral collapse and kyphosis deformity are particularly suggestive of tuberculosis.⁷² Vertebral intraosseous abscess, disk abscess, abnormal paraspinal signal intensity, and involvement of multiple vertebral bodies are commonly seen in tuberculosis. There are few reports of TB spondylitis in pediatric population. In a retrospective study of patients with Pott's spine, MRI showed contiguous involvement of two or more vertebral bodies in 85 percent of cases.⁷³ An intraspinal or paraspinal soft tissue mass or abscess was present in 98 percent, subligamentous extension was noted in 64 percent patients and ring enhancement of the soft tissue mass was present in 65 percent patient after gadolinium.⁷³

Abdominal TB

Abdominal TB is less common in children than in adults.²⁰ A high index of suspicion is required to make the diagnosis as TB mimics several other conditions. The chest X-ray may be normal in 50 to 65 percent of these patients.^{74,75} Both US and CT play a role in the diagnostic imaging of abdominal TB.

The most common site of gastrointestinal TB is the ileocecal region (90%),⁷⁴ because of the abundance of lymphoid tissues and relative stasis. Early involvement of the ileocecal region manifests on single-contrast barium studies only as spasm and hypermotility with edema of the valve. Thickened ileocecal valve and/or wide gaping of the valve with narrowing of the terminal ileum (Fleischer sign) have been described as characteristic of TB.⁷⁶ Ulceration in the early stage of the disease can be visualized with the use of double contrast barium. These ulcers are shallow with characteristic elevated margins, typically linear or stellate and follow orientation of the lymphoid follicles, longitudinal in the terminal ileum and transverse in the colon. Characteristic deformities include symmetric, annular "napkin ring" stenosis and obstruction, shortening retraction and pouch formation.⁷⁷

Peritonitis is a rare manifestation of TB and occurs in less than four percent of patients.⁷⁶ It is seen in association with widespread abdominal disease involving lymph nodes or bowel, and may arise from lymphatic or hematogenous spread. The "wet" type is the more common form and is characterized by large amounts of viscous ascitic fluid that is diffusely distributed or loculated into complex pockets. The less common "fibrotic-fixed" type is characterized by large omental masses (cakes), matted loops of bowel and mesentery and occasionally, loculated ascites.⁷⁹

Ultrasonology

Ultrasonology (US) is better than CT for detecting ascites and can also demonstrate organ lesions, lymph nodes and masses. On ultrasound, the diseased intestine may be seen as nonspecific bowel wall thickening (hypoechoic halo measuring more than 5 mm). Pitfalls are that it is a non-specific and observer dependent sign.

The nodes may be seen as large conglomerate masses or as scattered enlarged nodes with caseous necrosis resulting in hypoechoic/anechoic centers especially in the para-aortic, paracaval and mesenteric groups.

USG readily demonstrates intra-abdominal fluid, which may be free or loculated with varying amounts of echogenic debris.^{78,79}

Computed Tomography

Computed tomography (CT) demonstrates lymphadenopathy, organ lesions, conglomerate masses and omental 'cakes' as findings suggestive of abdominal TB. Typical lymphadenopathy is in the porta hepatis and in the para-aortic region, but can also involve the mesenteric nodes with typical fanning out of the vessels and marginalization of the bowel loops. Lymph nodes may be calcified or show calcification over time, but the most characteristic appearance is that of ring enhancing nodes with low-density centers. Organ lesions are seen as low-density multifocal areas, occurring most commonly in the liver and spleen, and rarely in the pancreas. Over time these lesions may show calcification.

Inflammatory masses composed of bowel loops with adherent omentum and lymphadenopathy are best demonstrated on CT. Forty-five percent of cases show circumferential bowel wall thickening up to 3 cm in thickness in the terminal ileum and cecum, enlargement of the ileocecal valve on CT. A combination of the above features, along with a lymphadenopathy which is ring enhancing or calcified, is highly suggestive of the tuberculosis.

Ascitic fluid on CT fluid has high attenuation values, due to high protein and cellular content of the fluid.⁷⁸

CONCLUSION

Tuberculosis can affect any organ in the body and lung is the most common site of infection as it is the portal of entry. Imaging should be directed at not only making the diagnosis, but also at detecting the complications of TB. Imaging should be as basic as possible at first, including the continued use of chest radiographs. Equivocal results should prompt further imaging. When results are negative, rely on clinical suspicion to guide further imaging. As a generalization it may be said that for investigating pulmonary TB, begin with a chest radiograph; for intracranial TB, begin with a CT and for abdominal TB begin with ultrasound examination. Further investigations should be individualized based on the findings of the initial imaging.

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Fig. 2: Clinical photograph of neonate with varicella



Fig. 5: Clinical photograph of a newborn with congenital rubella showing blue berry muffin rash



Fig. 3: Cloudy cornea due to glaucoma in a neonate with congenital rubella syndrome



Fig. 6: Clinical photograph showing cluster of vesicles in a child with congenital herpes infection

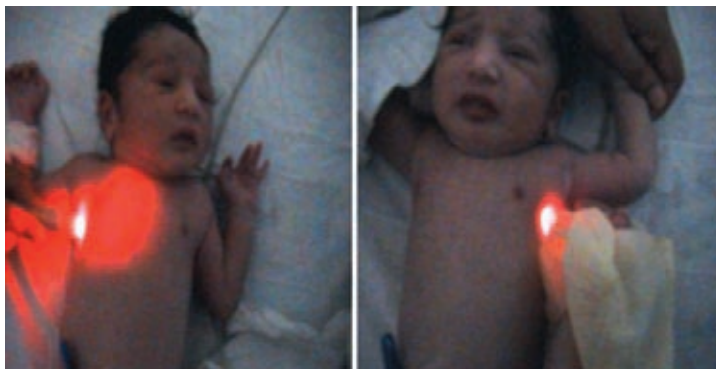


Fig. 6A: Pneumothorax demonstrated by fiberoptic light. The other baby is with normal chest for comparison



Fig. 9: Imperforate anus

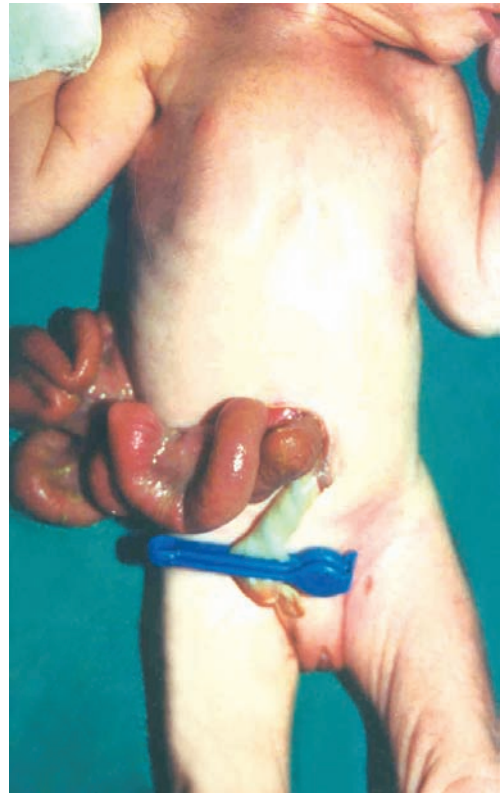


Fig. 17: Gastroschisis



Fig. 15: Omphalocele



Fig. 16: Omphalocele (Ruptured sac)

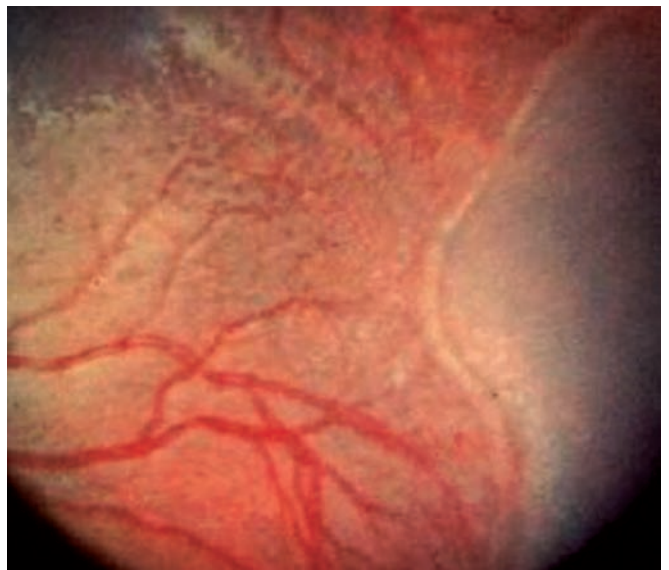


Fig. 2: Stage 1 ROP showing demarcation line

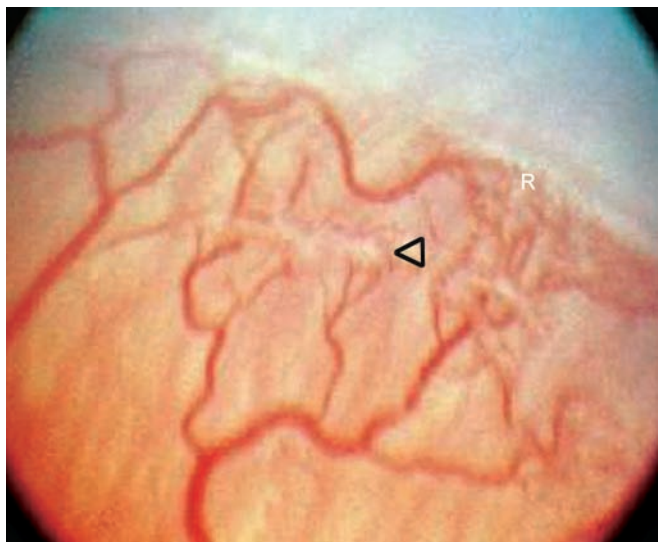


Fig. 3: Stage 2 ROP showing a ridge (R)



Fig. 5: Plus disease with dilatation and tortuosity of vessels at the posterior pole

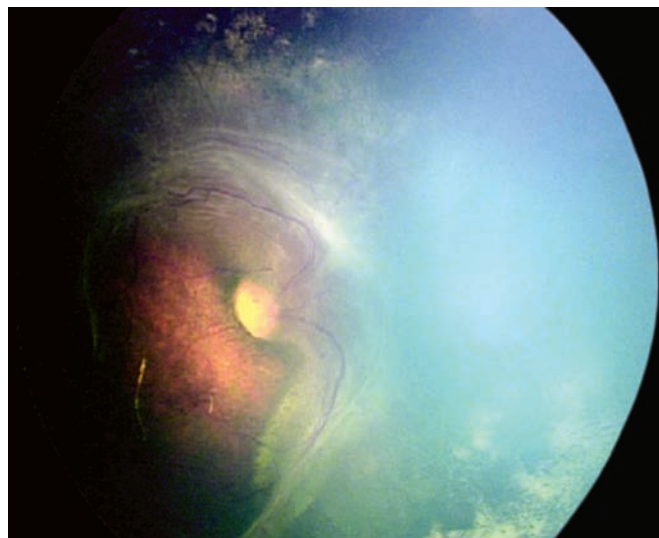


Fig. 4: Stage 3 ROP showing extraretinal fibrovascular proliferation

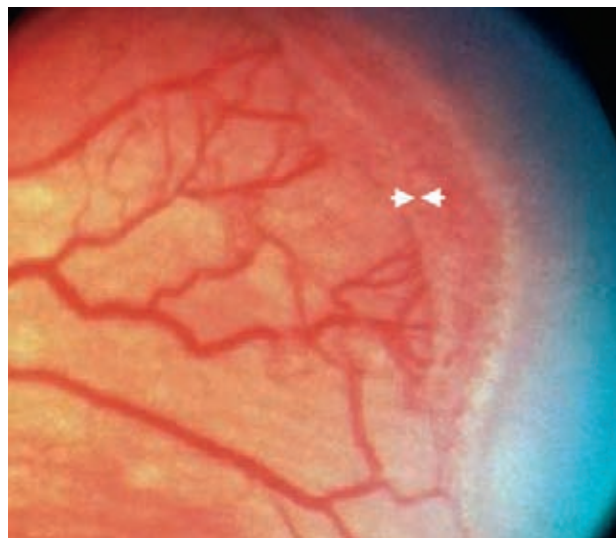


Fig. 6: Stage 4 ROP with subtotal retinal detachment

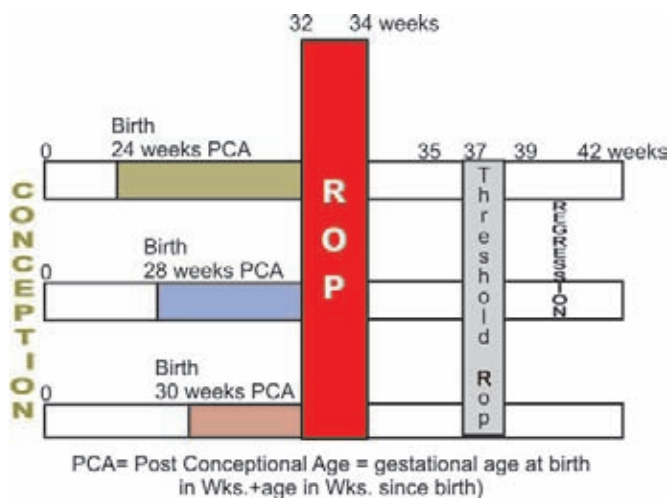


Fig. 7: Occurrence of ROP and subsequent events

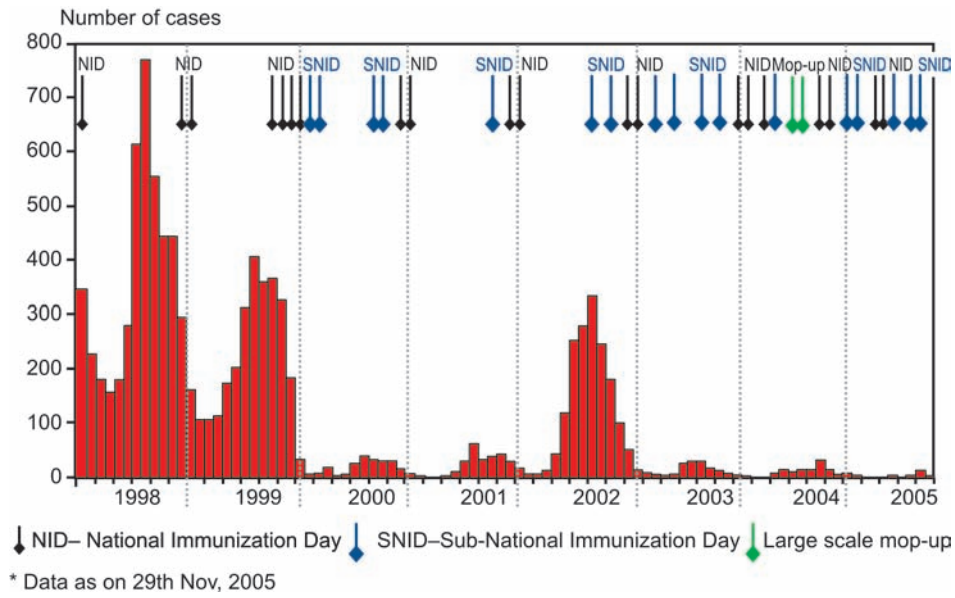
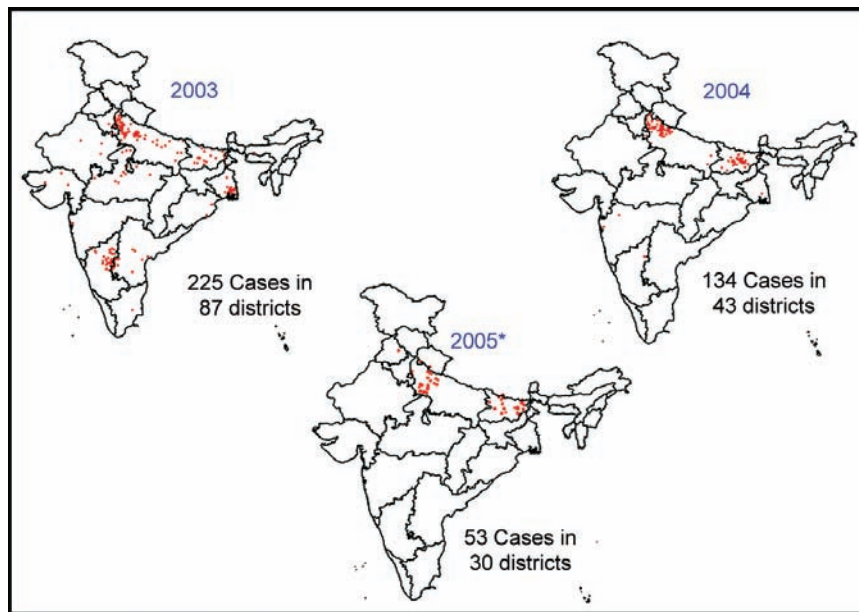
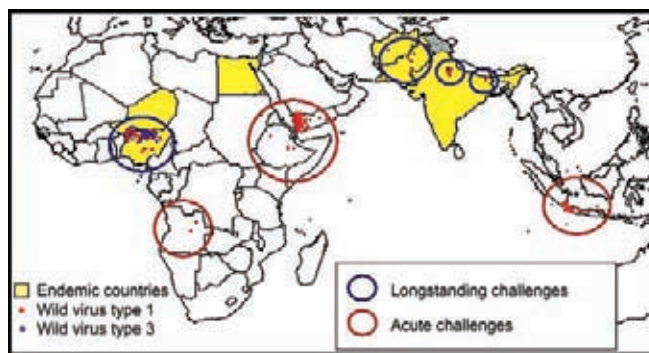


Fig. 1: Monthly incidence of polio in India (January 1998-September 2005)



* Data as on 29th Nov, 2005

Fig. 2: Location of poliovirus, India 2003-2005



Data in WHO HQ, Oct. 2005

Fig. 5: Wild Poliovirus since 1 June 2005

1. Fill out appropriate paperwork: DBS card lab order form, clinic logbook.

2. Choose the puncture site

Small Infants (<4mos, <5kg)
 • Puncture the heel
 • Not finger, since risk of hitting bone

Medium infants (4-10 mos, 5-10kg)
 • Puncture the toe
 • If malnourished, still use heel

Larger Infants (>10 mos, >10 kg)
 • Puncture 4th finger
 • Slightly lateral side



3. Warm the puncture site



4. Wash hands, put on gloves



5. Position baby with foot down

6. Clean the site with an alcohol swab and allow to dry for 30 seconds



6. Press lancet on to site, prick skin

8. Wipe away first drop



9. Allow large drop to collect

10. Touch blood drop to card

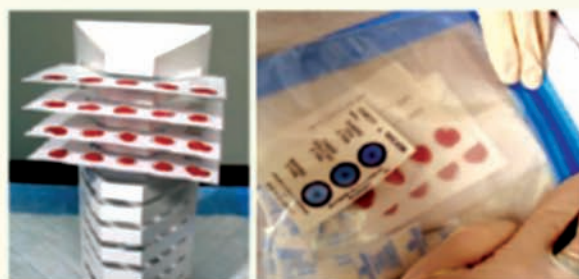
11. Fill entire circle with drop

12. Fill all 5 circles (at least 3)

13. Apply mild pressure and clean the puncture site



14. Dry and package the DBS samples for storage and transport to the laboratory



Job well done!



Fig. 3: Method of collection of DBS sample (Photos courtesy of Julian Kim, MD: Baylor Initiative for Paediatric AIDS 2010)⁴

How-to stage HIV (Continued)

Imaged depicting common manifestations of WHO clinical staging diseases

Stage 2 diagnosis - selected examples



Papular pruritic eruption



Unexplained persistent hepatomegaly



Verruca planus

Verruca vulgaris

Two examples of extensive wart virus infection:



Herpes zoster



Fungal nail infection



Recurrent oral ulcerations



Extensive molluscum contagiosum



Unexplained persistent parotid enlargement

Fig. 4: Common manifestations of WHO clinical estaging diseases



Fig. 1: Rashes on the soles of feet



Fig. 3: Necrotic rash



Fig. 2: Palpable purpura



Fig. 4: Gangrene of digits



Fig. 5: Gangrene of ear lobe

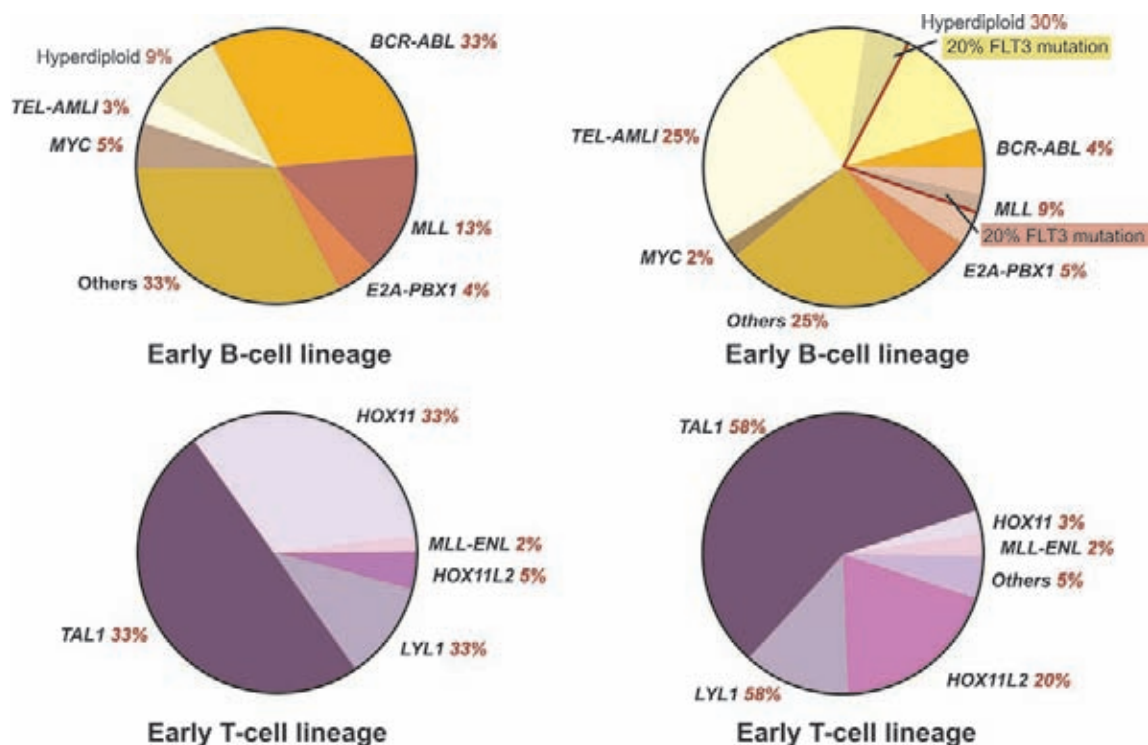


Fig. 1: Chromosomal abnormalities in acute lymphoblastic leukemia. The relative frequencies of chromosomal aberrations found in lymphoblastic leukemias are shown for (A) adult and (B) childhood (right) acute lymphoblastic leukemias. The groups are divided into early B-cell lineage and early T-cell lineage

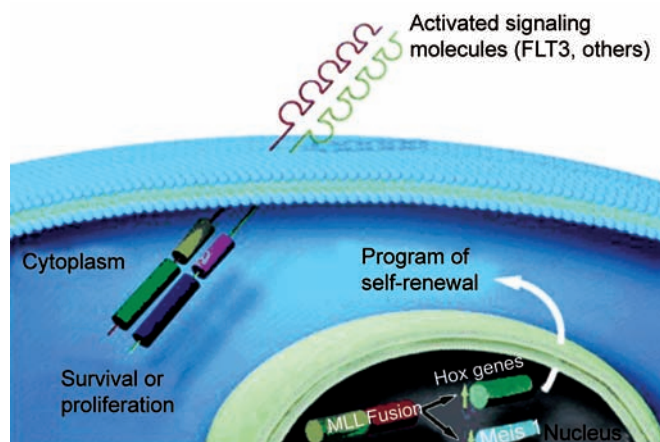


Fig. 2: Multi step pathogenesis of MLL-rearranged lymphoblastic leukemias. MLL translocations induce self-renewal in hematopoietic progenitors as a first step in leukemogenesis. The presence of FLT3 mutations in MLL-rearranged ALLs support activation of FLT3 or other kinases as cooperating events in this disease. Clinical trials designed to assess the efficacy of FLT3 inhibitors in MLL-rearranged ALL are being developed.

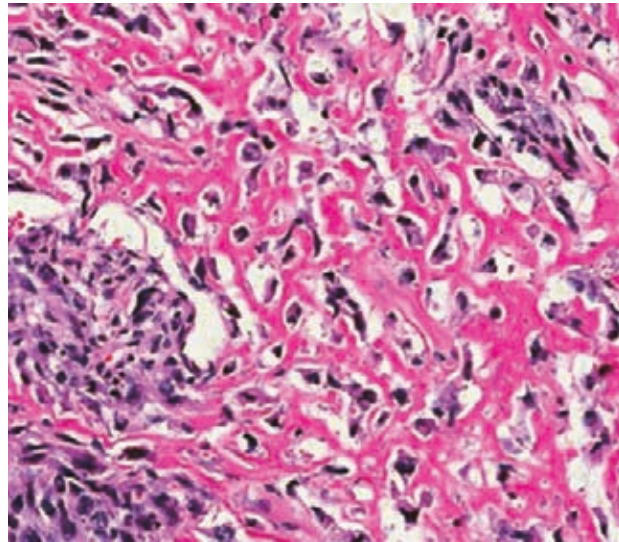
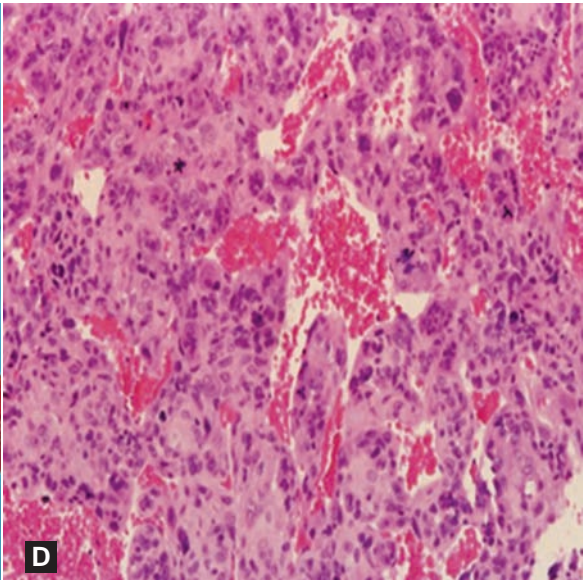
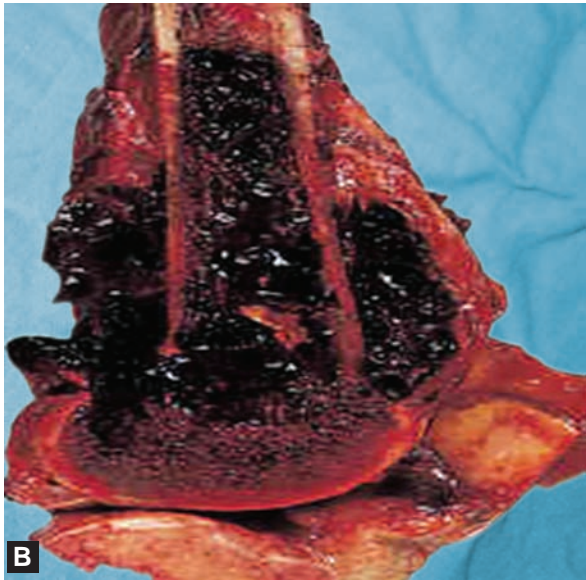
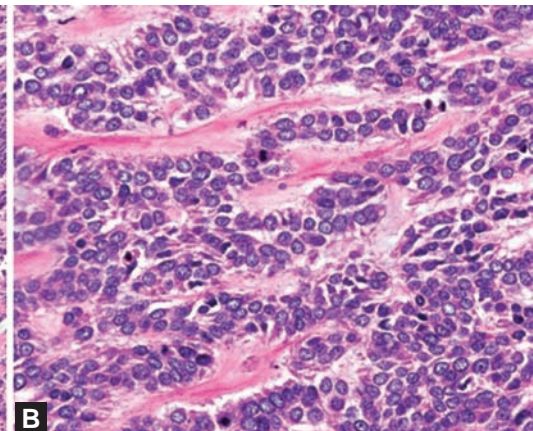
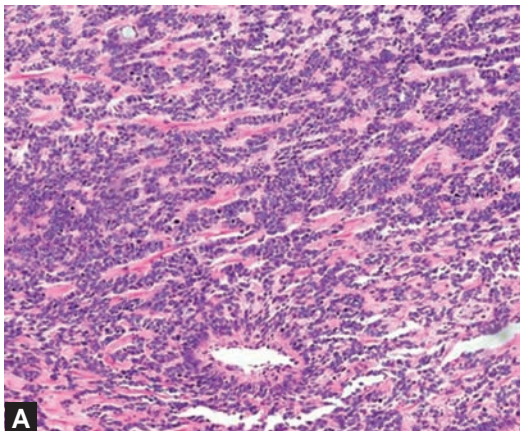


Fig. 1D: Skiagram of the osteogenic sarcoma and the histopathological features



Figs 2B and D: Telangiectatic osteosarcoma



Figs 3A and B: Small cell osteosarcoma

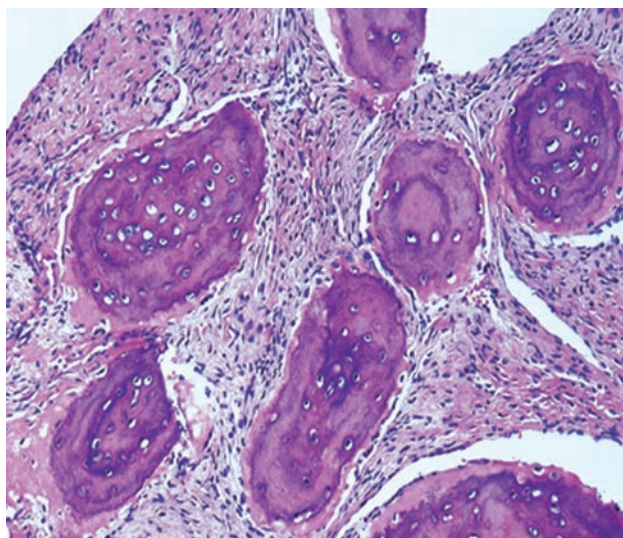


Fig. 4A: Low-grade central osteosarcoma

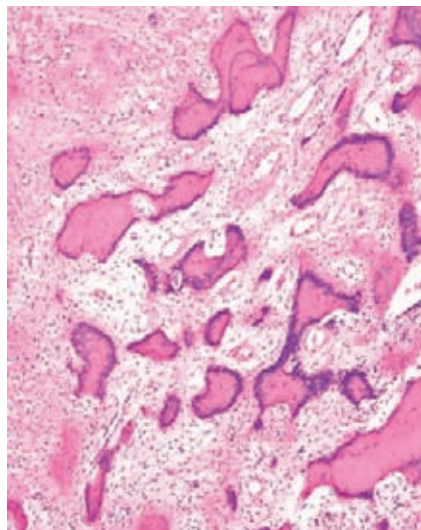


Fig. 5A: Parosteal osteosarcoma

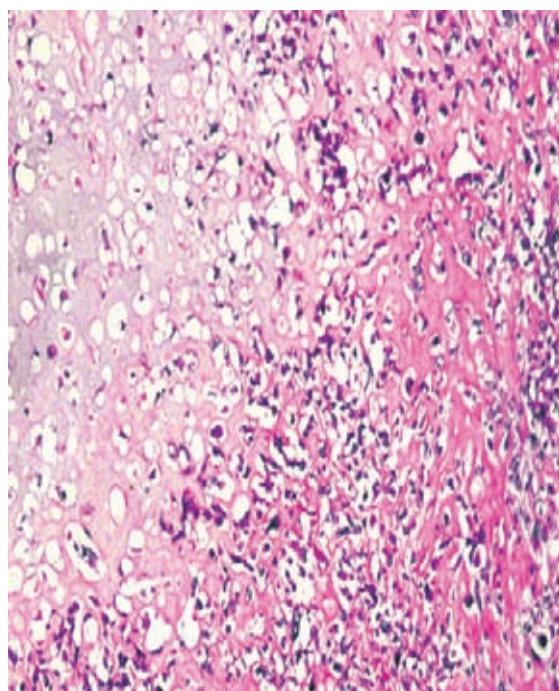
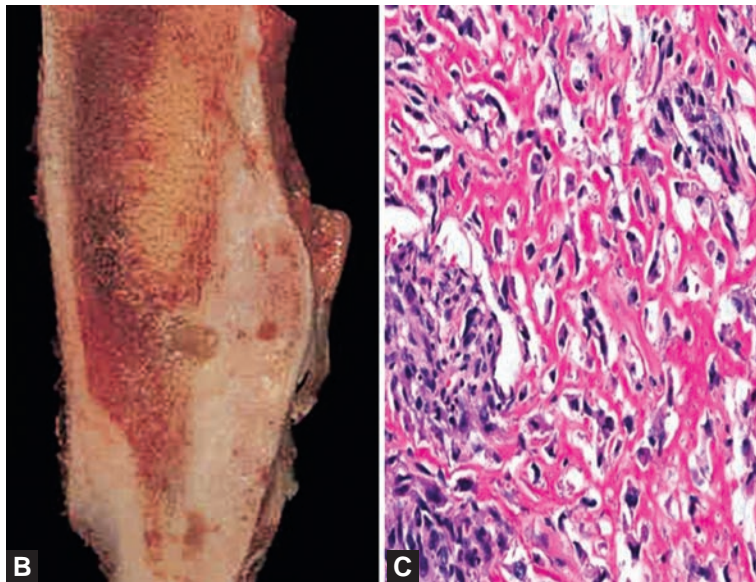
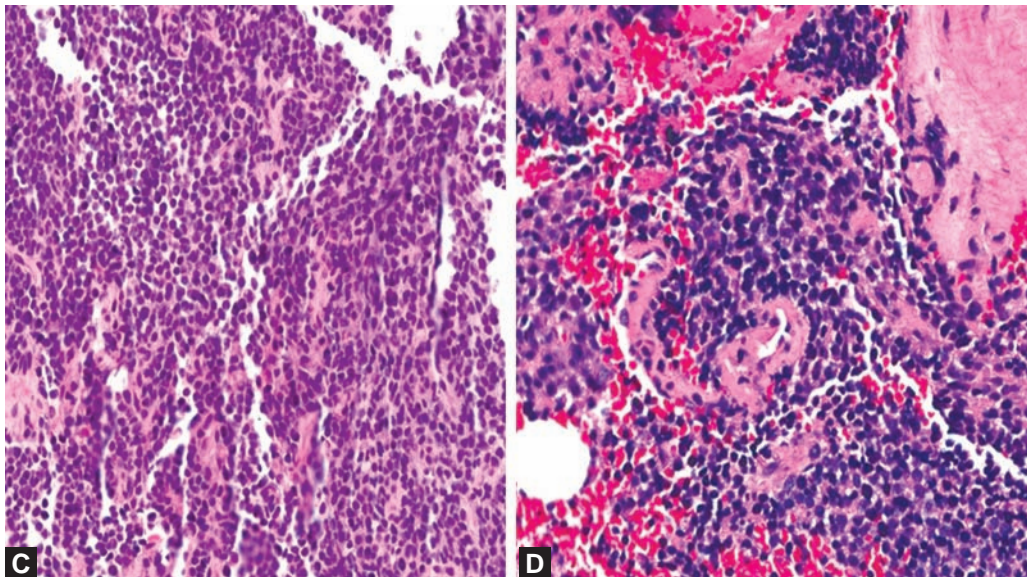


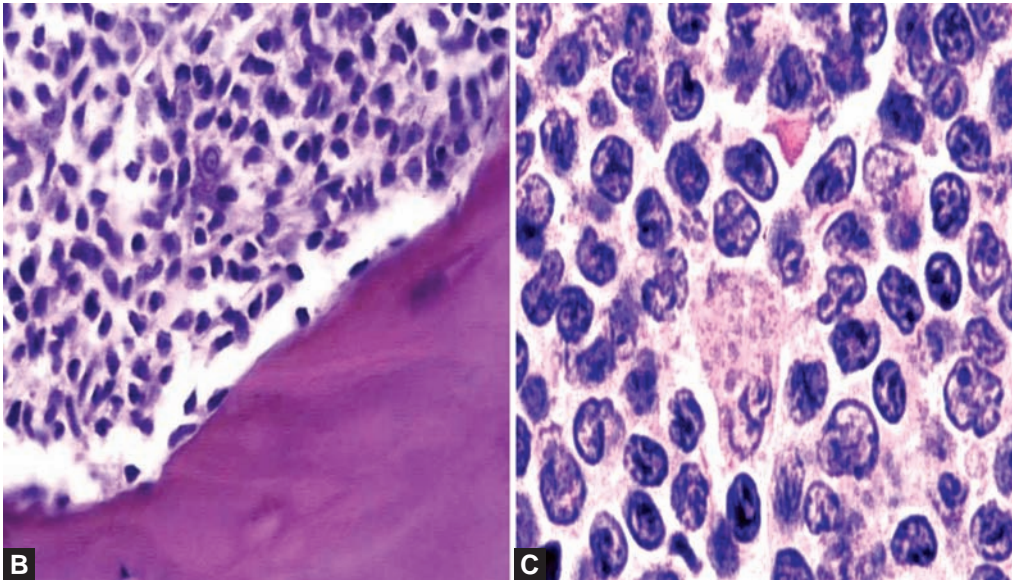
Fig. 6B: Periosteal osteosarcoma



Figs 7B and C: High-grade surface osteosarcoma



Figs 8C and D: Ewing's sarcoma



Figs 9B and C: Lymphoma of bone

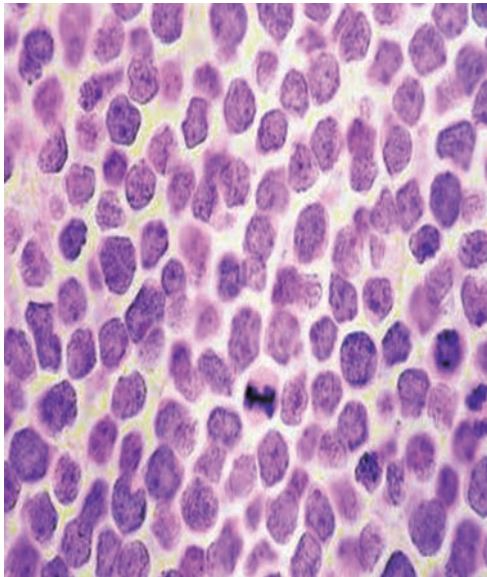


Fig. 1: Lymphoblastic lymphoma demonstrating the fine, blastic chromatin pattern without significant nucleoli and scanty cytoplasm. There is a high mitotic rate and diffuse effacement of nodal structures. Occasional tangible body macrophages are noted admixed with the neoplastic cells

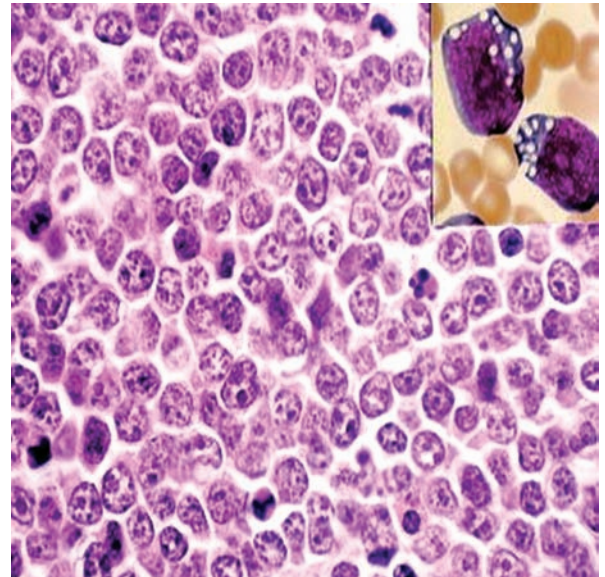


Fig. 2: Burkitt's lymphoma demonstrating the uniform neoplastic cells of intermediate size with coarser chromatin and several indistinct nucleoli and scanty cytoplasm. The inset shows a touch imprint of the tumor demonstrating the characteristic lipid vacuoles in the cytoplasm and the rounded nuclear contours



Fig. 2: Young female with spastic quadriplegic cerebral plays, GMFC IV, in power wheelchair with her service dog (Photography credit: M Sholas, 2003)



Fig. 1: This two-week-old girl was referred for evaluation of clitoromegaly. She was diagnosed as prominent clitoris. On follow-up at the age of six months, the girl had normal genital appearance



Fig. 3: Solid AFO (Ankle-Foot-Orthosis)



Fig. 4: Articulated AFO (Ankle-Foot-Orthosis)



Fig. 2: This three-week-old neonate presented with genital ambiguity. Examination revealed Prader stage IV genitalia, single urogenital opening, no palpable gonads and generalized hyperpigmentation. Investigations showed hyponatremia (sodium 112 mmol/L), hyperkalemia (potassium 6 mmol/L) and elevated 17OHP levels (200 nmol/L, 6000 ng/dl) confirming the diagnosis of salt wasting 21-hydroxylase deficiency



Fig. 1: Infant with severe malnutrition and PD



Fig. 3: This three-month-old boy presented with small phallic size (stretched penile length 1.5 cm), penoscrotal hypospadias and asymmetric genital appearance. Investigations were suggestive of gonadal dysgenesis (karyotype 46 XY/XO)



Figs 2A and B: (A) Acanthosis nigricans and; (B) Acrochordons

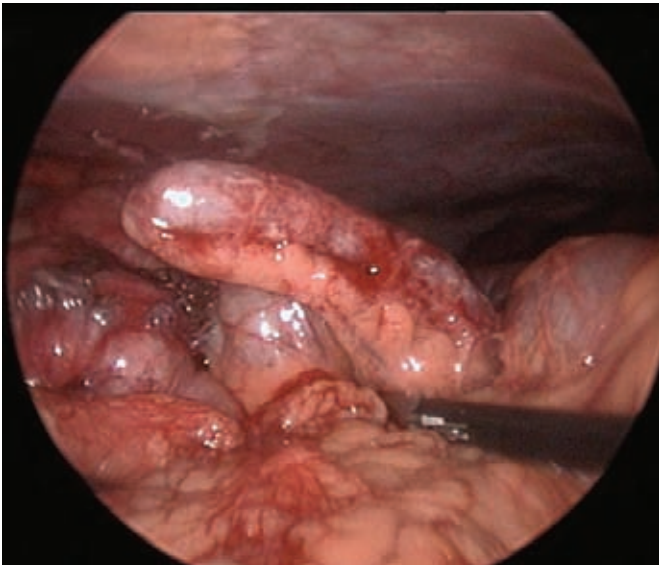


Fig. 3: Laparoscopic appendicectomy



Fig. 4: Open appendicectomy



Fig. 5: Meckel's diverticulum



Fig. 8: Intussusception



Fig. 9: Torsion left testis with retraction



Fig. 6: Lead point for intussusception



Fig. 10: Gangrene of testis



Fig. 1: Large left sided inguinal hernia



Fig. 4: Penoscrotal hypospadias with chordee



Fig. 2: Bilateral small hydroceles



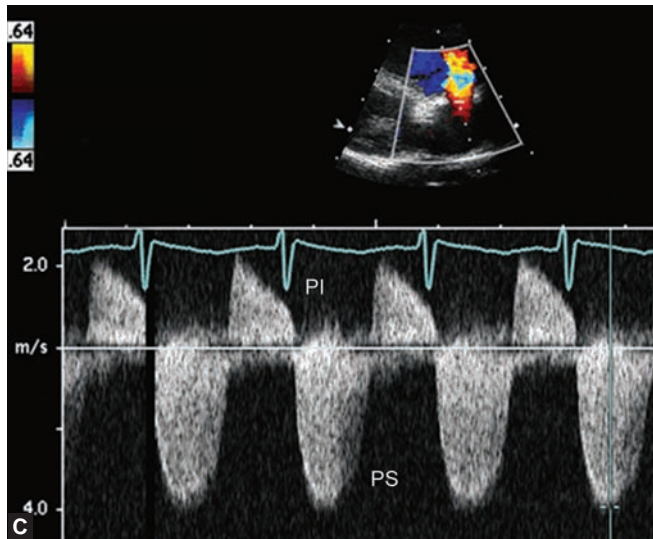
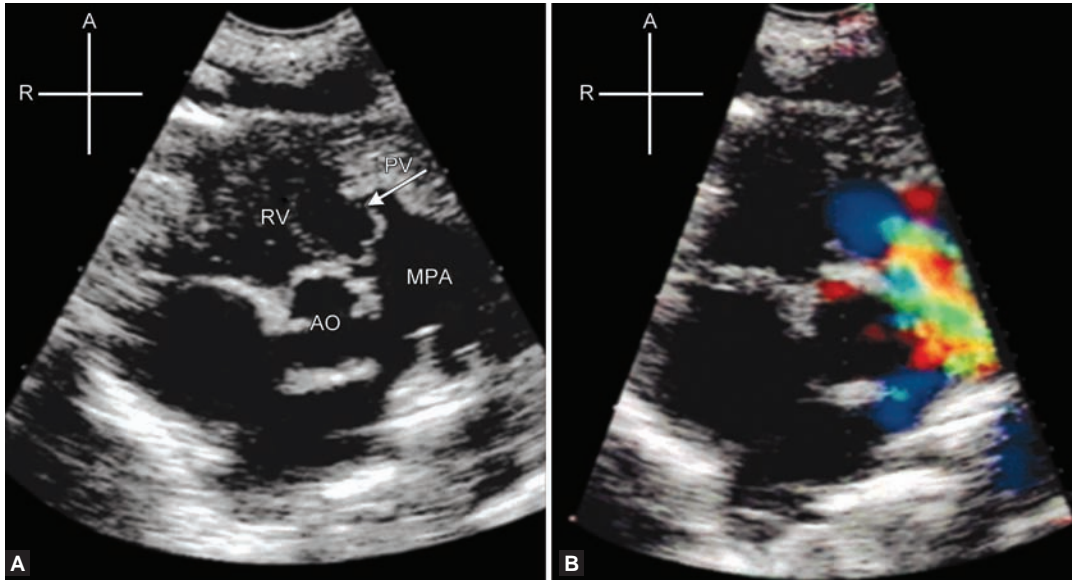
Fig. 5: Distal penile hypospadias with left congenital hydrocele



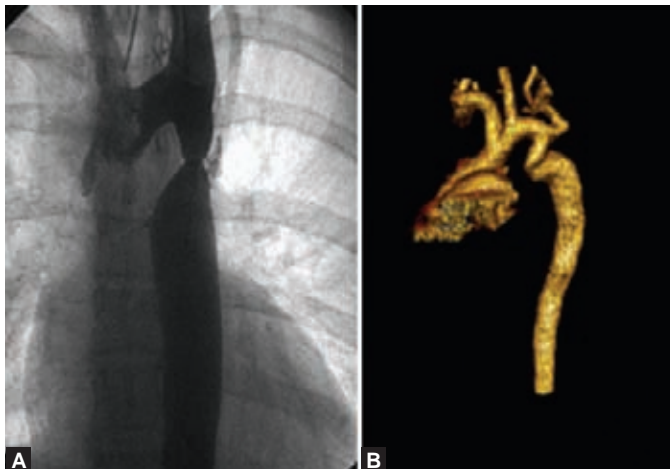
Fig. 3: Bilateral undescended testis



Fig. 6: Phimosis (pathological)



Figs 4A to C: A and B: The echocardiography image of pulmonary valve in parasternal short axis showing stenotic valve with doming of cusps A, Color Doppler through the stenotic pulmonary valve shows a mosaic pattern; C: Continuous wave Doppler imaging in a patient with pulmonary valve stenosis. Note the peak pressure gradient of 61 mm Hg with concurrent pulmonary valve insufficiency; C and D: The ventriculogram in anteroposterior view D and lateral view E, showing stenotic pulmonary valve and characteristic doming of the cusps and dilated segment of MPA. RV: Right ventricle, Ao: aorta, MPA: main pulmonary artery, PV: pulmonary valve



Figs 13A and B: (A) The Three-dimensional reformatted CT angiogram in a left-lateral projection showing discrete coarctation and a tortuous transverse arch and isthmus, (B) The aortogram showing typical discrete juxtraductal coarctation with moderated poststenotic dilatation



Figs 1A to D: Face mask and face shield for protection

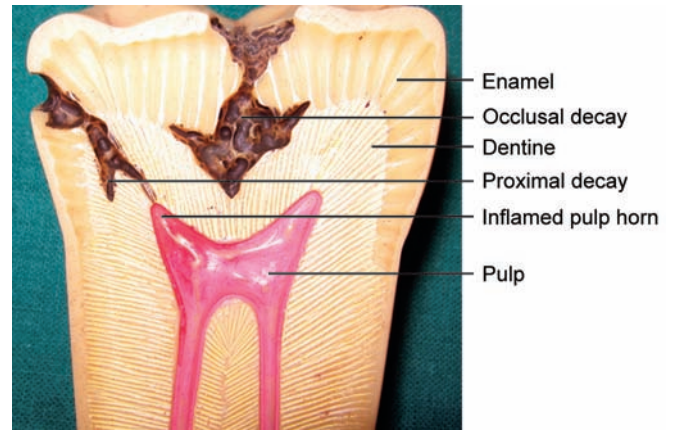


Fig. 3: Sagittal section of a tooth model showing decayed area occlusally and proximally



Fig. 1: Dental caries in the maxillary anterior dentition



Fig. 8: Lip injury and crown fracture for the upper left central incisor exposing the pulp and with lateral luxation



Fig. 2: Dental caries in the lower posterior dentition



Fig. 9: Same patient as in Figure 8 with a closer view



Fig. 10: Upper right central incisor with enamel and dentine crown fracture and extrusive luxation. The Upper left central incisor with lateral luxation



Fig. 15: Modeling



Fig. 13: Patient undergoing orthodontic treatment with a fixed appliance



Fig. 16: Treatment under general anesthesia



Fig. 14: Oral hygiene instruction for a group of children in a child friendly non-threatening environment as a method of desensitization



Fig. 17: Extraction in the lower right quadrant

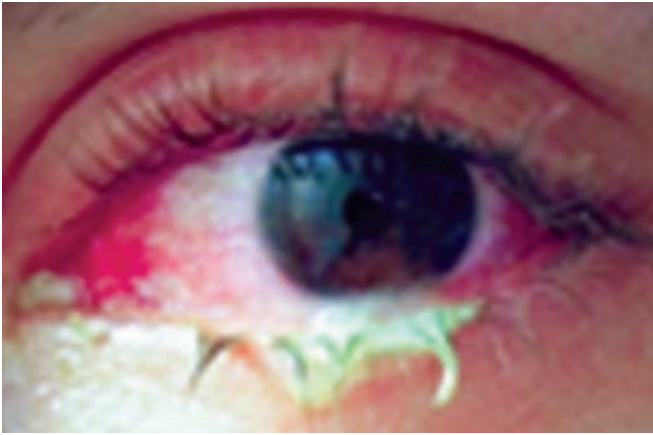


Fig. 1: Bacterial conjunctivitis

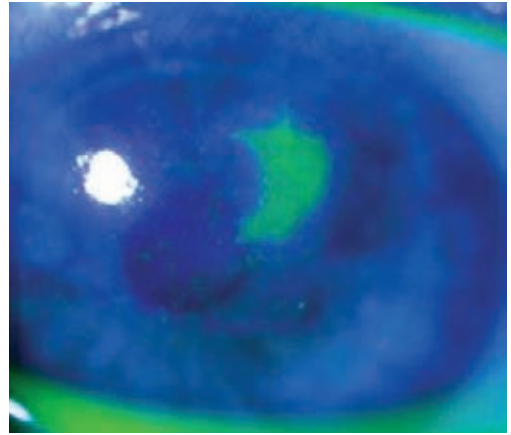


Fig. 4: Shield ulcer



Fig. 2: Giant papillary conjunctivitis with cobblestone appearance

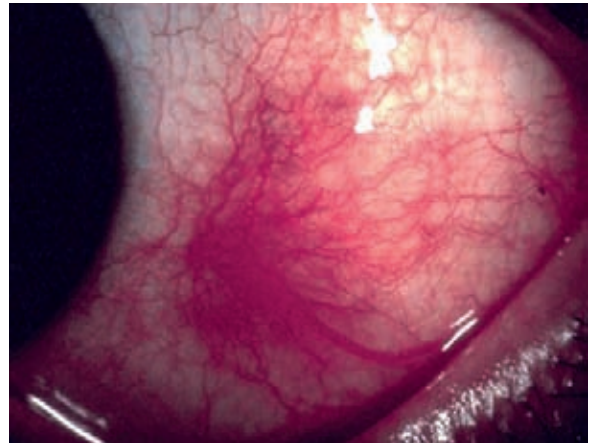


Fig. 5: Localized congestion in scleritis

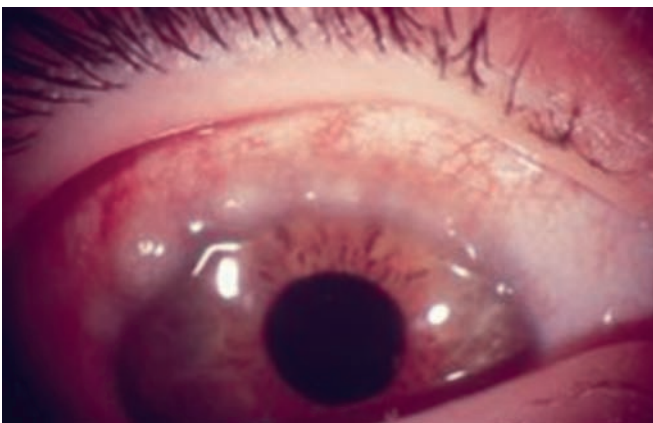


Fig. 3: Limbal VKC with Horner-Trantas dots

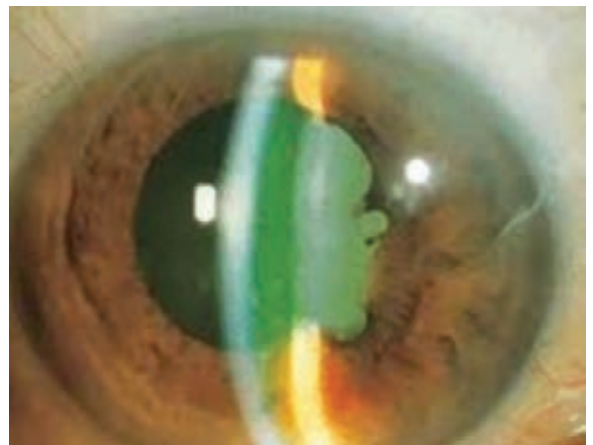


Fig. 6: Anterior uveitis with posterior synechiae



Fig. 7: Blepharitis with crusting around base of cilia



Fig. 3: Showing fully accommodative squint
courtesy: visioncentreindore.com/eyedisease_children.html



Fig. 8: Sty



Fig. 4: Twenty four year old male showing divergent squint in the left eye

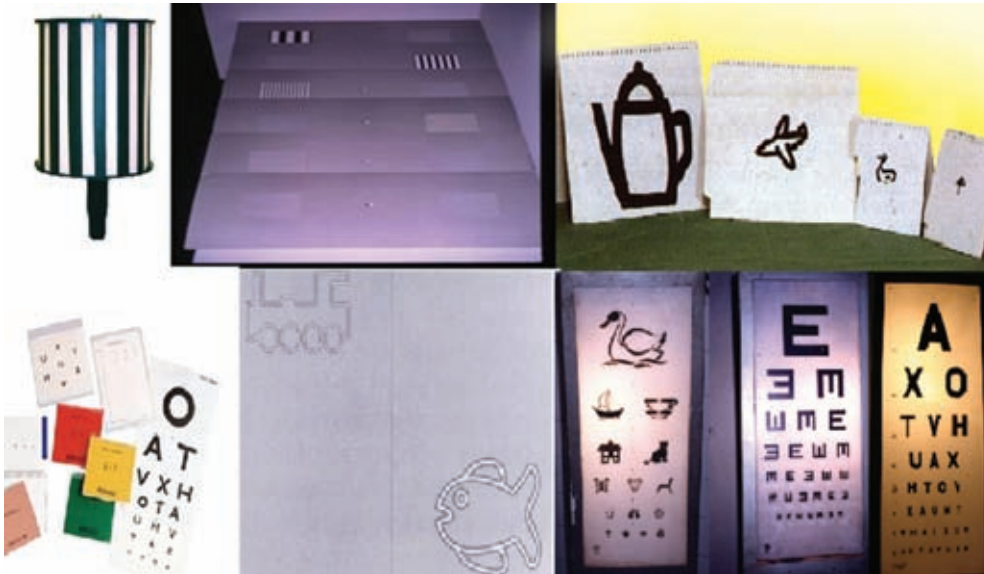


Fig. 1: Top Row (Left to right): Optokinetic nystagmus drum; Teller cards; Kay picture test

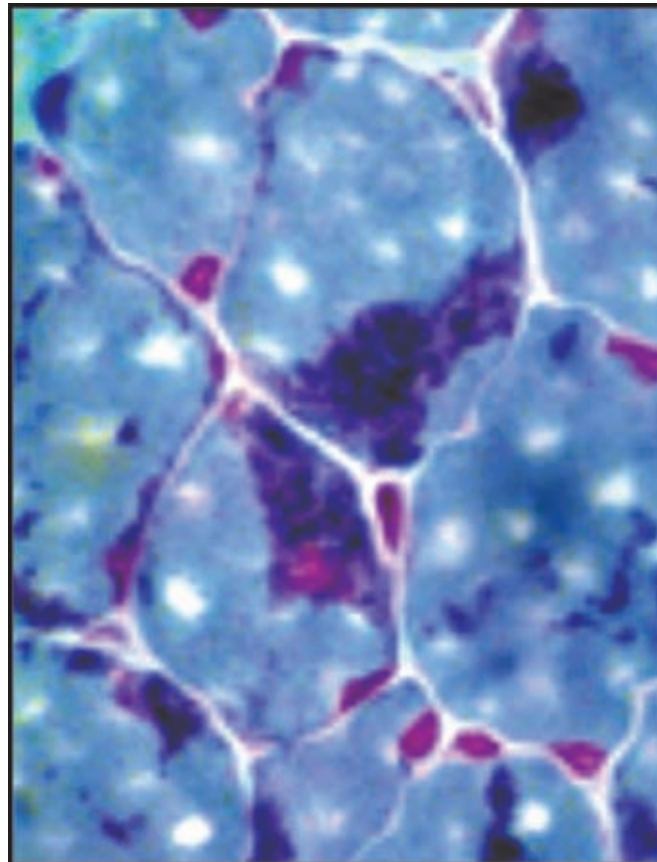


Fig. 1: Muscle biopsy stained with modified trichrome stain showing nemaline rods

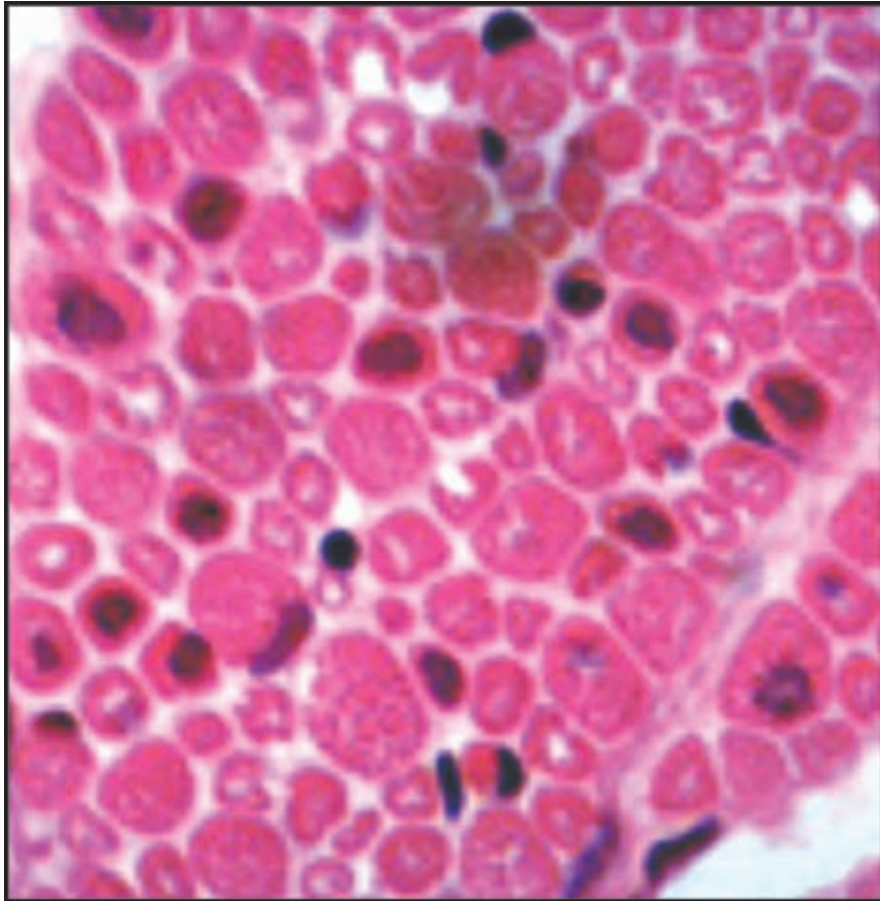


Fig. 2: Myotubular myopathy. H&E stain, showing many muscle fibers with central nucleus

Section 5

Pulmonology

Editors
K Chugh
Varinder Singh

INTRODUCTION

Pneumonia probably is one of the oldest diseases, as old as antiquity known to human kind and has always remained a subject of challenge to medical science, despite extensive research.

Pneumonia is number one cause of under 5 childhood mortality across the globe particularly in developing countries. Unfortunately, over the years the mortality remained almost the same and hence it is also been called as “Forgotten Killer” or “Silent Killer”.

EPIDEMIOLOGY

Approximately 150 million episodes of childhood pneumonia are reported every year from the world out of which 95 percent are from developing countries. Fifteen countries account for nearly 75 percent and 6 countries including India account for 50 percent. India alone bears the brunt of 40 percent disease burden.

Out of the 9.73 million under 5 childhood mortality world over 19 percent, i.e. 1.9 million deaths are due to pneumonia. More than 90 percent of deaths due to pneumonia among young children occur in 68 poor nations, mostly from Africa and Asia.

In India, the disease burden is huge. Forty-five million episodes are estimated annually with 6.6 million hospitalizations, which contribute to 24 percent national disease burden and 0.41 million deaths annually.

DEFINITION

An inflammatory process involving lung parenchyma usually due to microorganisms. It is referred to as “Pneumonitis” when the cause is non-infective.

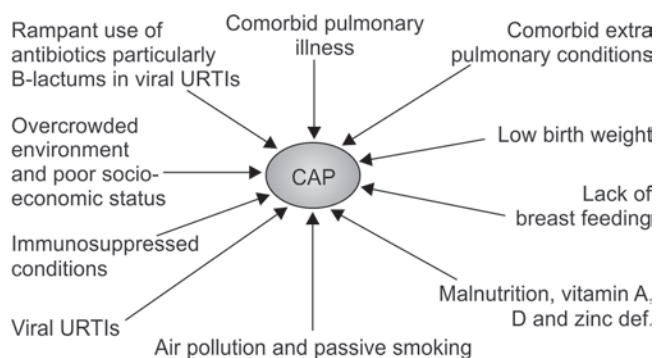
Usually pneumonias are mainly classified as:

- *Community acquired*: Pneumonia acquired outside the hospital environment in a previously healthy immune competent subject. The patient should not have been hospitalized within 14 days prior to the onset of symptoms.
- *Nosocomial pneumonia*: Pneumonia acquired within hospital setting more than 48 hours after hospitalization (HAP) or more than 48 to 72 hours after endotracheal intubation (VAP).

This classification does not include “Recurrent Pneumonia” which is defined as two episodes of pneumonia in 1 year or 3 episodes in any time frame, and “Aspiration Pneumonia” which occurs due to aspiration of foreign materials in the lower airways.

ETIOLOGY

It depends on various factors like age, immune status, underlying co-morbidity and various risk factors like:



(Study by: Burman et al. Epidemiology of ARI in children of developing countries. Rev Int Dis, 1991)

The causative agents may be either viral, bacterial or atypical pathogens. They are usually age specific:

0–3 months	<ul style="list-style-type: none"> • Gram-negative enterobacteriaceae • Enterococci • <i>Chlamydia trachomatis</i> • Group B streptococci • <i>H. influenzae</i> • <i>S. pneumoniae</i> • <i>Listeriae</i>
3 months–5 years	<ul style="list-style-type: none"> • <i>S. pneumoniae</i> • Viruses (35%) • <i>H. influenzae</i> • <i>Staphylococcus</i> • <i>Mycoplasma pneumoniae</i>
>5 years	<ul style="list-style-type: none"> • <i>S. pneumoniae</i> • <i>Mycoplasma pneumoniae</i> (24-30%) • Viruses • <i>Staphylococcus</i> • <i>S. pyogenes</i>

Most common bacterial pathogens are *S. pneumoniae* and *H. influenzae* which together are responsible for 60 to 70 percent of total pneumonia cases, followed by viruses which account for 30 to 35 percent of pneumonia cases.

Mycoplasma pneumoniae and *Chlamydia* are most common causes of “Atypical Pneumonia” in a school-going child older than 5 years of age accounting for 11 to 30 percent cases.

Significant proportion of pneumonia is due to mixed infection (8-40%) and in 20 to 60 percent of cases pathogens are not identified.

PATHOGENESIS

Pneumonia is usually preceded by respiratory viral infection which disturbs the defense mechanism of the lungs and also disrupts the normal epithelial layer of respiratory tract, as a result there is dysfunction of ciliary brush border clearing mechanism. There is inhibition of phagocytosis by alveolar macrophages. Thus, bacteria and other organisms invade the lung parenchyma and produce a pneumonic lesion. The invasion could be either direct spread from nasopharyngeal tract by respiratory droplet infection or could be by invasion through hematogenous dissemination within the lung parenchyma. When the spread is hematogenous. It is called “Invasive/Bacteraemic Pneumonia” and when the spread is direct it is called “Non-bacteraemic Pneumonia”.

CLINICAL FEATURES

Constellation of symptoms triad of fever, cough, rapid breathing and or difficult breathing are classical clinical manifestations of pneumonia. Diagnosis of pneumonia is essentially clinical. Tachypnea is single most sensitive and specific sign to diagnose pneumonia, as sensitive as 66 to 88 percent of auscultation.

Clinical features may differ from neonate to older child. In the neonate there could be absence of cough and fever, and common presenting features are excessive irritability or lethargy, difficulty in feeding, intermittent apneic spells, cyanosis +/-, progressive air hunger, rapid clinical deterioration with or without evidence of sepsis.

WHO Endorsed Age Specific Cut Off's for Tachypnea

Age	Respiratory rate (breaths/min)
<2 months	60 or more
2 months up to 12 months	50 or more
12 months up to 5 years	40 or more

Based on symptoms WHO has graded pneumonia as:

Pneumonia	Fever < 38.5°C, no feeding difficulties, no dehydration, cough and tachypnea.
Severe pneumonia	High grade fever > 39°C, difficulty in feeding, tachypnea, respiratory distress with ICR/SCR, dehydration, grunt, bronchial breath sounds on auscultation with or without crackles, SpO ₂ ≥ 92 at room air, radiological opacity on chest X-ray +/-.
Very severe pneumonia	Inability to feed, altered sensorium, intermittent apneic spells, cyanosis, excessive diaphoresis, narrow pulse pressure, acidemia, SpO ₂ < 92 at room air

Assessment and grading of severity is most important for an optimum and successful management.

DIAGNOSIS

Diagnosis of pneumonia is essentially clinical and seldom requires lab support. Absence of past history of recurrent cough and presence of fever with fast breathing is a hallmark presentation in clinical diagnosis of pneumonia. It should always be remembered that there are no definite markers between viral, bacterial and atypical pneumonia.

However, there are certain clinical clues which can help to nail down on etiological diagnosis.

Predisposing factors	Organisms (apart from usual ones)
Pyoderma, measles, pneumatoceles	<i>Staphylococcus</i>
HIV	<i>Pneumocystis</i>
Neutropenia,	Gram-negative, <i>Aspergillus</i>
Cystic fibrosis	<i>Pseudomonas</i> , <i>Staphylococcus</i>
Severe PEM	Gram-negative, <i>Staphylococcus</i>
Preceding coryza, wheeze	Viral
Young afebrile infant with neonatal conjunctivitis	<i>Chlamydia</i>
Multisystem involvement (rash, anemia, hepatitis, encephalitis)	<i>Mycoplasma</i>
Marked leukocytosis	Bacterial
AOM	<i>S. pneumoniae</i> / <i>H. influenzae</i>

Characteristics of viral pneumonia

- Acute—sudden onset
- Younger age
- Preceding upper respiratory catarrh
- Wheeze with crackles
- Clinical importance of hyperinflation with scattered exudates on radiology due to segmental atelectasis.

For optimum antimicrobial management of pneumonia it is prudent to differentiate between bacterial, viral and atypical pneumonia, clinically, as it is often very difficult to isolate the offending pathogen.

Features	Typical pneumonia	Atypical pneumonia
Age	More common in young infants and children, older children also	School going children adolescents and adults
Onset	Acute/sudden	Gradual/insidious
Facies	Toxic	Well
Rigors	Shaking chills	Chilliness
Wheeze	Rare or nil	Common
Cough	Productive	Non-productive/paroxysmal
Sputum	Purulent/bloody	Mucoid
Temperature	High, 102-104F	Mild, Mod <102F
Pleurisy	Frequent	Rare
Consolidation	Frequent	Rare
Extra pulmonary manifestations	Uncommon	Common
Gram-staining (Sputum)	Neutrophils	Mono-nuclear cells
Sputum culture	Occasional growth of microbe	Rarely any growth
WBC count	>15000/cumm shift to left	>15000/cumm no shift
Chest radiography	Defined density	Non-defined infiltrates

Lab Diagnosis

- *Acute phase reactants* like CBC, CRP, ESR, have poor sensitivity and specificity. They do not distinguish between viral and bacterial etiology, nor help in making decision of antibiotic choice; however, they may be useful tools for monitoring the course of the disease.
- *Radiology* is not routinely required in non-severe pneumonia to confirm the diagnosis. At times it may not correlate with the clinical signs there is also wide variation in the interpretation by radiologists. Moreover, reliability in predicting the etiology is poor. However, CXR may be indicated in very severe disease,

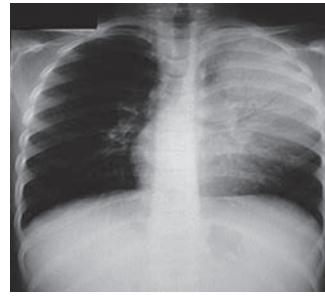


Fig. 1: X-rays—Bacterial lobar consolidation



Fig. 2: Bronchopneumonia



Fig. 3: Interstitial pneumonia

ambiguous picture, no improvement/worsening >48 to 72 hours of therapy, suspected complications and known immunocompromised child.

- *Microbiology:* Sputum culture/blood culture though may be more specific, but the yield is very poor (10-15%). There is also a risk of growing normal nasopharyngeal flora.
- *Serology:* Serology, urinary antigens, rapid antigen detection test (RADT) and cold agglutinins for mycoplasma are not easily available, expensive with time lagging and have poor sensitivity.
- *Invasive procedures* like bronchoscopy, BAL and lung aspiration have high sensitivity and specificity; however they are too invasive to be advised in office practice.
- *Pulse oxymetry* is a mandatory tool for monitoring the course of the disease in all the hospitalized children.

Differential Diagnosis

Though symptom complex of *fever, cough and rapid/difficult breathing* is classical presentation of pneumonia; it is prudent to differentiate pneumonia from other conditions which may mimic the symptomatology.

Management

The mainstays of management are antibiotics and supportive treatment. It is imperative to understand that all pneumonias deserve antibiotics as differentiation between viral and bacterial are difficult. *Empirical antibiotics are prudent and rational in pneumonia.*

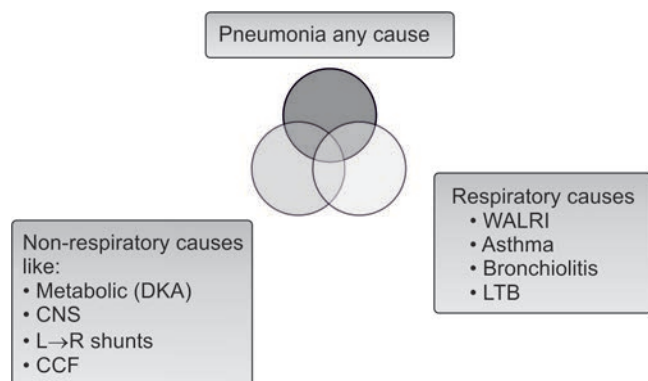


Fig. 4: Differential diagnosis of rapid breathing

Non-severe pneumonia above the age of 3 months can be managed at domiciliary level with oral antibiotics however any pneumonia below the age of 3 months should be hospitalized and treated with parenteral antibiotics. The choice of antibiotics though empirical should be determined by age, severity, pre-disposing conditions if any and local epidemiology and drug resistance pattern.

Out patient Management

All non-severe pneumonias >3 months of age, when the child is not toxic, accepting oral feeds, not dehydrated, maintaining normal saturation and fever < 38.5°C can be managed at domiciliary level with supportive care like maintenance of hydration, nutrition and anti-pyretic and adjuvants if needed. The choice of oral antibiotic is as below:

Age	First line	Second line
3 months-5 years	Amoxicillin*	Coamoxiclav/Cefuroxime/Chloramphenicol
>5 years	Amoxicillin*	Macrolide**/Coamoxiclav/Cefuroxime

* Standard doses 40 to 45 mg/kg/day in two or three divided doses

** Erythromycin 30 to 40 mg/kg/day in three divided doses

** Clarithromycin 15 mg/kg/day in two divided doses

** Azithromycin 10 mg/kg/day in OD dose

First-line oral antibiotics should be given minimum for 5 days and second-line for 7 days. Child should be followed up after 48 hrs, if there is clinical improvement the child should be continued with the same management. If the condition clinically deteriorates after 48 hours, one should revise the diagnosis, look for associated complication and co-morbidities, changing the antibiotic to second-line and if need be, the child should be hospitalized.

Indications for Hospitalization

- Infants less than 3 months
- Severe malnutrition
- More than two risk factors

- Comorbidities
- Associated complications
- Respiratory rate > 70/min in infants
> 50/min in older children
- Respiratory distress-grunting, alae nasi flare, ICR or SCR
- Cyanosis or SpO₂ <92 percent in room air
- Poor oral intake/dehydration
- Inappropriate observation or supervision at home

In patient Management

Management comprises of specific antimicrobial along with supportive care of nutrition, hydration, oxygen if needed, antipyretics (Paracetamol) and bronchodilators along with chest physiotherapy if needed.

Age	First-line	Second-line
< 3 months	***	**
3 months-5 years	****	*****
>5 years	*****	*****
Suspected <i>Staphylococcus</i>	Cefuroxime Or Coamoxiclav Or IV 3rd gen cephalosporins + cloxacillin	Ceftriaxone/ Cefotaxime and Macrolides Ceftriaxone/ Cefotaxime and Vancomycin/teico/ linezolid

* Coamoxiclav 30 to 40 mg/kg – dose

** Ceftriaxone 50 to 100 mg/kg – day

*** Cefotaxime 100 to 200 mg/kg – day

**** Cefuroxime 20 to 30 mg/kg – day

***** Aminoglycosides 15 mg/kg – day in single or two divided doses

In case of MSSA the duration should be for 2 weeks and in case of MRSA it should be 4 to 6 weeks. The duration for IV antibiotics should be for 5 to 7 days in uncomplicated cases, however switch over to oral antibiotics may be considered if accepted orally. The switch over therapy for injection 3rd generation cephalosporin should be either cefpodoxime (10 mg/k/d in 2 divided doses) or cefdinir (15 mg/k/d in 2 divided doses) and should never be cefixime as it has no activity against *Pneumococcus* and poor activity against community pathogens responsible for pneumonia.

Despite rational choice of antibiotics in right dose and for optimal duration, if there is failure in clinical improvement, one needs to:

- Check the diagnosis and reading of Foreign body aspiration pneumonia and interstitial lung disease.
- Look for underlying co-morbidity like lung abscess, empyema, bronchiectasis, L→R shunts, GERD, asthma, cystic fibrosis and ciliary dyskinesia.

- Immunosuppression in the host like HIV, hypogammaglobulinemia.
- Phagocytic dysfunctions like CGD
- Drug-resistance, particularly if child is from day care center, has received multiple courses of beta-lactams and corticosteroids.
- Possibility of polymicrobial etiology.

There is no need to chase for follow-up X-rays since total radiological resolution may take 4 to 12 weeks time depending on offending organisms.

Complications

Empyema, pneumothorax, bronchogenic dissemination, septicemia, osteomyelitis, multiple systemic abscesses, septic arthritis and meningitis.

Prognosis

Prognosis is fairly good provided there is appropriate recognition and proper referral by the health care provider

and early initiation of antibiotics. Unfortunately, only 15 to 20 percent cases of pneumonia receive proper and adequate antibiotics, which is the main reason for high infant mortality due to pneumonias particularly in developing countries.

Prevention

A multifaceted approach is needed to prevent and control childhood pneumonia:

- Exclusive breastfeeding for first six months of life
- Weaning to solid foods after six months of age, preferably with home-made foods
- Avoidance of risk factors like overcrowded environment, exposure to pollution and bottle-feeding
- Protection from malnutrition and supplementation of vitamin A and D
- Optimum immunization with DPT, measles, Hib, pneumococcal vaccines at appropriate age.

Role of Epinephrine, Hypertonic Saline and Steroids in Acute Bronchiolitis

Varinder Singh, Ankit Parakh

INTRODUCTION

Acute bronchiolitis is a viral illness causing acute lower respiratory infection (LRTI) that affects children less than two years of age. It is characterized by fever, nasal discharge and dry, wheezy cough. On examination, there are fine inspiratory crackles and/or high-pitched expiratory wheeze.¹ It is the most frequent acute LRTI in infants and is one of the main reasons for hospitalization/health care utilization.

Bronchiolitis involves acute inflammation of the bronchiolar airways initiated by viral infection, regardless of the causative agent. Airway edema, necrosis and mucous plugging are the hallmark pathological features, and air flow obstruction ensues. The standard treatment for acute bronchiolitis remains supportive care and includes ensuring adequate oxygen exchange, fluid intake and feeding of the infant.²⁻⁵ Despite the frequency of the condition, there is lack of robust evidence for almost all the interventions that are usually tried, including nebulized epinephrine, bronchodilators, steroids, anticholinergics, antibiotics, surfactant and chest physiotherapy. This has resulted in substantial practice variation both within centers and across geographic regions, reflecting the absence of clear evidence for any single treatment approach.⁶⁻⁸ This controversy stems from the fact that infants with bronchiolitis resemble older children with asthma. For example, both groups commonly present with the symptoms of a recent viral illness, respiratory distress and wheezing. Since pathophysiologically bronchiolitis and asthma are, in fact, distinct conditions, treatment used for children with asthma does not seem to have similarly predictable response in children with bronchiolitis. To complicate the matter further, sometimes a first attack of asthma may present early and mimic asthma in a young child.

The role of bronchodilators (epinephrine, salbutamol) and steroids (nebulized, oral, parenteral) in the treatment

of bronchiolitis has been the subject of many studies and systematic reviews/meta-analysis.⁶⁻⁸ Interpretation of results is confounded by the variety of therapies and outcome measures. The dose, frequency and duration of nebulization have been variable across studies. The clinical outcomes used have also been variable. These ranges from short-term clinical severity scores obtained soon after treatment to broader clinical outcomes such as duration of hospitalization, pulmonary function, quality of life, adverse events, etc. Even score-based studies are difficult to compare, because many of the measures used do not have established validity or proven correlation with clinically significant improvement. Pooling the results of clinical scores from a large number of studies may result in a statistically significant difference of questionable clinical importance.

This chapter discusses the role of epinephrine, hypertonic saline and steroids in the management of children with bronchiolitis in context of the recent evidence. Details of the definitions, clinical manifestations, pathophysiology and differential diagnosis is out of scope of this chapter and readers are referred to the excellent recent reviews^{4,5} and guidelines published by the American Academy of Pediatrics (AAP) and scottish intercollegiate guideline and network (SIGN).^{2,3}

EPINEPHRINE

How Epinephrine might Work?

Epinephrine has also alpha adrenergic properties in addition to the beta adrenergic effect. Children with bronchiolitis may benefit from the vasoconstricting effects and reduction of edema offered by the alpha adrenergic effect.

How it is Used?

Racemic epinephrine is the only available form in India. L-epinephrine is not available.

What dose is Used?

A dose of 0.03 to 0.3 ml/kg/dose in 1 in 1,000 solution (max 3 ml) diluted with saline to make 3.5 to 5 ml fill volume may be used.

What is the Evidence for Epinephrine Use?

A recent Cochrane systematic review and meta-analysis (19 RCT; total 2256 participants) evaluated the efficacy and adverse events of nebulized epinephrine with placebo and other comparators (salbutamol, steroids).⁹

Data was analyzed into subgroups: epinephrine vs placebo, epinephrine vs salbutamol, epinephrine vs steroids, epinephrine and steroid vs placebo, epinephrine and steroid vs salbutamol, epinephrine vs salbutamol and ipratropium bromide.

The studies were heterogeneous in several respect to the manner in which epinephrine was used (5 used racemic epinephrine; 12 used L-epinephrine; 2-not clear), dosing schedule (12 trials epinephrine in multiple doses; rest single dose) and the comparator used (placebo in 9 studies; saline in 8).

When epinephrine was compared to placebo (9 studies) there was no statistically significant difference in length of hospital stay (mean difference (MD) -0.35; 95% CI -0.87 to 0.17), clinical scores, oxygen saturation, respiratory rate at any of the time points measured for inpatients. For outpatients epinephrine group had significantly reduced admission rate at Day 1 (RR 0.67; 95% CI 0.50 to 0.89), however, admission rate by Day 7 was not significantly different between groups. When analyzes for admission at Day 1 were restricted to trials with low-risk of bias, results were no longer statistically significant (RR 0.77; 95% CI 0.56 to 1.07; three studies, 842 participants). Results also favored epinephrine in terms of change in clinical score at 60 and 120 minutes although oxygen saturations were similar in both subgroups.

When epinephrine was compared to salbutamol a prediction towards shorter stay with epinephrine was seen (MD -0.28; 95% CI -0.46 to -0.09). Also result was not significant when restricted to one trial at low-risk of bias. There were significant differences favoring epinephrine for change in clinical score at both 60 minutes and 120 minutes post-treatment, change in oxygen saturation at 60 minutes and change in respiratory rate at 60 minutes but not 120 minutes. There were no significant differences in hospital readmissions after discharge. For outpatients there was no difference in the admission rate at Day 1 and Day 7 although clinical scores were better in the epinephrine group. However, the implications of these results need to be interpreted in light of the findings showing no difference for epinephrine versus placebo.

Comparison of epinephrine vs steroids showed no difference in admission rates at Day 1 and Day 7 although, results favored epinephrine over steroids in terms of

change in clinical score at 60 minutes. There were no studies for comparison for inpatients.

The Canadian Bronchiolitis Epinephrine Steroid Trial (CanBEST) compared epinephrine and steroid vs placebo for 399 outpatients. The admission rates were similar at Day 1, however a significant difference favoring epinephrine and dexamethasone was observed for Day 7 (RR 0.65; 95% CI 0.44–0.95). The number needed to treat for this comparison was 11 (95% CI 7 to 76).¹⁰ A significant difference favoring epinephrine and dexamethasone was also observed for clinical score at 60 minutes. Although the results of this combination appear to be significant it needs to be replicated in inpatients and adverse events need to be carefully evaluated before the findings are generalized.

Studies comparing epinephrine and steroid vs salbutamol or epinephrine vs salbutamol and ipratropium bromide are few and included small number of participants for any meaningful interpretation.⁵

STEROIDS

A recent Cochrane meta-analysis including 17 trials (2596 participants) evaluated the role of steroids in children with bronchiolitis. Steroids did not significantly reduce outpatient admissions by days 1 and 7 when compared to placebo (pooled risk ratios (RRs) 0.92; 95 percent CI 0.78 to 1.08; and 0.86; 95% CI 0.7 to 1.06, respectively). Also there was no benefit in length of hospital stay for inpatients (mean difference -0.18 days; 95% CI -0.39 to 0.04).¹¹

Inhaled corticosteroids have been used to prevent post bronchiolitis wheezing. A systematic review of 5 studies involving 374 infants found no evidence of benefit although the authors were unable to provide strong recommendations as they felt the number of participants was small and they were unable to pool all the clinical outcomes.¹²

Another recent meta-analysis using mixed treatment analysis evaluating the role of steroids and bronchodilators for bronchiolitis reported similar outcomes.¹³ Meta-analysis evaluating the efficacy of interventions for critically ill infants including those on mechanical ventilation concluded that there is no clearly effective intervention available to improve the outcome of critically ill infants with bronchiolitis.¹⁴

Hypertonic Saline (HS)

Nebulized hypertonic saline (HS) is increasingly being used for treatment of infants with acute bronchiolitis.

How Hypertonic Saline Might Work?

The postulated mechanisms of benefit are as follows:

- Hypertonic saline (HS) induces an osmotic flow of water into the mucus layer, rehydrating the airway surface liquid and improving mucus clearance
- HS breaks the ionic bonds within the mucus gel, thereby reducing the degree of cross-linking and

entanglements and lowering the viscosity and elasticity of the mucus secretion

- HS stimulates cilia beat via the release of prostaglandin E₂.
- Moreover, by absorbing water from the mucosa and submucosa, HS solution can theoretically reduce edema of the airway wall in infants with acute bronchiolitis.
- HS inhalation can also cause sputum induction and cough, which can help to clear the sputum outside of the bronchi and thus improve airway obstruction.¹⁵

How it is Used?

It is a common practice to treat hospitalized children with inhalation of epinephrine diluted in normal saline (NS). Simple substitution of NS with HS in the inhalation mixture for delivering epinephrine can be done. Some studies have used HS without using bronchodilators.

What Percentage of Saline is Used?

Usually 3 percent saline is used. It is freely available commercially.

What is the Evidence that Hypertonic Saline?

The Cochrane meta-analysis¹⁶ included 7 trials (581 infants) (2-8) with mild to moderate acute viral bronchiolitis (282 inpatients, 65 outpatients and 234 emergency department patients). Patients treated with nebulized 3 percent saline had a significantly shorter mean length of hospital stay compared to those treated with nebulized 0.9 percent saline (MD -1.16 days, 95% CI -1.55 to -0.77, $P < 0.00001$) with no significant heterogeneity between studies. This represents a 24.1 percent reduction from the mean length of hospital stay in the 0.9 percent saline group.¹⁷⁻²⁰

One outpatient trial²¹ and two emergency department trials^{22,23} with a combined total of 262 participants assessed the efficacy of nebulized 3 percent saline in reducing the risk of hospitalization. There was no significant reduction in rate of hospitalization. The pooled RR was 0.63 (95% CI 0.34 to 1.17, $P = 0.14$) with no significant heterogeneity between studies.

The pooled results of these trials did not demonstrate significant benefits of nebulized 3 percent saline in reducing the risk of readmission (pooled RR 0.92, 95% CI 0.47 to 1.81, $P = 0.82$). The 3 percent saline group also had a significantly lower postinhalation clinical score than the 0.9 percent saline group in the first 3 days of treatment (day 1: MD -0.95, 95% CI -1.52 to -0.39, $P = 0.0009$; day 2: MD -1.31, 95% CI -1.87 to -0.75, $P < 0.00001$; day 3: MD -1.31, 95% CI -2.01 to -0.61, $P = 0.0003$). The effects of improving clinical score were observed in both outpatients and inpatients although significant heterogeneity between studies was present. Two emergency

department-based trials failed to show significant short-term effects (30-120 minutes) of up to two doses of nebulized HS in improving clinical score and oxygen saturation. No significant adverse events related to 3 percent saline inhalation were reported.

Nebulized 3 percent saline produces a 1.2 day reduction in the mean length of hospital stay, compared to nebulized normal saline, among infants hospitalized with nonsevere acute bronchiolitis. This therapy also significantly reduces clinical severity score among outpatients and inpatients with mild to moderate bronchiolitis. Given the clinically relevant benefit and good safety profile, nebulized 3 percent saline used in conjunction with bronchodilators should be considered an effective and safe treatment for infants with mild to moderate acute viral bronchiolitis.

However, all seven trials have included only infants with mild to moderate bronchiolitis, so caution should be taken when extrapolating the findings of this review to patients with more severe bronchiolitis, such as those requiring mechanical ventilation, intensive care or having an oxygen saturation reading below 85 percent on room air. Further trials are needed to assess the potential effects of nebulized hypertonic saline in infants hospitalized with severe acute bronchiolitis.

Expert Opinion and Clinical Implications for Clinical Practice?

The treatment of bronchiolitis remains controversial. RCTs have failed to demonstrate a consistent benefit from alpha-adrenergic or beta-adrenergic agents. Bronchodilators may produce short-term improvements in some clinical scores but have never been shown to affect any important clinical outcome, such as obviating the need for ventilation or reducing inpatient stay. Furthermore, even these minor improvements must be set against the cost of the medications, and the need to handle and thus distress the infant. The least ineffective bronchodilator is nebulized epinephrine.

Hence, the treatment of bronchiolitis remains largely supportive with oxygen therapy and maintenance of hydration. Nebulized adrenaline, anticholinergics (ipratropium), and β_2 agonists (salbutamol, terbutaline) are not recommended as routine treatments. Although there is no evidence from RCTs to justify routine use of bronchodilators, clinical experience suggests that, in selected infants, there is an improvement in the clinical condition after bronchodilator administration. Hence the American Academy of Pediatrics has recommended that a carefully monitored trial of nebulized adrenaline or salbutamol is an option (Evidence level B). Inhaled bronchodilators should be continued only if there is a documented positive clinical response to the trial using an objective means of evaluation. Because of a lack of studies, short duration of action, and potential adverse effects, epinephrine is

usually not used in the home setting. Therefore, it would be more appropriate that a bronchodilator trial in the office or clinic setting use albuterol/salbutamol rather than racemic epinephrine.²

The combination of bronchodilators have not been studied and hence not recommended for clinical practice. Steroids appear to have no significant benefit and hence are not recommended in any form (oral, IV/IM or nebulized). Recent evidence does suggest benefit when steroids are combined with epinephrine but needs to be confirmed in other settings. Till further studies are available this combination should wait to be generalized in clinical practice.

HS appears to have benefits on some outcomes of treatment of children with acute bronchiolitis. Since it has no effects on the rates of hospitalizations in OPD and emergency department patients, the use of HS in non-admitted patients should wait. Also it would increase the complexity of the prescription since mixture of HS and bronchodilator is not available commercially. At present we do not have data on children with severe bronchiolitis (requiring ICU care, ventilation) and hence cannot be recommended for this population as well.

The group which could benefit is mild-moderate admitted children with bronchiolitis, where use of HS has shown benefits in two outcome measures namely early discharge (approximately 1.2 days) and some reduction in symptom scores (although trials had significant heterogeneity for this outcome). The protocols for treatment are variable and not standardized.

It is ironical that despite so many advances in the field of medicine, the search to find an effective and universal therapy for bronchiolitis still remains inconclusive.

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Management of Chronic Asthma: Current Guidelines

Satyen D Gyani

INTRODUCTION

Asthma is broadly defined as a chronic disease of the airways that is characterized by variable airflow obstruction, bronchial hyper-responsiveness, and underlying inflammation. Although recent declines in the rates of asthma—related hospitalization and mortality suggest an improvement in disease management, these benefits have not been realized universally across the affected population. Asthma most commonly begins in young children as wheezing in conjunction with respiratory infections. If these episodes become more frequent and severe, the asthma is most likely to persist into adult years. There is ample evidence that early initiation of asthma treatment, particularly with inhaled corticosteroids (ICSs), can reduce the severity and frequency of later episodes and result in improved disease control. The National Asthma Education and Prevention Program (NAEPP), coordinated by the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health, has issued asthma management guidelines that reflect the latest treatment advances in this field. The guidelines were first published in 1991, and revised in 1997, 2002, and 2007. The Global Initiative for Asthma (GINA) guidelines were undertaken jointly between the NHLBI and the World Health Organization and updated most recently in 2006. This article reviews the current guidelines of management of asthma. The level of evidence for statements and recommendations is included, when possible.

INITIAL ASSESSMENT

Once asthma has been diagnosed, the physician should determine the degree of severity in the individual patient. Severity is determined best at the time of diagnosis, before initiation of therapy. There are four categories of asthma severity: intermittent, mild persistent, moderate

persistent, and severe persistent. The most important distinction is between intermittent and persistent asthma because all individuals who have persistent asthma should be started on long-term control medication. The 2007 Guidelines provide tables for determining asthma severity and initial treatment recommendations for three different age groups: children 0 to 4 years of age, children 5 to 11 years of age, and children 12 years of age and older and adults (Tables 1 to 3).

The category of asthma severity is based on the amount of “impairment” and “risk”. Impairment includes the frequency and severity of day-time and night-time asthma symptoms, frequency of short-acting beta-2 agonist (SABA) use other than for exercise-associated symptoms, degree of interference with activity, and results of pulmonary function testing. Risk is based on the frequency of asthma exacerbations requiring the use of oral corticosteroids. The level of severity always is determined by the most severe level of symptoms, medication use, and other factors. For example, a 6-year-old boy who experiences rare day-time symptoms, rarely uses SABAs, and has a normal activity level and no exacerbations in the past year would be categorized as having “moderate persistent asthma” if he has night-time symptoms twice a week. Exercise-induced symptoms and the use of a SABA to prevent or treat such symptoms are not included in the determination of asthma severity. However, frequent or severe exercise-associated symptoms often are a sign of poorly controlled asthma.

The determination of severity category based on the 2007 Guidelines is not reduced easily to a simple rule. The severity criteria vary with age. Children 0 to 4 years of age may have asthma that is categorized as persistent based on day-to-day impairment or frequent exacerbations (>2 in 6 months or >4 in 1 year) along with risk factors for asthma (Table 1). Major risk factors (one required) are: 1. parental history of asthma, 2. atopic dermatitis, and

Table 1: Classifying severity and initiating treatment: Children 0 to 4 years

Severity category	Impairment		Risk	
	Days and nights with symptoms	Interference with normal activity	Exacerbations	Preferred treatment
Severe persistent	Throughout (days) > 1 night/week (nights)	Extremely limited	(see below)	Step 3: Medium-dose ICS and consider short-course OCS
Moderate persistent	Daily (days) 3 to 4 nights/month	Some limitation	(see below)	Step 3: Medium-dose ICS and consider short-course OCS
Mild persistent	3 to 6 days/week (days) 1 to 2 nights/months (nights)	Minor limitation	2 or more/6 months or >4 episodes of wheezing/year with risk factors for asthma	Step 2: Low-dose ICS
Intermittent	<2 days/week (days) 0 night/month (nights)	None	0 to 1/year	Step 1: SABA PRN

Exacerbation: Episode requiring OCS.

Risk factors for asthma: Parent history of asthma, patient has eczema, patient sensitized to aeroallergens, or two of following: patient sensitized to foods, eosinophilia, wheezing apart from colds.

ICS: inhaled corticosteroids, LABA: Long-acting beta-2 agonist, OCS oral corticosteroids, SABA: Short-acting beta-2 agonist. *Adapted from the National Asthma Education and Prevention Program. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma, 2007. NIH Publication No. 07-4051. Bethesda, Md: National Heart, Lung, and Blood Institute; 2007.*

Table 2: Classifying severity and initiating treatment: Children 5 to 11 years

Severity category	Impairment		Risk		
	Days and nights with symptoms	Interference with normal activity	Pulmonary function	Exacerbations	Preferred treatment
Severe persistent	Throughout (days) often (nights)	Extremely limited	FEV ₁ : <60% FEV ₁ /FVC: <75%	2 or more/year	Step 4: Medium-dose ICS LABA and consider short-course OCS Step 3: Medium-dose ICS and consider short-course OCS
Moderate persistent	Daily (days) >1 night/week (nights)	Some limitation	FEV ₁ : 60–80% FEV ₁ /FVC: 75–>80%	2 or more/year	Step 3: Medium-dose ICS and consider short-course OCS
Mild persistent	3–6 days/week (days) 3–4 nights/month (nights)	Minor limitation	FEV ₁ : >80% FEV ₁ /FVC: >80%	2 or more/year	Step 2: Low-dose ICS
Intermittent	<2 days/week (days) 2 nights/month (nights)	None	FEV ₁ : >80% FEV ₁ /FVC: >85%	0 to 1/year	Step 1: SABA PRN

FEV₁: forced expiratory volume in 1 second, FVC: Forced vital capacity, ICS: Inhaled corticosteroids, LABA: Long-acting beta-2 agonist, OCS: Oral corticosteroids, SABA: Short-acting beta-2 agonist. *Adapted from the National Asthma Education and Prevention Program. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma, 2007. NIH Publication No. 07-4051. Bethesda, Md: US National Heart, Lung, and Blood Institute; 2007.*

Table 3: Classifying severity and initiating treatment: youth 12 years of age and older

Severity category	Days and nights with symptoms	Impairment		Risk	
		Interference with normal activity	Pulmonary function	Exacerbations	Preferred treatment
Severe persistent	Throughout (days) often 7/week (nights)	Extremely limited	FEV ₁ : <60% FEV ₁ /FVC: Reduced >5%	2 or more/year	Step 1: High-dose ICS LABA and consider short-course OCS Step 1: Medium-dose ICS ABA and consider short-course OCS
Moderate persistent	Daily (days) 2–6 night/week (nights)	Some limitation	FEV ₁ : 60–80% or more/yr FEV ₁ /FVC: Reduced 5%	2 or more/year	Step 3: Low-dose ICS LABA or Medium dose ICS and consider short-course OCS
Mild persist	3–6 days/week (days) 3–4 nights/months (nights)	Minor limitation	FEV ₁ : >80% FEV ₁ /FVC: Normal	2 or more/year	Step 2: Low-dose ICS
Intermittent	<2 days/week (days) <2 nights/month (nights)	None	FEV ₁ : >80% FEV ₁ /FVC: Normal	0 to 1/year	Step 1: SABA PRN

FEV₁: Forced expiratory volume in 1 second, FVC: Forced vital capacity; ICS: Inhaled corticosteroids, LABA: Long-acting beta-2 agonist, OCS: Oral corticosteroids, SABA: Short-acting beta-2 agonist *Adapted from the National Asthma Education and Prevention Program. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma, 2007. NIH Publication No. 07-4051. Bethesda, Md: National Heart, Lung, and Blood Institute.*

3. sensitization to aeroallergens. Minor risk factors (two required) are: (1) Sensitization to foods, (2) More than 4 percent eosinophilia, and 3. wheezing apart from colds. Another key component of initial assessment is to identify and address precipitating factors (asthma “triggers”).

The most common categories of asthma triggers in children are: respiratory infections, allergens, airway irritants (e.g. environmental tobacco smoke and air pollution), exercise, and medications (e.g. nonsteroidal anti-inflammatory medications and β -blockers). The 2007 Guidelines contain sample questionnaires that should be used to help identify and reduce exposure to potential asthma triggers. Respiratory infections are a common asthma trigger and are difficult to avoid in young children. All individuals afflicted with asthma should receive an annual influenza vaccination, although data have not shown that the influenza vaccine improves health outcomes. Many children who have asthma are exposed to environmental tobacco smoke, which is a potent airway irritant for all individuals who have asthma. Children experiencing high degrees of tobacco smoke exposure are more likely to have moderate or severe asthma and decreased lung function compared with those whose exposures are low. Every child who has asthma deserves a smoke-free home, car, and school or child care environment. Household members and other close associates who smoke should be referred to smoking cessation resources.

Most children who have asthma (60–80%) are sensitized to at least one aeroallergen. Common indoor allergens include house dust mite, cockroach allergen, animal dander, and molds. Prick skin testing or blood testing

(allergen-specific immune globulin E [IgE] concentrations) to detect sensitization to common indoor allergens should be considered for any child experiencing persistent asthma, so treatment recommendations can be tailored to the individual child and family. Immunotherapy should be considered for children who have documented sensitivities and mild or moderate persistent asthma (Evidence level B for house dust mite, animal dander, and pollen).

The most effective programs to reduce indoor allergens are intensive, multifaceted interventions that address more than one allergen. House dust mite is a common indoor allergen. Dust mite levels can be decreased by reducing indoor humidity, laundering bedding in hot water, placing mite-impenetrable covers on pillows and mattresses, and reducing “dust catchers” (stuffed animals, curtains, books, carpet) in the bedroom. Sensitization and exposure to cockroach allergen has been associated with frequent exacerbations and healthcare use among inner-city children who have asthma. Decreasing cockroach antigen in the home often requires an intensive integrated pest management program. Because cockroaches require food and water, basic elimination strategies include placing food and garbage in closed containers, fixing water leaks, and keeping food out of the bedroom. For children who are sensitized to pets, animal dander can be a significant asthma trigger, and efforts should be made to remove pets from the home.

Exercise is a common precipitant of asthma symptoms in children. For some individuals, exercise-induced bronchospasm (EIB) may be the only manifestation of asthma. Children who have EIB experience cough, shortness of

breath, and rarely, wheezing, which begins during vigorous activity, reaches a peak 5 to 10 minutes after stopping exercise, and resolves 20 to 30 minutes later. Bronchospasm occurs as a result of hyperventilation of air that is cooler or dryer than the air found in the respiratory tract, which leads to loss of heat or water from the lung. Air pollutants, including ground-level ozone, nitrogen dioxide, and small particulate matter, are airway irritants and worsen the severity of EIB. Current guidelines recommend that individuals afflicted with asthma “avoid, to the extent possible, exertion or exercise outside when levels of air pollution are high”. The symptoms of EIB can be prevented or diminished by the administration of a SABA or sodium cromolyn 15 to 20 minutes prior to vigorous activity. Brief warm-up periods prior to vigorous activity may lessen the severity of EIB. Although exercise-associated asthma symptoms are not considered when determining asthma severity, severe or poorly controlled EIB often is a sign of persistent or poorly controlled asthma. Use of daily inhaled corticosteroids often results in improvement of EIB.

The differential diagnosis of asthma includes other causes of lung disease (Table 4). In children, acute viral respiratory infections are common causes of wheezing and need to be distinguished from asthma. Wheezing may be due to local airway obstruction caused by an inhaled foreign body. Vocal cord dysfunction may mimic asthma, particularly in young adults.

Comorbid conditions that can coexist with asthma and mimic and complicate or aggravate asthma include gastroesophageal reflux disease (GERD), allergic bronchopulmonary aspergillosis, and sinusitis. If not recognized and treated appropriately, these conditions can cause severe morbidity and further confound asthma management.

The pediatrician should screen for these conditions both at the initial assessment and as part of ongoing care for children who have asthma.

MEDICAL MANAGEMENT

Long-term Control Medications

Two types of medications are used to treat asthma: long-term control (*prevention*) medications and quick-relief medications, which reverse acute airflow obstruction. All children who have persistent asthma should be started on a long-term control (*prevention*) medication. Such anti-inflammatory medications are taken daily to reduce airway inflammation. The recommended type and dose of long-term control medication depends on the level of asthma severity and the age of the child. The 2007 Guidelines provide tables with treatment recommendations (Tables 1 to 3).

Inhaled corticosteroids (ICSs) are the medication of choice for all individuals suffering persistent asthma. ICSs are the most effective anti-inflammatory medication for asthma (evidence level A). ICSs reduce asthma symptoms,

Table 4: Differential diagnosis of asthma for adults and children

Infants and children

- Upper airway diseases
- Allergic rhinitis and sinusitis
- Large airway obstruction
- Foreign body aspiration
- Vocal cord dysfunction
- Vascular rings or laryngeal webs
- Laryngotracheomalacia, tracheal stenosis, or bronchostenosis
- Enlarged lymph nodes or tumor
- Small airway obstruction
- Viral bronchiolitis or obliterative bronchiolitis
- Cystic fibrosis
- Bronchopulmonary dysplasia
- Heart disease
- Other causes
- Recurrent cough not due to asthma
- Aspiration due to GERD or swallowing mechanism dysfunction

Adults

- COPD
- Congestive heart failure
- Pulmonary embolism
- Laryngeal dysfunction
- Mechanical obstruction of the airways (tumors)
- Pulmonary infiltration with eosinophilia
- Cough secondary to drugs (e.g. ACE inhibitors)
- Vocal cord dysfunction

GERD = Gastroesophageal reflux disease; ACE = Angiotensin-converting enzyme.

improve lung function, reduce acute exacerbations of asthma, and reduce the risk of death from asthma. Recent data show that ICSs are well-tolerated, safe medications at the recommended dosages (Table 5).

ICSs act topically on lung epithelium to inhibit cell migration and activation and to reduce airway hyper-responsiveness. ICSs block the late-phase (inflammatory) reaction to allergen, but not the early-phase (bronchospasm) reaction. With daily administration, some effects from ICSs may be seen within 1 to 2 weeks, but the full anti-inflammatory effect may not be seen for 4 weeks. Similarly, if a child stops taking ICSs, some protective anti-inflammatory effects continue for several weeks after the medication has been stopped. Potential local adverse effects of ICS include oral candidiasis (thrush), dysphonia (hoarseness), reflex cough, and bronchospasm. Such adverse effects may be minimized by using a valved holding chamber (VHC) (“spacer”) with metered dose inhalers

Table 5: Estimated equipotent daily dosage of ICS in children

<i>Drug</i>	<i>Low daily dose (μg)</i>	<i>Medium daily dose (μg)</i>	<i>High daily dose (μg)</i>
Beclomethasone dipropionate	100 – 200	200 – 400	>400
Budesonide*	100 – 200	200 – 400	>400
Ciclesonide*	80 – 160	160 – 320	>320
Fluticasone	100 – 200	200 – 500	>500

*Approved for once-daily dosing in patients with mild asthma.

As CFC preparations are taken off the market, medication inserts for HFA preparations should be reviewed for the equivalent correct dosage.

(MDIs) (evidence level A), slowing the rate of inhalation, as well as rinsing the mouth with water (rinse and spit) following inhalation.

In general, the effectiveness of ICSs far outweighs the potential adverse effects. A low-to-medium dose of ICS may have a small adverse effect on linear growth velocity. Data from the Childhood Asthma Management Program study show that this effect occurs in the first few months of treatment, is usually small, and is not progressive. No data suggest that ICSs affect final adult height. High doses of ICSs may have a greater potential to decrease growth velocity. Because of the potential risk of decreased growth velocity, height should be monitored closely in children taking ICSs, VHCs always should be used to decrease systemic absorption, and the ICS dose should be titrated to the lowest possible effective dose. ICSs have not been shown to decrease bone mineral density or to cause cataracts in children. Low-to medium doses of ICSs have little, if any, effect on hypothalamic-pituitary-adrenal axis function in children. However, some individuals may be more sensitive to adverse effects of ICSs, even at recommended doses.

Cromolyn sodium and nedocromil are anti-inflammatory medications that stabilize mast cells and interfere with chloride channel function. They prevent both the early- and late-phase response to inhaled allergens. These agents are alternative medications for long-term control in children who have mild persistent asthma and can be used to prevent EIB. Despite their excellent safety profile, these medications are not preferred for long-term control therapy because they are less effective than ICSs.

Leukotriene modifiers interfere with the action of leukotrienes, potent inflammatory mediators that are released from mast cells, eosinophils, and basophils. Two types of medications are available: the leukotriene receptor antagonists (LTRAs), which include montelukast and zafirlukast, and the 5-lipoxygenase inhibitor zileuton. LTRAs are alternative, not preferred, therapy for children who have mild persistent asthma. They also can be used as “add-on” therapy for patients who do not achieve good control with medium-dose ICSs. However, for individuals 12 years of age and older, long-acting beta-2 agonists (LABAs) are preferred adjunctive therapy with ICSs because of demonstrated superiority compared with

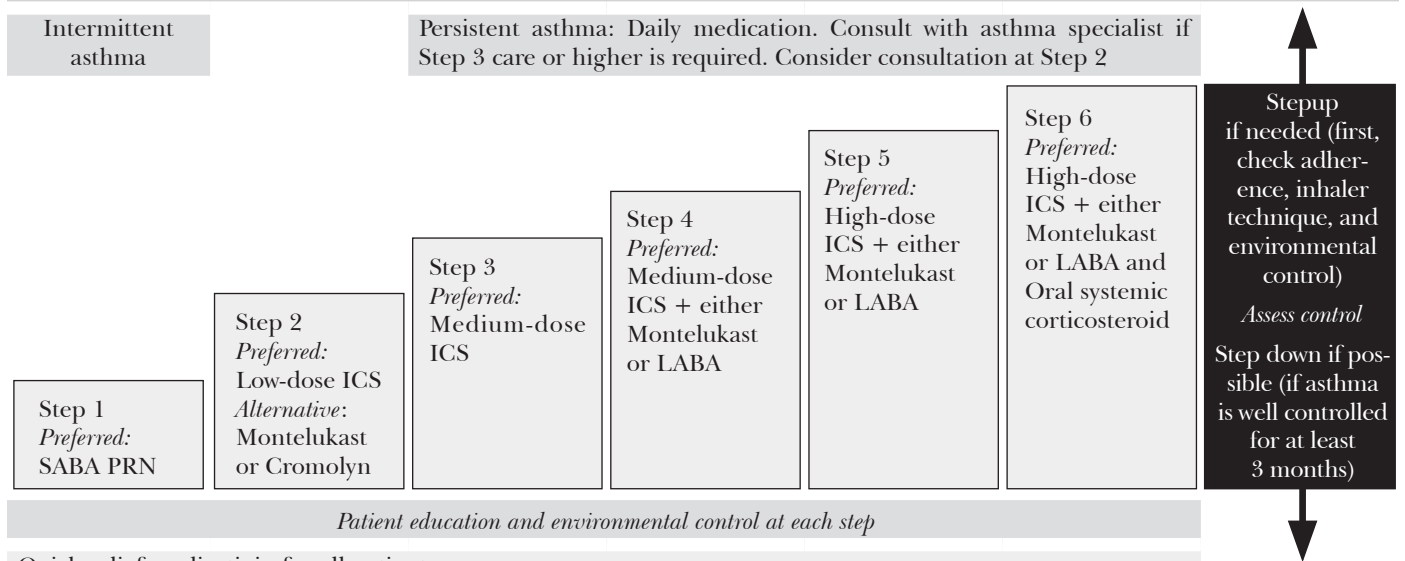
the addition of LTRAs to ICSs. LTRAs can decrease the severity of EIB.

LABAs provide at least 12 hours of bronchodilation by stimulating beta-2 receptors in the airway, which increases the concentration of cyclic adenosine monophosphate, causing relaxation of airway smooth muscle. LABAs are available in a dry powder inhaler (DPI) (formoterol) and in combination with ICSs as either DPI (salmeterol) or MDI (salmeterol and formoterol). Recent studies have raised concerns about the safety of LABAs and about the potential for increased risk of exacerbations and adverse events in individuals taking these medications. LABAs are not anti-inflammatory medications and should not be used as monotherapy in asthma. They should not be used to treat acute exacerbations. These medications prevent EIB, but the duration of this effect deteriorates with long-term administration. Therefore, LABAs are not recommended for chronic use before exercise. LABAs are used along with ICSs for children who have severe persistent asthma and do not achieve good control and for those who have moderate persistent asthma and do not achieve good control with medium dose inhaled ICSs (Step 3 level care or higher for children 5 years of age and older; Step 4 level care for children 0 to 4 years of age, although few data are available on the use of LABAs in this age group). LABAs are the preferred adjunctive therapy to be added to ICSs for youth 12 years of age and older and for adults (Tables 6 to 8).

Theophylline is a phosphodiesterase inhibitor that increases cyclic adenosine monophosphate and causes bronchodilation. It may have a small anti-inflammatory effect. Theophylline is an alternative, not preferred, monotherapy for children 5 years of age and older who have mild persistent asthma and an alternative adjunctive therapy to combine with ICS. Theophylline is primarily a bronchodilator and is much less effective than ICSs for long-term control. For these reasons and because of concerns about potential toxicity, theophylline has a limited role in the treatment of childhood asthma.

Other Options

Omalizumab is a monoclonal anti-IgE antibody that prevents binding of IgE to receptors on basophils and mast cells. This medication can be used as adjunctive therapy

Table 6: Stepwise approach for managing asthma in very young children (0-4 years of age)**Quick-relief medication for all patients**

- SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms.
- With viral respiratory infection: SABA q 4 to 6 hours up to 24 hours (longer with physician consult). Consider short course of oral systemic corticosteroids if exacerbation is severe or patient has history of severe exacerbations.
- Caution: Frequent use of SABA may indicate the need to stepup treatment.

SABA = Inhaled short-acting β_2 -agonist, ICS = Inhaled corticosteroid; LABA = Inhaled long-acting β_2 -agonist.

Notes:

- The stepwise approach is meant to assist, not replace, the clinical decision-making required to meet individual patient needs.
- If alternative treatment is used and response is inadequate, discontinue it and use preferred treatment before stepping up.
- If clear benefit is not observed within 4 to 6 weeks and patient/family medication technique and adherence are satisfactory, consider adjusting therapy or alternative diagnosis.
- Studies on children 0 to 4 years of age are limited. Step 2 preferred therapy is based on Evidence A. All other recommendations are based on expert opinion and extrapolation from studies in older children.

for patients 12 years of age and older who have demonstrated sensitivity to aeroallergens and severe persistent asthma that is not controlled well with high-dose ICSs and LABAs. Because severe allergic reactions may occur following infusion of omalizumab, physicians who administer this medication must be prepared to treat anaphylaxis.

Immunotherapy

The Expert Panel of the USA's Department of Health and Human Services recommends that allergen immunotherapy be considered for patients who have persistent asthma if there is clear evidence of a relationship between symptoms and exposure to an allergen to which the patient is sensitive (Evidence B).

Macrolides

Macrolide antibiotics have recognized anti-inflammatory properties in addition to their antimicrobial effects. Although some benefits have been reported in adults with chronic persistent asthma, a meta-analysis of seven randomized controlled clinical trials involving both children and adult patients with chronic asthma and treated with

macrolides or placebo for >4 weeks, reported insufficient evidence to support their use in patients with chronic asthma.

Antihistamines

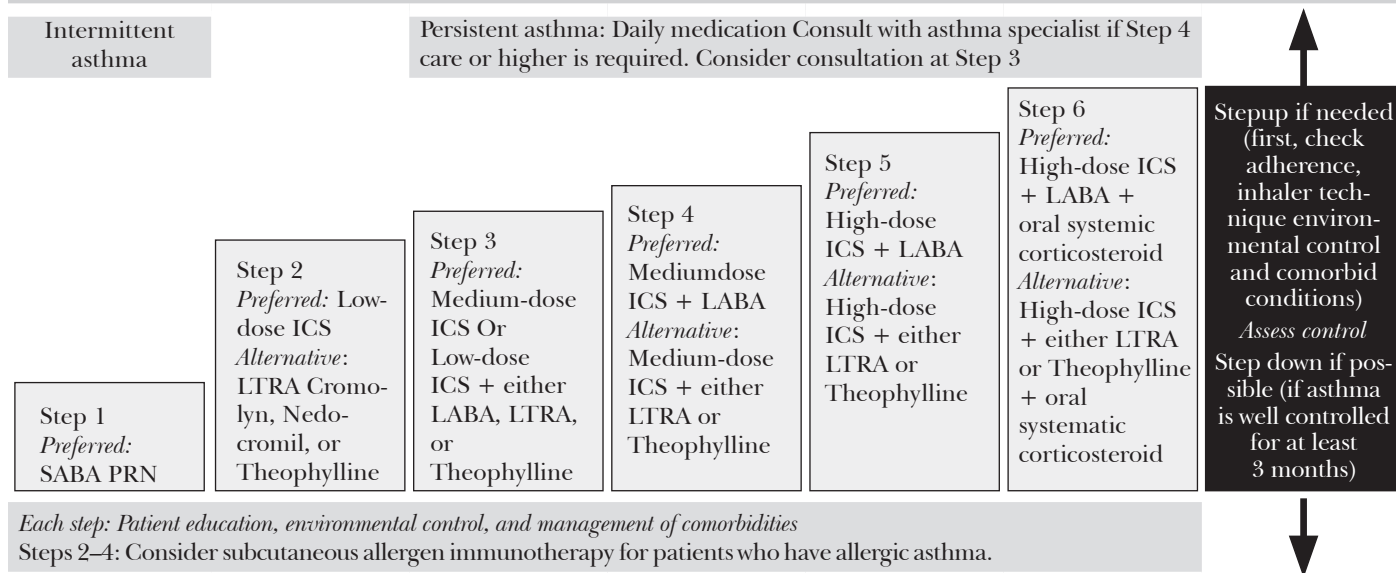
Antihistamines have no proven symptom control, but may be useful for control of symptoms of coexisting allergic diseases such as rhinoconjunctivitis, urticaria and atopic eczema.

Unnecessary Therapy

The following are of no benefit in the treatment of childhood asthma: antibiotics, cough syrups, mucolytics, ionisers and breathing exercises. Complementary and alternative medications and interventions bear insufficient evidence to permit recommendations. Physiotherapy is indicated in children only where lobar collapse is documented.

Quick-relief Medications

Quick-relief medications are used in all patients who have asthma to reverse acute airway obstruction. This category of medication includes the SABAs and anticholinergic

Table 7: Stepwise approach for managing asthma in young children (5–11 years of age)**Quick-relief medication for all patients**

SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms: up to 3 treatments at 20 minutes intervals as needed. Short course of oral systemic corticosteroids may be needed.

- Caution: Increasing use of SABA or use >2 days a week for symptom relief (not prevention of EIB) generally indicates inadequate control and the need to step-up treatment.

SABA = Inhaled short-acting β_2 -agonist; ICS = Inhaled corticosteroid; LABA = Inhaled long-acting β_2 -agonist; LTRA = Leukotriene receptor antagonist, EIB = Exercise-induced bronchospasm.

Notes:

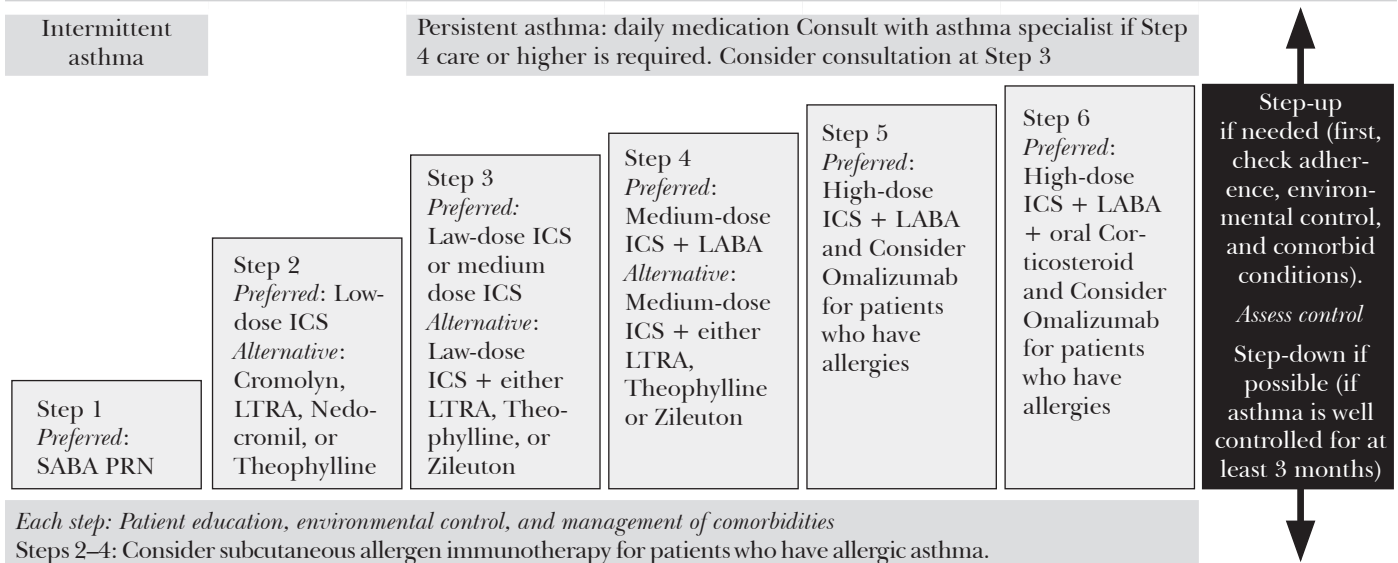
- The stepwise approach is meant to assist, not replace, the clinical decision making required to meet individual patient needs.
- If alternative treatment is used and response is inadequate, discontinue it and use the preferred treatment before stepping up.
- Theophylline is a less desirable alternative due to the need to monitor serum concentration levels.
- Step 1 and Step 2 medications are based on Evidence A. Step 3 ICS and ICS + LABA are based on Evidence B for efficacy of each treatment and extrapolation from comparator trials in older children and adults—comparator trials are not available for this age group; Steps 4–6 are based on expert opinion and extrapolation from studies in older children and adults.
- Immunotherapy for Steps 2–4 is based on Evidence B for house-dust mites, animal danders, and pollens; evidence is weak or lacking for molds and cockroaches. Evidence is strongest for immunotherapy with single allergens. The role of allergy in asthma is greater in children than in adults. Clinicians who administer immunotherapy should be prepared and equipped to identify and treat anaphylaxis that may occur.

medications. Systemic corticosteroids also are included in the category of quick-relief medications. Although systemic corticosteroids have a more delayed onset of action, they are used to treat acute exacerbations of asthma.

The SABAs (albuterol, levalbuterol, pirbuterol) relax airway smooth muscle, resulting in bronchodilation within minutes of administration. Peak effect is seen within 15 to 30 minutes and wears off within 4 to 6 hours. SABAs are the treatment of choice for acute exacerbations of asthma and are used to prevent EIB. Common adverse effects include tachycardia, tremulousness, and irritability. With prolonged use or at high doses, these medications can cause hypokalemia. Excessive or frequent use of SABAs (>2 days/week) is associated with poorly controlled asthma and an increased risk of hospitalization and death.

The anticholinergic medications (e.g. ipratropium) act as bronchodilators by inhibiting muscarinic cholinergic receptors and reducing vagal tone of the airways.

They are used in acute, moderate, or severe exacerbations of asthma. Anticholinergics are effective adjuvant therapy in combination with inhaled albuterol during the initial emergency treatment of moderate or severe exacerbations of asthma and are not recommended for the inpatient setting. Systemic corticosteroids are used in the treatment of moderate or severe exacerbations of asthma. They improve airway responsiveness to SABAs, improve lung function, and decrease the risk of relapse from an acute exacerbation. Onset of action is within 4 to 6 hours of administration; oral administration is as effective as intravenous administration. The adverse effects from systemic corticosteroids depend on the dose and duration of use. Most studies report few adverse effects from short “bursts” (3 to 10 days). Frequent use of systemic corticosteroids (e.g. daily or >2 “bursts” per year) is a sign of poorly controlled asthma and may be associated with mild adrenal suppression. Table 6 summarizes

Table 8: Stepwise approach for managing asthma in youths >12 years of age*Quick-relief medication for all patients*

SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms: up to 3 treatments at 20 minutes intervals as needed. Short course of oral systemic corticosteroids may be needed.

- Use SABA >2 days a week for symptom relief (not prevention of EIB) generally indicates inadequate control and the need to step-up treatment.

Notes:

- The stepwise approach is meant to assist, not replace, the clinical decision making required to meet individual patient needs.
- If alternative treatment is used and response is inadequate, discontinue it and use the preferred treatment before stepping up.
- Zileuton is a less desirable alternative due to limited studies as adjunctive therapy and the need to monitor liver function. Theophylline requires monitoring of serum concentration levels.
- In Step 6, before oral systemic corticosteroids are introduced, a trial of high-dose ICS + LABA + either LTRA, theophylline, or zileuton may be considered, although this approach has not been studied in clinical trials.
- Steps 1, 2, and 3 preferred therapies are based on Evidence A; Step 3 alternative therapy is based on Evidence A for LTRA, Evidence B for theophylline, and Evidence D for zileuton. Step 4 preferred therapy is based on Evidence B, and alternative therapy is based on Evidence B for LTRA and theophylline and Evidence D for zileuton. Step 5 preferred therapy is based on Evidence B. Step 6 preferred therapy is based on (EPR-2 1997) and Evidence B for omalizumab.
- Immunotherapy for Steps 2–4 is based on Evidence B for house-dust mites, animal danders, and pollens; evidence is weak or lacking for molds and cockroaches. Evidence is strongest for immunotherapy with single allergens. The role of allergy in asthma is great in children than in adults.
- Clinicians who administer immunotherapy or omalizumab should be prepared and equipped to identify and treat anaphylaxis that may occur.

a stepwise approach to managing asthma in different age groups.

Medication Delivery Devices

Asthma medications can be administered from a variety of aerosol delivery devices, including MDIs, breath actuated MDIs, DPIs, and nebulizers. MDIs should be used with a VHC, which is interposed between the MDI and the child. VHCs improve deposition of medication in the airways and reduce the amount of medication deposited in the mouth and throat, thereby decreasing local and systemic adverse effects.

VHCs are available with a mouthpiece or with a face-mask. Effective use of a VHC with a mouthpiece requires that the child be able to exhale, seal his or her lips around the mouthpiece, actuate the MDI (with help), take a slow (3 to 5 seconds) and controlled inhalation, and hold his or

her breath for 5 to 10 seconds. Thus, this device is most appropriate for school-age children. A VHC with face-mask can be used even in very young children, with the help of an adult. This device is placed on the face, with the mask covering the nose and mouth. After the MDI has been actuated, the child is allowed to take 6 to 8 breaths with the mask in place.

Several types of inhaled corticosteroids as well as combination medicines (ICS + LABA) are available in DPIs. DPIs offer the convenience of a compact device that does not require use of a spacer. Although most of the DPI devices are approved for children 4 years of age and older, use of these devices requires coordination and the ability to generate inspiratory flow, obviating their use by most preschool-age children. The device must be “loaded” prior to use so an aliquot of dry powder is available for inhalation. To use a DPI, the child must exhale away from

the device, seal his or her lips around the mouthpiece, and take a 2 to 3 seconds inhalation with an inspiratory flow rate of 60 to 90 L/min.

Both long-term control and quick-relief medications are available as solutions that can be nebulized. Jet nebulizers can be used by children of all ages with either a mouthpiece or face mask. If a child is capable of holding the mouthpiece correctly, this is the preferred method of use. If a mask is used, it should fit tightly around the nose and mouth to maximize medication delivery to the airways.

The “blow-by” method (administration of nebulized medication without using a face mask or mouthpiece) is not effective and should not be used. Jet nebulizers are useful for very young children or cognitively impaired children who have difficulty using other devices. However, because each nebulizer treatment takes 10 to 15 minutes to administer and because the machines may be more difficult to use away from home, most children should be instructed in the use of an MDI with VHC to deliver quick-relief medication. Quick relief medications delivered by MDIs with VHCs are equivalent to nebulizer therapy for children who have acute asthma (Evidence level A). (Albuterol 4 puffs by MDI is equivalent to albuterol 2.5 mg nebulized). A general inhaler strategy for children is given in Table 9.

The Physician-family Partnership for Care

Effective partnership between physicians and families is critical in effective asthma management. Interventions to improve physician communication and patient education skills result in improved patient satisfaction and health outcomes. At each visit, the clinician should elicit family treatment goals and their concerns about asthma and medications used to treat asthma. Key educational messages include: basic facts about asthma, the role of medications (quick relief versus long-term control), and patient skills (how to take medications correctly, how to minimize exposure to asthma “triggers,” and the use of a written asthma action plan). Providing pediatric asthma self-management education improves lung function, reduces school absenteeism, and reduces emergency department visits (Evidence level A).

Table 9: Choice of inhaler device for children

Age group	Preferred device
Younger than 4 years	Pressurized metered-dose inhaler plus spacer with facemask
4–6 years	Pressurized metered-dose inhaler plus spacer with mouthpiece
Older than 6 years	Pressurized metered-dose inhaler with spacer and mouthpiece, or dry powder inhaler (DPI), or breath-actuated pressurized metered-dose inhaler

All patients should be given a written asthma action plan that includes instructions for how to control asthma every day and how to recognize and manage asthma symptoms as well as a list of signs and symptoms that indicate the need to seek immediate medical care. Some plans also include instructions about air quality alert days and permission for children to self-carry and self administer asthma medications. Symptom-based plans are just as effective as peak flow-based plans (evidence level A). Sample asthma action plan templates are provided in the 2007 Guidelines.

Periodic Monitoring

All patients who have persistent asthma should be monitored at regular intervals (1 to 6 months, depending on the category of asthma severity and asthma control). Routine spirometry should be undertaken every 1 to 2 years to assess airway function or more frequently during periods of poor asthma control. At each visit, the clinician should determine the level of asthma control (Table 10). Asthma control is based on impairment (day-time and night-time symptoms, interference with normal activity, use of SABA, and lung function) as well as risk (frequency of exacerbations requiring oral corticosteroids).

Excessive use of SABAs can be a sign of poorly controlled asthma and is associated with increased mortality. If control is poor, the clinician should assess medication administration technique, adherence to therapy, and environmental controls. Factors contributing to poor asthma control should be addressed first, before adjusting therapy. If no obvious explanation for poor asthma control is identified, therapy should be “stepped up” to the next level. For very poor control, a short course of oral corticosteroids as well as a “step-up” in therapy should be considered. The patient should be re-evaluated in 2 to 6 weeks. If control has been good for at least 3 months, a “step down” in care and re-evaluation in 4 to 6 weeks should be considered. Daily peak flow monitoring or monitoring during exacerbations should be considered for patients who have a history of severe exacerbations, who have moderate-to-severe persistent asthma, or who have difficulty perceiving airway obstruction.

Management of Acute Exacerbations

Patients who have any degree of asthma severity can have a severe exacerbation. Signs and symptoms of a severe exacerbation include dyspnea at rest, peak flow rate less than 40 percent of predicted or personal best, accessory muscle use, and failure to respond to initial treatment. The initial management of an acute exacerbation should include a brief assessment, followed by administration of a SABA either as repeated doses or continuously to reverse airway obstruction. Inhaled anticholinergic medications, given in combination with a SABA for moderate-to-severe

Table 10: Asthma control

	Well-controlled	Not well-controlled	Very poor control
Child 0 to 11 years	<2 days/week	> 2 days/week	Throughout
Day symptoms	0 to 1/month	>2/month	>2/week
Night symptoms	>80%	60–80%	<60%
FEV ₁ percent predicted	>80%	75–80%	<75%
FEV ₁ /FVC ratio	0 to 1/year	>2/year	>2/year (>3/year for 0 to 4 year)
Exacerbations	Maintain; consider step down	Review ICE	Review ICE
Action	(if well-controlled for 3 months) Recheck in 1 to 6 months	Step-up Recheck in 2–6 weeks	Step up 1 to 2 steps Consider OCS Recheck in 2–6 weeks
12 years to adult	<2 days/week	>2 days/week	Throughout
Day symptoms	0 to 2/month	1–3/week	>4/week
Night symptoms	>80%	60–80%	<60%
FEV ₁ percent predicted	0 to 1/year	>2/year	>2/year
Exacerbations	Maintain; consider step down	Review ICE Step	Review ICE
Action	(if well-controlled for 3 months) Recheck in 1 to 6 months	up 1 Step Recheck in 2–6 weeks	Step up 1–2 steps Consider OCS Recheck in 2 weeks

ICE: Inhaler technique, compliance, environmental control and comorbidities, FEV₁: Forced expiratory volume in 1 second FVC: Forced vital capacity OCS: Oral corticosteroids. Adapted from the National Asthma Education and Prevention Program, Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma, 2007. NIH Publication No. 07-4051. Bethesda, Md: National Heart, Lung, and Blood Institute; 2007.

exacerbations in the acute-care setting, reduce the risk of hospitalization. Oxygen should be administered to most patients, particularly those experiencing hypoxemia or a moderate or severe exacerbation. Systemic corticosteroids should be administered early in the treatment of moderate or severe exacerbations and to any patient who does not respond promptly to initial treatment. Corticosteroids improve airway sensitivity to beta-2 agonists and decrease inflammation; their effect is seen 4 to 6 hours following administration. Small areas of atelectasis are common during an acute exacerbation and do not require specific treatment. Similarly, antibiotics are not indicated unless there is evidence of a bacterial infection.

At discharge from the emergency department, patients should be given instructions for administration of a SABA at home and a 3 to 10 days course of oral corticosteroids. Medical follow-up should be scheduled within 1 week.

SUMMARY

- Initial management of asthma includes assignment of severity category, identification of asthma “triggers”, and development of a treatment plan based on degree of severity.
- Inhaled corticosteroids are the medication of choice for treatment of persistent asthma (evidence level A).
- Environmental control is an important component of asthma management.
- Patient education, including how to use a written asthma action plan, is critical in managing asthma (evidence level A).

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Pediatric Wheeze- Adult Asthma?

Satyen D Gyani

Complex biological processes and pathways underlie the complex disease manifestation we call childhood-onset asthma. Asthma is a syndrome characterized by multiple phenotypical expressions produced by manifold environmental determinants and a pluralism of individual responses. Current knowledge of the natural history of asthma reflects the various disciplinary approaches that have led to a composite picture. The best evidence so far comes from a relatively few longitudinal studies, which have shown that 80 percent of children who progress to develop asthma experience their earliest episode of wheezing before their sixth birthday.

At least 40 percent of children who contract a wheezing lower respiratory tract illness during their first 3 years of life still suffer from wheezing episodes when aged 6 years.

Young wheezing children form a heterogeneous group with different genotypes and phenotypes, leading to different outcomes. Both genes and environmental factors, like viruses, tobacco smoke and inhaled allergens, modify the phenotypes of early childhood wheezing. In addition, there seems to be an interaction between genetic and environmental factors and both have an association with the age and the immunological maturity of the children.

Currently, early childhood wheezing is generally classified into three main phenotypes: transient early wheezing (60% of the cases), nonatopic persistent wheezing (20%) and atopic persistent wheezing (20%). The wheezing tendency and increased bronchial responsiveness recover by the age of 3 years in transient wheezers and by the age of 6 years in nonatopic persistent wheezers, but both seem to continue through childhood and adolescence in atopic persistent wheezers. Abnormalities in lung function after early childhood wheezing seem to continue at least until teen age, as documented in both birth cohort and post bronchiolitis studies. Asthma or asthma-like symptoms are more common in young adults than in adolescents. There

is increasing evidence that these cases may more likely be relapses after early childhood wheezing than novel asthma cases (Table 1).

Less than half (40%) of early childhood wheezers have persistent wheezing from 3 to 6 years of age, and about half of them become sensitized to inhaled allergens before school age. These sensitized persistent wheezers are called atopic wheezers. The first wheezing episode usually takes place during the second or third year of life, and is later followed by repeated wheezing episodes, allergic sensitization and subnormal lung function, continuing through the whole childhood. In contrast, persistent wheezers with no allergic sensitization usually start wheezing before 1 year of age, typically induced by RSV infection. They subsequently wheeze only during respiratory infections, with a decreasing tendency by age. At the age of 13 years, the risk for wheezing is only slightly greater than in control children. Whereas, lung function remains subnormal through the childhood—also in nonsymptomatic cases.

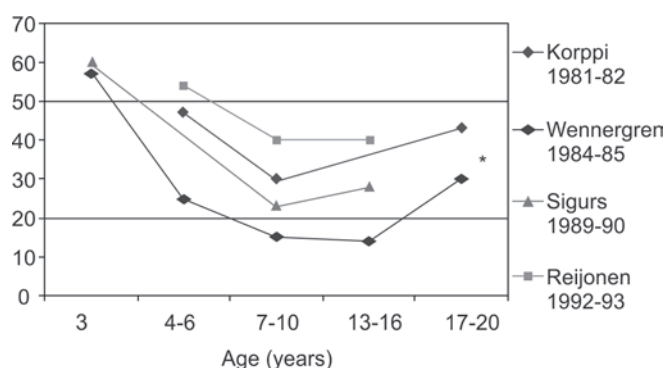
WHEEZING AND ASTHMA

Children with wheezing severe enough to need hospital treatment at less than 24 months of age form a group at a particular risk for asthma and other respiratory disorders in later life. There are only four prospective follow-up studies after hospitalization for bronchiolitis, which have continued until more than 10 years of age (Fig. 1). Over half of the former bronchiolitis patients have suffered from recurrent wheezing episodes at 2 to 3 years of age, and 25 to 54 percent have been symptomatic at 4 to 6 years of age. Although the tendency for wheezing decreases over time, still 15 to 30 percent have asthma during the early school years.

Many cohort studies have suggested that children with wheezing symptoms, or even with asthma, outgrow their disease by the second decade of life. The experience from clinical practice is similar, as are also the recent

Table 1: Three phenotypes of early childhood wheezing

	Age (years)			
Wheezing phenotype (%)	<3 yrs	6 yrs	11-13 yrs	16 yrs
Transient early wheezers (60%)				
Wheezing	+	–	–	–
Subnormal lung function	+	+	+	+
BHR ¹ /PEF variability ²	?	?	–	–
Nonatopic persistent wheezers (20%)				
Wheezing	+	+	–	–
Subnormal lung function	–	+	+	+
BHR ¹ /PEF variability ²	+	?	–	–
Atopic persistent wheezers (20%)				
Wheezing	–	+	+	+
Subnormal lung function	–	+	+	+
BHR/PEF variability	–	+	+	+

¹Bronchial hyper-reactivity.²Significant peak expiratory flow variability.**Fig. 1:** Subsequent asthma unit school age after hospitalization for bronchiolitis in early life. Results from four cohorts prospectively followed up until teenage or adulthood

research-based observations on the phenotypes of childhood wheezing. Over half of the wheezing children have transient wheezing and become symptom free before 6 years of age. In addition, nonatopic children with wheezing persisting until 6 or more years of age become symptom-free by 11 to 13 years of age. Studies have revealed that many former wheezers become symptomatic again in adulthood, often after many symptom-free years. Relapsing symptoms seem to be particularly typical for children with severe bronchiolitis and pneumonia needing hospitalization.

As seen in Figure 1, 14 to 40 percent of former bronchiolitis patients had asthma in adolescence and/or at teenage. The prevalence of modest to severe asthma at 17 to 20 years of age was 16 to 30 percent, and the prevalence of all asthma cases was 41 to 43 percent. The figures are

1.5 to 3.0 fold when compared with the figures at 7 to 10 years of age in the same cohorts and about 5-fold when compared with age specific population data. When the studies are compared, a clear secular trend is to be seen.

LUNG FUNCTION

Longitudinal studies have revealed permanent loss of lung function after bronchiolitis. Later lung function abnormalities have been documented after severe bronchiolitis in infancy and after mild early-life wheezing, and even years after cessation of wheezing. It is observed that adulthood lung function remains persistently impaired in subjects with childhood asthma, when compared with healthy controls. Instead, children with periodic wheezing with no asthma tend to have normal lung function until 40 years of age, but thereafter show a rapid decline. In atopic wheezers, lung function deteriorates with time and with continuing symptoms. In nonatopic transient and persistent wheezers, lung function gradually improves, but on average, remain subnormal through childhood—even after 5 to 10 symptom-free years. All these observations speak for the presence of a subgroup of children who are prone to permanent airway damage caused by early viral infections, along with other environmental factors such as early passive smoking. In later life, they are at risk for other respiratory disorders, like rapid deterioration of lung function from the age of 40 years onwards.

Viral Associated Wheeze

Viral respiratory tract infections are the most important trigger of asthma in children. Recurrent wheezing and asthma are common for some years after hospitalization for RSV bronchiolitis, but then decrease at preschool and school age with continuing tendency until early adolescence. Similar trends have been observed after hospitalization for pneumonia caused by RSV. It is observed that children with mild RSV bronchiolitis or other RSV infection treated at home before 3 years of age had a 3 to 5-fold risk of wheezing at 6 years of age, but the risk was no longer increased at the age of 11 to 13 years. However, their lung function still was lower than in controls.

Studies reveal hospitalization for RSV bronchiolitis at less than 12 months of age was a significant risk factor for both asthma and atopy at 7 to 8 and 13 to 14 years of age. The long-term follow-ups of these children have stressed the role of bronchiolitis not caused by RSV, or caused by rhinoviruses, as a risk factor for later asthma.

Other picornaviruses like enteroviruses, and parainfluenza viruses, human metapneumovirus and the newly found bocavirus have recently been established as triggers for wheezing in early life. In two recent studies, metapneumovirus bronchiolitis had similar presentation and outcome as had RSV bronchiolitis, but follow-up data have thus far been available only until 5 years of age.

The role of viruses in the development of asthma may be causal which means that viral infection in early life alters the normal lung development. On the other hand, viruses may act as triggering factors and reveal those infants who have a pre-existing aberration of either airway function or immune system. Probably, the association between viral infection and asthma is more complex, consisting of genetic constitution, concomitant exposure to multiple environmental factors and the maturation of the infants' airways and immune system at the time of infection.

Risk Factors

Parental asthma, parental atopy, elevated total serum IgE, early sensitization to inhaled allergens assessed either by allergen-specific IgE in serum or positive skin prick tests and blood eosinophilia have been predictive for asthma at teenage and also in young adults.

Table 2 summarizes early predictors for teenage or adult asthma. Asthma in parents, atopic asthma in particular, was a major predictor for wheezing and/or asthma at teenage and in adulthood, stressing the role of inheritance in the development of asthma. In a recent study, the authors identified a link from atopy in family members to the development of atopy and further to the development of adulthood asthma after early childhood wheezing. Since early childhood wheezing is more common in

boys than in girls, the female gender seems to be an independent risk factor for later asthma.

Early exposure to inhalant allergens may lead, depending on the timing and quantity of exposure and on inherited properties, to sensitization with increased risk for allergy and asthma or to tolerance with decreased risk. Thus, population-based studies on early exposure to furred pets have given varying results, from increased asthma risk in children with asthma in parents to decreased asthma risk, at least until 13 years of age, in children with no asthma in parents.

Eosinophils are involved in the inflammatory process of airway obstruction, at least in adults with asthma, and have been suggested to contribute to the development of subsequent symptoms and later asthma in wheezing children. Lack of eosinopenic response to acute viral infection, elevated blood eosinophils in infancy during acute bronchiolitis, and persistently high blood eosinophil counts at control visits have predicted wheezing and asthma until school age.

Wheezing induced by other viruses than RSV, and recurrent wheezing episodes before the age of 24 months, are significant predictors of later asthma, and the influence is to be seen until adulthood.

Maternal smoking, particularly if present during pregnancy, seems to increase the risk for later wheezing during childhood. Although the harmful effects seem to decrease with time, there is increasing retrospective evidence of permanent damage to the airways, manifesting as reduced lung function, increased risk for asthma or wheezing symptoms continuing until adulthood. The effect is intensified by later active smoking. The influence of paternal smoking is less evident, but a significant association with active smoking later and an increased prevalence of asthma until adulthood has been observed.

There is increasing evidence that an early exposure to tobacco smoke leads to increased airway reactivity and further to adult asthma. Such an early exposure leads to subnormal lung function in adulthood. The harmful effects are mediated by nonreversible changes in the airways, persistence or development of bronchial hyper-responsiveness and increased active smoking in young adulthood.

Distinguishing which bronchiolitis patients are at a particular risk for persistent wheezing and asthma in later life is essential for planning of an optimal treatment for early life wheezers. This means avoiding both under-treatment with a risk of complications, like permanent impairment of lung function, and over-treatment with potentially harmful medicines like steroids. Therefore, algorithms based mainly on the recurrence of wheezing and clinical manifestations of atopy in children, and asthma in parents, have been constructed for clinical use. However, waiting for the recurrence of symptoms may delay the treatment, and not all atopics present with clinically evident symptoms in early childhood.

Table 2: Early childhood factors associated with the development of teenage or adult asthma: postbronchiolitis studies

<i>Factor</i>	<i>Author</i>
Inheritance	
Parental asthma	Sigurs 2005 Hyvärinen 2005 Piippo-Savolainen 2006
Atopy in family	Goksör 2006
Gender	
Female	Goksör 2006
Serum allergen-specific IgE	
Food allergens	Hyvärinen 2005
Inhalant allergens	Hyvärinen 2005
Eosinophilia	Piippo-Savolainen 2007
Early atopy	
Total Serum IgE	Hyvärinen 2005
Atopic dermatitis	Hyvärinen 2005
Repeated wheezing <24 months age	Hyvärinen 2005 Piippo-Savolainen 2006
Parental smoking	Goksör 2006

Table 3: Algorithm to define those wheezing children who are at particular risk for subsequent asthma

<i>Major criteria</i>	<i>Minor criteria</i>
1. Physician-diagnosed asthma in a parent	1. Physician-diagnosed allergic rhinitis*
2. Physician-diagnosed atopic dermatitis	2. Wheezing apart from colds
	3. Blood eosinophilia ($\geq 4\%$)

*Sensitization to inhaled allergens.

Table 4: Revised algorithm to define those children who are at particular risk for subsequent asthma after hospitalization for early childhood wheezing

<i>Major criteria</i>	<i>Minor criteria</i>
1. Physician-diagnosed asthma in a parent	1. Sensitization to inhaled allergens*
2. Parental, especially maternal smoking	2. Wheezing induced by other viruses than RSV
3. Physician-diagnosed atopic dermatitis and/or food allergy	3. Blood eosinophilia or lack of eosinopenic response during viral infection

*Either positive skin prick tests or serum allergen-specific IgE.

An algorithm based on a large prospective birth cohort study including wheezing children, mainly treated at home, below 3 years of age has been developed (Table 3). Wheezing at <3 years of age and at least one major criterion or two minor criteria—means moderate risk for later asthma. Repeated wheezing at <3 years of age and at least one major criterion or two minor criteria—means high risk for later asthma.

Studies stress the roles of early wheezing not induced by RSV infection, early atopy and early recurrence of wheezing as risk factors for adult asthma. All these factors were associated with asthma in parents. Early exposure to tobacco smoke, maternal smoking in particular, was associated with lung function abnormalities persisting until adulthood.

Based on these studies algorithms have been revised to be more suitable for infants and toddlers treated and examined for wheezing in hospital (Table 4). There is stress on significant predictive role of asthma in parents and atopy in children as major risk factors for later asthma. In addition to atopic dermatitis, food allergy, at least when presenting with rash or respiratory symptoms, might be included in the model. Likewise, there is a role of early childhood eosinophilia, or merely the lack of normal eosinopenic response to infection, as a risk factor for adult asthma.

However, the recent observations question the roles of allergic rhinitis and wheezing apart from viral infection even as minor criteria in young children. Allergic rhinitis is rare in young children, and moreover, difficult to separate from viral rhinitis, or from rhinitis with involvement with both allergens and viruses. Moreover, new sensitive virological methods have revealed new viruses, and made it possible to find viruses in an increasing number of children with varying respiratory symptoms. Early sensitization to inhaled allergens, assessed by allergen-specific IgE or skin

prick tests, precedes clinical atopic symptoms and predicts also later asthma, and therefore belongs to the algorithm.

Early exposure to tobacco smoke seems to be justified to be included as a major risk factor, stressing the importance of the careful monitoring and treatment of wheezing children with tobacco smoke exposure also emphasizes the necessity of counseling against tobacco smoking, especially targeted to the mothers and fathers of tomorrow.

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Flexible Fiberoptic Bronchoscopy in Children, Infants and Neonates

K Chugh

INTRODUCTION

Amongst the various technological advances, in the field of pulmonary medicine one of the prime examples which has been revolutionary, is that of flexible bronchoscopy.¹ In today's date, it has become one of the most frequently performed invasive procedures in pulmonary medicine.

A little more than a decade back the only indication and utility of bronchoscopy that was recognized by all pediatricians was removal of a foreign body from the airways. The instrument used was a metal tube through which a light could be reflected down into the airways and a forceps could be passed to hold the foreign body and remove it. The rigid scope has improved considerably in recent times. However, it still is made of a metal tube and can be passed into the tracheobronchial tree only under general anesthesia.

Flexible fiberoptic bronchoscopy (FFB) has indeed become an integral part of pediatric pulmonology, neonatology, critical care, laryngology, cardiothoracic surgery, etc. Even the anesthetists use these instruments.

Fiberoptic bronchoscopy allows inspection and biopsy of superficial airway structures, typically including epithelium, basement membrane, and lamina propria. Thus, mucosal structures and events can be studied, but the technique is less applicable to studies of smooth muscle.² In addition to visualization, bronchoscopes also provide an effective means to obtain specimens from the lungs and the airways.

SETTING UP A BRONCHOSCOPY UNIT

Bronchoscopy Suite

Any dedicated bronchoscopy suite should include space for patient preparation and recovery, a procedure area and a cleaning and maintenance area. FB does not require a surgical operating room or dedicated facility and can be

safely performed in many different areas, for example, a side room on a ward, an intensive care unit, fluoroscopy lab or neonatal ward, if adequate mobile equipment is available.

Personnel

The minimum personnel involved during bronchoscopy performed under sedation with local anesthesia are the bronchoscopist, an adequately trained nurse, and another trained person who is responsible for administration of sedation and for monitoring of the patient.

Instrumentation

The nomenclature of the sizes of bronchoscope can be confusing. In general rigid instruments are defined by the diameter of the largest instrument that will pass through the scope, while flexible bronchoscopes are defined by their outer diameter.³

The flexible bronchoscope is a solid instrument composed of thousands of glass fibers that carry the light for illumination and the image. The tip of the instrument can be deflected to guide it into the desired path or location.³

For children, the most important consideration is the size of the bronchoscope because of their narrow airways. Since the patient has to breathe around the flexible bronchoscope (unlike with a rigid scope), the flexible scope should not be more than two-thirds the diameter of the trachea. Thus, for neonates, flexible scopes with a diameter of around 2.5 mm and for infants 3.5 mm diameter scopes are used.

We have used Olympus bronchoscopes with outer diameter of 2.8 mm and 3.6 mm with a suction channel of 1.2 mm in them with ease. This size of the suction channel is sufficient to suck out secretions but is clearly a limitation for obtaining sufficient tissue for biopsy. Ultrathin bronchoscopes (e.g. 1.8 mm) are also available. However,

we have used the 2.8 mm scope for neonates even smaller than 1 kg with success on several occasions.

The most common instruments used with flexible bronchoscopes are flexible biopsy forceps and cytology or microbiology brushes. Small grasping forceps and folding retrieval baskets are also available.

Equipment

The instruments differ in terms of the length and diameter of the instruments and suction channel. Examples of the various types of pediatric flexible bronchoscopes commonly used are listed (Table 1).⁴

In general, the smallest bronchoscope available should be used, in order to ensure that the blockage of the airway is minimized, unless an endobronchial biopsy is to be performed. Here, there is an argument for the use of the instrument with the biggest available biopsy channel, provided it is safe for the child.

If the flexible bronchoscope is to be passed through an endotracheal tube, the recommended difference in diameter is at least 1 mm so that the instrument can move inside the tube without getting stuck or the bronchoscope being damaged.

The correct diameter of the flexible bronchoscope for pediatric use depends on the diameter of the child's cricoid cartilage,⁵ which is the narrowest point in the larynx. It is assumed that there must be at least a 2 mm difference

between the gauge of the bronchoscope and the diameter of the larynx in order to ensure that FB can be performed safely. In infants and children, the most frequently used instruments are those with an outside diameter of 2.8, 3.5 and 3.6 mm. From about the age of 6 years, instruments with larger diameters (4.9 mm) can be used, ultimately arriving at the bronchoscope used in adults (6 mm) by the time the child has reached puberty.

Mobile Bronchoscopy Unit

A mobile bronchoscopy unit permits the procedure to take place in any part of the hospital. A mobile cart has to be equipped with a bronchoscope, light source, ECG monitor and a pulse oximetry, video equipment and a suction device. The basic accessories (forceps, brushes, mucus traps, etc.) should also be stored in the cart along with the basic resuscitation equipment (endotracheal tubes, laryngoscopes, suction catheters, ventilation bag).⁶

Equipment Storage Area

Flexible bronchoscopes are expensive and fragile instruments that require delicate handling and storage to guarantee their reliable function for the maximum period of time.⁶

Flexible bronchoscopes should always be stored hanging in a straight vertical position to prevent development of unwanted curves of the shaft.

Table 1: Pediatric flexible bronchoscopes⁴

<i>Maximum diameter</i>	<i>Working channel*</i>	<i>Working length</i>	<i>Tip deflection</i>	<i>Field of vision</i>	<i>Depth of vision</i>
2.2 mm	Not present	550 mm	Up 160° Down 90°	75°	2–50 mm
2.8 mm	1.2 mm	550 mm	Up 180° Down 130°	95°	2–50 mm
3.5 mm	1.2 mm	600 mm	Up 180° Down 130°	95°	3–50 mm
3.6 mm	1.2 mm	550 mm	Up 180° Down 130°	120°	3–50 mm
4.9 mm	2.2 mm	600 mm	Up 180° Down 130°	100°	3–50 mm
5.0 mm	2.2 mm	550 mm	Up 180° Down 130°	120°	3–50 mm
3.8#	1.2 mm	600 mm	Up 180° Down 130°	120°	3–100 mm
4.9 mm#	2 mm	600 mm	Up 180° Down 130°	120°	3–50 mm
5.3 mm#	2 mm	600 mm	Up 180° Down 130°	120°	3–100 mm

#: Videobronchoscope; *: mm of maximum diameter

A dedicated storage cabinet is essential to avoid contamination. The cabinet should be easy to clean, and preferably no other equipment should be stored with the bronchoscopes, to avoid damage or contamination to the instruments.

It should be noted that flexible bronchoscopes should never be stored in an area routinely exposed to X-rays as this may damage the fiberoptic system.⁴

CARE AND MAINTENANCE OF BRONCHOSCOPES

Bronchoscopy is definitely not a sterile procedure, since the instruments pass through a non sterile area (the nose and/or the mouth).³

However bronchoscopes and all the associated instruments must be cleaned and sterilized before use in a patient,⁷ to avoid cross infection from one patient to another.^{8,9}

Flexible bronchoscopes are cleaned by careful scrubbing of the exterior with a soft cloth and enzymatic detergent, the suction channel by a cleaning brush, and the lenses scrubbed and polished with a soft cloth. Thorough rinsing is followed by high level disinfection^{10,11} (with glutaraldehyde or peracetic acid) or sterilization (with ethylene oxide).

PROCEDURE IN CHILDREN

Pre-requisites for flexible bronchoscopy in children are listed in Box 1.

Hospitalization

Hospitalization for flexible fiberoptic bronchoscopy is not necessary. In fact, the procedure can be performed on out-patient basis also. We have done FFB in as many as 37 percent cases on day-care basis whereby the patient is sent back from the hospital within 3 to 4 hours.

Box 1: Pre-requisites of FFB in children and neonates

- A clear indication for the procedure – where the risk/benefit is in patient's favor
- Appropriate instrument – size of the scope is the main consideration
- Facilities and skills for bronchoscopy in a child/neonate
- Facilities for monitoring the child clinically and with electronic monitors before, during and after the procedure
- Facilities and skills for cardiopulmonary resuscitation of the neonate/child in the event of a mishap
- Microbiology and cytopathology laboratory back-up for analysis of the broncho-alveolar lavage fluid
- Preferably, facilities for video-recording the bronchoscopic findings

Preparing the Patient

Details of the procedure and the discomfort that it may cause must be explained to the parents (and the child, in case of older children). Possible risks must be discussed with the parents, always emphasising the overall safety of the procedure. The child should be preferably fasting for the past few hours. Cooperation of an older child is best obtained by talking to him directly and establishing a rapport with him.

Anesthesia

No general anesthesia is used during FFB procedure in majority of the centers. Local anesthesia is given in the nose and pharynx using lidocaine instillation in the nose. As the bronchoscope is passed down into the pharynx more lidocaine is instilled through suction-cum-working channel of the bronchoscope, taking special care to spray adequate amount on the laryngeal structures. After waiting for a few minutes the bronchoscope is inserted down into the trachea. As we go down the bronchial tree, more lidocaine is sprayed all along, thereby suppressing the cough reflex and minimizing patient discomfort.

Premedication and Analgesia/Sedation During Procedure

Premedication with a sedative is commonly used before the procedure at many centers.¹² However, FFB has been performed at other centers without any premedication also.¹³ We used trichloryl/chloral hydrate in a dose of 50 to 80 mg/kg about an hour before the procedure routinely in the early phase of our FFBs. But, now we use sedation in only selected cases as we feel the procedure can be performed just as easily without the premedication sedation in a majority of cases.

Several choices are available for sedation and analgesia for FFB in children and neonates (Box 2). Although standard doses are known, the usual practice is to give a smaller dose initially and titrate the further doses according to the need.

Often FFB can be done in smaller children and infants without any sedation, using appropriate restraints so that the patient does not move too much during the procedure. While this may cause some discomfort and pain to the child, it enhances the safety of the procedure by avoiding the side-effects of the sedation-analgesia. It has been suggested that fentanyl, either alone or in combination with midazolam, should not be given to infants younger than 3 months of age for fear of respiratory depression or chest wall rigidity.

Positioning the Patient

Although the procedure can be performed in the sitting posture also, we prefer to do it with the child lying supine.

Box 2: Sedation and analgesia for FFB in children*Premedication*

Especially for apprehensive children in the age group 1 to 6 years

Chloral hydrate—in the dose of 50-80 mg/kg few hours before the procedure, orally

Local anesthesia

Used in all patients

2% lidocaine jelly/drops for nose

1% lidocaine for pharynx, larynx and tracheobronchial tree

Intravenous sedation +/- analgesia

Midazolam – 0.05 – 0.2 mg/kg

Morphine – 0.05 to 0.1 mg/kg

Pethidine – 1-2 mg/kg

Fentanyl – 1-3 mcg/kg (i.e. 0.001 mg/kg)

Ketamine – 1-3 mg/kg

Propofol – 2.5-3.5 mg/kg

Reversal agents

Naloxone – 0.01 – 0.1 mg/kg (max 2 mg)

Flumazenil – 0.01 mg/kg (max 0.2 mg)

This way it is easier to restrain the child's hands and feet by using small size bed sheets. We make the smaller children and infants lie down on a 'board' on which straps are tied across the child's chest and knees. One of the assistants manually restrains the head so that the child cannot move his head from side to side.

Precautions

Before starting the bronchoscopy resuscitative equipment and drugs are checked each time. Correct size endotracheal tubes, suction catheters, bag and reservoir, laryngoscope with appropriate blades and working lights, and correct size mask are kept in a tray within reach of the assistant. An extra suction machine/suction point should be available.

An intravenous line should always be placed and well secured before starting the procedure. We place an intravenous line well before the procedure in all cases (even those children who come 'walking in' for the bronchoscopy) to avoid causing pain by needle prick just before the bronchoscopy.

Oxygen by the other nostril (usually the left) is given in all cases as some degree of obstruction to the airways will inevitably be caused by the bronchoscope once it is passed below the glottis.

Finally, protection of the operator, assistants, nurses and any students is a must. Transmission of infection from the patient to the health personnel is possible through droplet inhalation, conjunctival inoculation or through minor cuts and abrasions on hands. Hence, gloves, goggles, gown, mask and cap are recommended. Hepatitis B protection by vaccine is also recommended. HIV transmission can only be guarded against by barrier methods.

Box 3: Flexible fiberoptic bronchoscopy in children*Routes of insertion*

- Nasal
- Through endotracheal tube
- Through LMA
- Through tracheostomy tube/stoma
- Through bag + mask assembly into the nostril (with ongoing positive pressure ventilation)
- Occasionally through mouth

Insertion of the Bronchoscope

In children nasal route of insertion is most commonly used. Other possible routes include the oral cavity, endotracheal tube, laryngeal mask or tracheostomy tube in cases where these tubes are already in place and sometimes through the rigid bronchoscope. When passing through the mouth there is always the danger of the patient biting on the scope thereby damaging the optical fibers (Box 3).

Negotiating the Larynx

Once the laryngeal structures have been examined the child's readiness for further insertion should be evaluated. This is done by checking adequacy of local anesthesia of the sensitive laryngeal structures and by checking that the child's oxygenation is well maintained. The tip of the bronchoscope is then gently moved downwards and the angle maneuvered carefully to cause minimum touching of the vocal cords. This will ensure that the child does not develop temporary hoarseness after the procedure. Evaluation of the subglottis is best performed at this stage.

During examination of the larynx extreme care has to be taken to avoid forceful coughing by the child. The dictum is "Never fight the vocal cords".

Examining the Tracheobronchial Tree

Having come past the glottis more lidocaine is sprayed and the bronchoscope advanced gently avoiding touching the walls of the trachea. All along the lower airways more lidocaine is required and same precautions are mandatory. The movements of the tracheobronchial walls are carefully studied to look for tracheomalacia and bronchomalacia. In the upper trachea often one is looking for that rare abnormality of H-shaped tracheoesophageal fistula in which a small opening may be seen along the posterior wall.

With experience the right and left main bronchi can be easily differentiated from each other. But, this differentiation is totally lost at the peripheral level where all subsegmental bronchi have the same appearances. The examination is carried out in a methodical, routine fashion to ensure no pathology is missed in any area. Any secretions must be delicately removed by suction and condition of the mucosa observed.

Manipulating the Fiberscope

Driving the fiber bronchoscope along the branching alleys of the bronchial tree may appear very easy at first sight but one tends to get lost inside, especially the beginners. A clear understanding of the anatomy, patience and gentleness are most helpful. The controls of the instrument, which are in the hands of the bronchoscopist, are very easy to manipulate but they can be mastered only by practice.

Monitoring

The child undergoing bronchoscopy is monitored closely during the procedure and for sometime after the procedure also. Heart rate, respiratory rate, oxygen saturation and end tidal carbon dioxide in intubated children is measured continuously throughout the procedure. A close watch is kept over the general condition of the child, color, pulse and type of respiration. Child is observed closely at least till he comes out of the heavy sedation (if used). Any bleeding, stridor or sudden deterioration in general condition is looked for.

INDICATIONS FOR FFB

Upper Airway

- Stridor
- Persistent hoarseness
- Postintubation problems
- Nasal obstruction
- Sleep-associated airway obstruction
- Suspected vocal cord paralysis
- Aspiration
- Nasotracheal intubation
- Difficult endotracheal intubation
- Epistaxis (not explained by anterior nasal findings).

Lower Airway

- Atelectasis
- Unexplained/Persistent/Localized wheeze
- Suspected foreign body (but not certain, equivocal)
- Post foreign body removal evaluation
- Recurrent pneumonia
- Interstitial pneumonia
- Suspected congenital anomalies
- Hemoptysis
- Suspected airway compression
- Unexplained, disturbing chronic cough
- Removal of excessive bronchial secretions
- Evaluation of airway in tracheostomy patients
- Confirmation of endotracheal tube position
- Assessment of thermal or chemical/toxic inhalational damage to the airway.

Radiographic Abnormalities

- Atelectasis
- Recurrent/Persistent consolidations
- Atypical and unknown infiltrates
- Localized hyperinflation
- Selective bronchography (rarely required).

Therapeutic Indications

- To remove mucus plugs or blood clots
- Restoration of airway patency
- To remove excessive secretions in the lower airways
- Alveolar filling disorders (alveolar proteinosis, lipid pneumonia).

Special Procedures

- To perform therapeutic BAL
- Endotracheal intubation
- Laser therapy of lesions obstructing the lower airways
- Guide to surgical interventions
- Plastic bronchitis of acute chest syndrome
- Brushing or biopsy of the bronchial mucosa
- Biopsy of endobronchial lesions
- Transbronchial biopsy
- Administration of drugs.

EXPERIENCE WITH FFB IN PEDIATRICS

In some of the centers in USA pediatric FFB started more than three decades back. By 1987, Reddy and Vauthy from Ohio¹³ had performed the procedure in over 4,000 cases. Wood had performed FFB in over 3,000 cases by 1992.¹² Similarly, Fan has been working with the flexible bronchoscope since at least 1981¹⁴ and Deblic reported therapeutic applications of FFB in pediatrics as early as 1984.¹⁵ Recently Nussbaum has published his 20 years experience with pediatric fiberoptic bronchoscopy (Box 4).¹⁶ In India too FFB was started by Somu and colleagues at Institute of Child Health, Madras (Chennai), Tamil Nadu, India quite early. They reported their experience of 630 cases from January 1989 to August 1995. However, only 12.3 percent of their patients were less than 4 years old and the youngest was 50 days. In our institution almost half (48%) of the children were less than one year age (Tables 2 to 6).¹⁷ In the Madras study almost 30 percent of the children had bronchiectasis, a condition that we see very seldom in young children at our center. In the Madras study no comment has been made about the dynamic problems of the airways. We encountered significant laryngomalacia in 22 percent, bronchomalacia in 14 percent and tracheomalacia in 5 percent cases (Tables 3 and 4).¹⁷ Nussbaum's series had 19 percent of subjects below 12 months age and the pathology diagnosed had a similar spectrum as ours.¹⁶

Box 4: FFB in children: How is it different

1. Smaller size of the airway does not leave sufficient space around the scope for breathing. Consequent hypoxia and hypercarbia are minimized by using smaller size scope, administering oxygen during the procedure and finishing the procedure in the shortest possible time.
2. Indications for FFB are different. Tumors are rare. Congenital malformations are more common.
3. Problems of upper airway are often the indication, e.g. stridor.
4. Dynamic problems of airway, e.g. laryngomalacia, bronchomalacia and tracheomalacia are important considerations.
5. Children can be restless, anxious and even combative. Adequate analgesia and sedation is required.
6. Biopsy is not commonly required. A study of the cytology of BAL is considered as a "liquid biopsy".
7. Transbronchial lung biopsy is rarely done; mainly because lung pathology requiring this procedure is uncommon in children.

Table 2: Age and sex distribution of FFB cases (Jul 1993 to August 2006)¹⁷ (n = 3226)

Age	No. of procedures	Percentage
<1 month	258	8%
1-3 months	580	18%
3-12 months	709	22%
1-5 years	1000	31%
>5 years	420	13%
>10 years	259	8%
Total	3226	100%
	M-57%	F-43%

Table 3: Common diagnosis in suspected pathology in upper airways (n=1490)¹⁷

Infections	164 (11%)
Foreign body	164 (11%)
Subglottic stenosis/edema	253 (17%)
Outside pressure on airway (Tracheal compression)	179 (12%)
Normal airways	59 (4%)
Laryngomalacia	328 (22%)
Tracheomalacia	74 (5%)
Vocal cord palsy	8 (0.5%)
Post-tracheostomy evaluation	164 (11%)
Others	97 (6.5%)

Table 4: Common diagnosis in suspected pathology in bronchi/ lungs (n=1123)¹⁷

Inflammation	280 (25%)
Foreign body	269 (24%)
Mucopurulent plugs	112 (10%)
Bronchomalacia	157 (14%)
Normal airways	102 (9%)
Others	203 (18%)
(Many children had more than one finding)	

Table 5: Rare diseases (n = 3226)¹⁷

Hemosiderosis	6
William Campbell syndrome	1
Situs inversus	3
Bronchopleural fistula	2
Agenesis of lobe/lung	9
Broncho-esophageal fistula	1
Tracheal injury (tear)	
Postsurgery	1
Post foreign body removal	1
Tracheomegaly	4
H-type fistula	5

Table 6: Results (n = 3226)¹⁷

Total FFB	3226
PICU	613 (19%)
Intubated	480
Via LMA	140
Via ET	340
Nonintubated	133
Via nasal/tracheostomy	
Non-PICU	2613 (81%)

COMPARATIVE ANALYSIS OF INDICATIONS AT SGRH AND TERTIARY REFERRAL CENTER (TABLE 7)

Comparing the indications for doing FFB in GRH and at a tertiary care referral center in New Delhi, most common indication in both the studies was nonresolving pneumonia.^{17,18} Other indications being stridor, foreign body in GRH study, and persistent collapse in the other study.

EVALUATIONS IN DIFFERENT CONDITIONS**Evaluation of Upper Airways and Larynx**

When the flexible scope is being passed through the nose and pharynx the bronchoscopist has an opportunity to examine these areas. Problems like choanal atresia and choanal stenosis are detected and evaluated.

However, the area of maximum interest to the pediatrician is usually the adenoids, larynx, the supraglottic structures, the vocal cords and glottis and the subglottis. Care and patience during examination of laryngeal area along with video recording (for possible review later) greatly enhance the diagnostic value of FFB. This also gives the opportunity to study the laryngeal structure and function during inspiration and expiration.⁴

Stridor or noisy breathing, that usually reflects an obstruction of the upper airways, is the most common indication for FFB in infants.⁴

Other congenital anomalies of the larynx causing stridor are: laryngoceles and saccular cysts, laryngeal webs and atresia, laryngotracheal stenosis, laryngeal and

Table 7: Comparative analysis of indications in 2 studies^{17,18}

Indications	GRH (n=3226)	AIIMS (n= 529)
Nonresolving pneumonia (NRP)	11%	41.77%
NRP in immunocompromised	–	4.91%
Inflammation	25%	–
Outside pressure on airway (Tracheal compression)	12%	–
Stridor	–	10.01%
Foreign body	24%	–
Vocal cord palsy	0.5%	–
Post-tracheostomy evaluation	11%	–
Normal FFB	24%	–
Bronchomalacia	14%	–
Mucopurulent plugs	10%	–
Resistant TB?	–	7.56%
Subglottic stenosis/edema	17%	–
Hemoptysis	–	7.93%
Pulmonary agenesis/H-type TEF	–	1.89%
Cystic fibrosis	–	6.4 %
Persistent collapse	–	15.5%
Interstitial lung disease	–	4.53%

tracheal clefts, congenital neoplasms such as hemangiomas, bifid epiglottis and ventral cleft of the larynx.¹⁹

Laryngeal cleft may be missed by FFB, and rigid bronchoscopy should be performed if this diagnosis is seriously considered.⁴ Abnormalities below the epiglottis were found in up to 68 percent of cases.²⁰

Laryngomalacia and paralysis of vocal cords are two most common abnormalities of the larynx besides laryngeal stenosis, congenital web, etc. The movements of vocal cords with each respiration and during phonation should be observed carefully. Nussbaum detected 14 cases of vocal cord dysfunction in his series of 2,836 cases.¹⁶ Paralysis of vocal cords and scar tissue formation may interfere with the movements of the cords.

Laryngomalacia is well studied by the flexible scope. The size, shape and floppy nature of the arytenoids, epiglottis and the aryepiglottic folds can be assessed during spontaneous quiet breathing (in well-sedated child) and during crying/ activity, etc. This is helpful in therapeutic decision making. Not all cases of laryngomalacia are benign and mild. We have performed tracheostomy for this indication and have seen a death occur after the diagnosis was made but tracheostomy refused by the parents in another child.

Evaluation of cases of croup before intubation, at the time of attempted extubation, at failed extubation, at time of deciding for tracheostomy and at the time of attempt at decannulation of tracheostomy has been advocated.²¹ Diagnosis of bacterial tracheitis by FFB can be very helpful in croup.²² Subglottis is crucial in cases of pathology in laryngeal area, especially in postintubation patients. Subglottic edema, congestion, mucosal injury, narrowing and granulation formation are the common abnormalities encountered. Failure to or difficulty in negotiating this area during endotracheal intubation is an indication for bronchoscopic evaluation.

Evaluation of Tracheostomy

Once a tracheostomy tube has been inserted, the child may require repeated bronchoscopic examinations of the larynx and lower structures to evaluate their present condition and possible readiness for decannulation. Granulation tissue at the stoma obstructing the trachea or in lower trachea may develop in such children. The anterior wall of the trachea at the site of stoma may move posteriorly, thereby narrowing the airway.¹²

When the main pathology was in the larynx, say stridor, the bronchoscope is passed through the nose and supraglottic structures, vocal cords and the subglottic space evaluated. If these are assessed to be better and child ready for decannulation the scope should be passed further down (after removing the tracheostomy tube if it cannot be passed by its side). This way the lower airways are also examined.

Sometimes, the bronchoscope can be passed through the stoma by the side of the tracheostomy tube without removing it. Passing the scope through the tracheostomy tube may be easier, unless the tube size is too small.

If the examination of the uppermost part of trachea is not possible through the glottis because of severe narrowing there, the scope can be passed retrograde through the tracheostomy stoma and the extent of subglottic narrowing evaluated. We have done this a few times and found it to be very useful.

Dynamics of Lower Airways

Collapse of the walls of trachea and/or bronchi during expiration is a common acquired abnormality in infants and young children (tracheomalacia and bronchomalacia). Many children who continue to have 'wheeze' after extubation are suffering from these conditions. Naturally, they respond poorly to anti-asthma treatment. Occasionally, the condition may be severe enough to result in hypoxemia, sleep disturbances and apnea.

Tracheomalacia and Bronchomalacia

Congenital malacia of the large airways is one of the few causes of irreversible airways obstruction in children, with symptoms varying from recurrent wheeze and recurrent

lower airways infections to severe dyspnea and respiratory insufficiency.²³⁻²⁶

Severe cases are usually detected in the neonatal period when children present with ventilator dependency or acute severe obstructive episodes with cyanosis.

Children with mild airway malacia often present after the neonatal period with nonspecific symptoms such as rattling, wheeze, stridor, exercise intolerance, cough, recurrent lower airway infections, and airways obstruction.^{25,27}

Primary airway malacia is defined as airway malacia in otherwise normal infants.²⁷ Secondary airway malacia was defined as airway malacia secondary to esophageal atresia, VATER/ VACTERL association (condition with vertebral anomalies, anal atresia, congenital heart disease, tracheoesophageal fistula or esophageal atresia, renourinary anomalies, or radial limb defects), vascular or other external compression of the airways, or specific syndromes.

Malacia was defined as collapse of at least 50 percent of the airway lumen, during expiration, cough or spontaneous breathing, or a ratio of cartilage to membranous wall area of <3:1.²⁷

Primary airway malacia is common. Ruben Boogaard et al reported its incidence to be 1 in 2,100.²⁸ As a correct diagnosis is important because of the therapeutic implications and perhaps lifelong consequences, bronchoscopy should be done in all patients with unexplained exercise intolerance, recurrent lower airways infection, and irreversible and/or atypical asthma.²⁸

Chronic Cough

Pediatric chronic cough is defined as a daily cough lasting for >4 weeks. Chronic cough is subdivided into specific cough (i.e. cough associated with other symptoms and signs suggestive of an associated or underlying problem) and nonspecific cough (i.e. dry cough in the absence of an identifiable respiratory disease of known etiology).²⁹

Chronic cough (atypical and persistent) in a patient with normal imaging, functional studies and hematological examinations, and that does not respond to medical therapy is another indication for flexible endoscopy in children.^{4,30}

ACCP evidence-based guidelines recommend FFB for following indications:

- Suspicion of airway abnormality,
- Localized radiology changes,
- Suspicion of an inhaled foreign body,
- Evaluation of aspiration lung disease, and
- Microbiological studies and lavage.²⁹

Stridor: Clinical Condition

Stridor in children indicates anatomical or functional obstruction of the upper airways. Age of presentation, besides the other clinical features can be a useful diagnostic clue. For example, laryngomalacia is the commonest cause of stridor in early infancy. If the stridor is mild and

classical features are present a clinical diagnosis of laryngomalacia can be made with reasonable certainty. However, if the obstruction is severe or atypical features are seen, a bronchoscopic evaluation of upper as well as lower airways should be done. Approximately, one-sixth of cases of laryngomalacia were associated with lower respiratory tract abnormalities in a large series.

Common Diagnostic Entities in Children with Stridor

- Congenital malformations of supraglottic, glottic, subglottic structures, trachea
- Post-extubation edema/inflammation
- Severe laryngomalacia, tracheomalacia
- Tracheoesophageal cleft
- Foreign body
- Vascular ring (e.g. double aortic arch)
- Infections, e.g. retropharyngeal abscess, diphtheria
- Hemangioma
- Laryngotracheal angioedema.

Bilateral Wheeze

Besides asthma, the following conditions can result in bilateral wheeze. When there is no response to anti-asthma treatment or there are other clues to the diagnosis (clinical or radiological), flexible bronchoscopy can be a useful tool in the evaluation of such a child.

Causes of Bilateral Wheeze in Children

- Tracheomalacia – primary or secondary
- Bronchomalacia – primary or secondary
- Stenosis
 - with complete tracheal rings
 - without complete tracheal rings
 - post-traumatic, e.g. postintubation, postburns
- Vascular ring compressing the trachea
- Foreign body at carina/in trachea
- External compression of trachea
 - enlarged lymph nodes
 - cardiac chambers
 - mediastinal cysts, masses
- Endobronchial tuberculosis, both sides
- Bronchiectasis
- Neoplasms, hemartomas
- Tracheal candidiasis.

Unilateral Wheeze

Persistent wheeze on one side or only in a localized area indicates a localized obstructive pathology. Such a patient is likely to benefit greatly by flexible bronchoscopy in diagnostic evaluation.

Unilateral/Localized Wheeze

- Foreign body
- Endobronchial tuberculosis

- Compression of bronchus from outside by
 - lymph nodes
 - mediastinal mass
 - vascular ring
 - cardiac chambers
- Bronchial stenosis
 - congenital
 - acquired, e.g. postintubation and vigorous tracheal suction
 - Congenital lobar emphysema
 - Endobronchial tumor.

Bronchial Asthma

Patients of bronchial asthma who respond poorly to steroids should undergo bronchoscopy and endobronchial biopsy.

Biopsy evidence of steroid resistant eosinophilic inflammation in a symptomatic child, with features of basement membrane thickening and increased smooth muscle, confirms asthma, and strengthens the argument for use of further anti-inflammatory therapy, such as cyclosporine.

Conversely absence of typical pathological features would help to take a reappraisal of diagnosis and treatment.³¹

Recurrent/Persistent Preschool Wheezers

Management of severe, recurrent wheezing is often difficult in infants and preschool children, particularly in those children who are refractory to conventional asthma therapy.

In such cases other diagnosis must be excluded. In a study conducted by S Saglani et al, children aged between 3 months and 5 years with severe recurrent wheezing, underwent a protocol of investigations including a chest computed tomography scan, blood tests, nasal ciliary brushings, fiberoptic bronchoscopy, bronchoalveolar lavage (BAL), endobronchial biopsy and passage of an esophageal pH probe.³²

The study revealed abnormal results in three-quarters of cases. Findings included atopy in 39 percent, two-thirds had evidence of gastroesophageal reflux, structural abnormalities (13 out of 37), excessive mucus (20 out of 37) and macroscopic inflammation (10 out of 37). BAL revealed bacterial growth in 12 out of 44 (27%) patients. Good quality endobronchial biopsies were obtained from 36 out of 46 (78%) patients; of these, 44 percent had tissue eosinophils and 28 percent had a thickened reticular basement membrane.³³

FFB in Immunocompromised Child

Detection of opportunistic organisms in the BAL in immunocompromised host (e.g. HIV, antimalignancy treatment, congenital immunodeficiency disorders) is a very rewarding experience as it helps in planning the specific treatment.^{32,34-39} The child with unexplained radiological opacity may be an immediate beneficiary sometimes

when an endobronchial tubercular lesion is detected or when *Mycobacterium tuberculosis* is identified on Ziehl Nelsen staining or by fluorescent techniques. Cultures of *M. tuberculosis* and its sensitivity tests with antitubercular drugs is another step that is critical in decision making regarding the specific antitubercular drugs to be used in such children.

However, the commonest pulmonary infections even in the immunocompromised host are due to the usual pathogens like *Pneumococcus*, *Staphylococcus*, etc. When these organisms are cultured with high colony counts and associated with a strong polymorphonuclear response in BAL fluid the clinician can choose the suitable antimicrobial drugs, especially when resistant strains are the offending agents.

In a study⁴⁰ conducted at Sir Ganga Ram Hospital, New Delhi, India, 30 children (age range 10 mon-14 yrs) with neutropenia (absolute neutrophil count less than 1500/cumm) and pulmonary infiltrates were subjected to BAL by FFB. All the cases had been on antibiotics without an adequate response. Four children showed *Pneumocystis carinii*, four fungus and two tuberculosis. Pyogenic pathogens were isolated in eight patients. A number of other studies have shown BAL to be a useful procedure in immunocompromised children.⁴¹

All the children tolerated the procedure well in GRH study except one who developed increased hypoxemia for a short while. Safety of the procedure, especially the low incidence of hemorrhage, in immunocompromised children has been emphasized in a review.⁴¹

A study conducted by Ori Efrati, which included a large number of immunosuppressed and patients of congenital heart disease, revealed that FFB and BAL contributed to a specific diagnosis in 79 percent of the patients.⁴²

Role of FFB in Pulmonary Tuberculosis

Suspected pulmonary tuberculosis is ordinarily not an indication for FFB. However, when the response to treatment is not adequate, radiological opacities persist, atelectasis does not clear, gastric lavage fails to show acid-fast bacilli,⁴³⁻⁴⁶ FFB may prove useful. When differentiation from a non-responding pyogenic pneumonia or a foreign body aspiration is not clearly possible by other noninvasive investigations.

FFB should be done. Since children cannot produce sputum confirming MDR tuberculosis is not easy. FFB provides an opportunity to examine the airways as well as obtain a sample for bacteriological examination. Endobronchial tuberculosis lesions can be identified on FFB examination. Their brushings or bronchoalveolar lavage cytology may show the specific cells. In older children it may be possible to take a biopsy also. Further, the specific organism may also be demonstrated.

FFB and BAL in Nonresolving Pneumonia in Immunocompetent Children

Persistent pneumonia which has not responded to the apparently correctly chosen antimicrobial treatment is not an uncommon situation in hospital practice. In the majority of such children there is no reason to believe that they have any immunodeficiency. There may not be enough evidence to label that pneumonia as tubercular either. In such cases after sufficient trial has been given or if the situation is deteriorating in spite of the well-chosen antimicrobials or if radiological/clinical features suggest the possibility of unusual/resistant organism FFB and BAL should be done.

In our experience FFB may help in diagnosis of an unexpected foreign body; compression of a bronchus, lung abscess missed on chest X-ray and computed tomography, etc. Further, BAL performed in these cases may yield a fungus, resistant bacteria (*Staphylococcus aureus* is not an uncommon pathogen), *Pneumocystis carinii*, etc. as the possible pathogen (thesis). Rock (1995) also found BAL to be useful in selected patients of nonresolving pulmonary infiltrates in immunocompetent children.⁴⁷

Many of the organisms identified in BAL fluid are also the commensals of upper respiratory tract through which the bronchoscope inevitably passes and contamination invariably occurs. To increase the specificity of BAL fluid cultures in diagnosing common bacterial pneumonia the concept of quantitative.

BAL cultures were introduced on the lines of urine culture colony counts. Using such quantitative cultures cut-off points of 10^4 or 10^5 colony forming units (cfu)/ml have been suggested in the literature.⁴⁸⁻⁵⁰ Our own studies⁵¹ have shown 10^4 cfu/ml to be a useful cut-off value between possible commensals and pathogens.

Aspiration Pneumonia

Children with suspected aspiration pneumonia may benefit from FFB. Tracheoesophageal cleft, H-type tracheoesophageal fistula, etc. can be diagnosed. Techniques for identifying the H-fistula using methylene blue dye have been described. Some children have frequent lower respiratory tract infections following repair of congenital tracheoesophageal fistula (TEF) with a tracheal character cough and/or wheeze. FFB evaluation of such children may yield tracheomalacia in the repaired segment, stenosis or just irregular architecture of the mucosa in this segment. Rarely, there may be a recurrence of the fistula or an incomplete repair may be the cause for recurrent aspiration pneumonia. Damage caused by repeated episodes of aspiration pneumonia can also be evaluated.

Atelectasis

Atelectasis of the whole lung, a lobe or a segment is a common condition encountered in the NICU, PICU and the

postoperative wards. This is often due to mucus plugs or mucopurulent thick secretions or granulations caused by suction catheter/endotracheal tube trauma. Sucking out of the mucus plugs proves useful in a number of such children, especially when hydration, humidification, nebulization, vibrations and chest physiotherapy have failed. Removal of the mucus plug may have an effect akin to removing the cork out of a bottle, i.e. opening a closed bronchus and allowing the relevant part of lung to expand immediately. However, the results are not as dramatic most of the times. Bar-Zohar and Sivan reported a success rate of 74 percent of treating lung atelectasis by FFB and lavage.⁵²

Bronchial stenosis, a mass lesion within the bronchus or compression of the airways from outside may be the cause of atelectasis. Some of these problems have not only been evaluated by FFB but even treated using laser.

Role of FFB in PICU

From July 1993 to January 1996, FFB was carried out 108 times in patients in the PICU in our institution. Majority of the patients were below 2 years age (69%), with the youngest child being 2 days old. Minimum weight of the child undergoing bronchoscopy was 1.5 kg. Males predominated. Common indications for FFB were stridor (16%), suspected foreign body (23%) atelectasis (24%), nonresolving pulmonary infiltrates (29%) and persistent or atypical wheeze (11%) (Table 8). In six cases, nasotracheal intubation was carried out with the aid of the bronchoscope.

Frequent findings included purulent material in airways, mucopurulent plugs, severe laryngomalacia,

Table 8: Indications for FFB in PICU: (July 1993 to Jan 1996)⁵³

Indications	July 1993-199 (n = 108)	Sept 2005- Oct 2006 (n = 140)
Stridor	16%	14.28%
Suspected foreign body	23%	11.42%
Atelectasis	24%	74%
Nonresolving pulmonary infiltrates	29%	—
Persistent or atypical wheeze	11%	—
Nasotracheal intubation	6	
Persistent lung collapse	—	53.57%
Assessment of airway for pathology	—	35%
Abnormal airway pathology/anatomy	—	9.28%
BAL	61%	46.42%
ET	—	14.28%
Mixed	—	23.57%

tracheomalacia, foreign body, postintubation granulations and tracheobronchomalacia.

Bronchoalveolar lavage was performed in 68 (61%) procedures and proved useful in planning further treatment in all these cases.

FFB was helpful in evaluation airways in all patients. It helped in clearing the airways of blocking secretions or plugs in 32 (29%) procedures. In two cases foreign material (thin peel of groundnut in one case and forcibly fed 'meal' in another case) was sucked out and rigid bronchoscopy was avoided. In all other cases of foreign body removal was carried out under general anesthesia by rigid bronchoscopy in the operation theater. Minor complications occurred in 11 percent patients, commonest being transient dip in oxygen saturation. No major complications were encountered.

Another retrospective study was done between September 2005 to October 2006 in our institution. One hundred and forty procedures were performed, out of which 120 (86%) were intubated. The common indications were persistent lung collapse 75 cases, assessment of airway for pathology,⁴⁹ (upper airway obstruction,²⁰ suspected foreign body,¹⁶ abnormal airway pathology/anatomy¹³), to obtain broncho-alveolar lavage,⁶⁵ to confirm position of endotracheal tube-20, and mixed indications.³³ No procedure related mortality, life-threatening complications, or significant changes in patient status occurred.⁵³

Role of FFB in VAP

Children on the ventilator often develop new opacities in their lungs when on the ventilator, especially when ventilation is prolonged. Identifying the causative organism of ventilator associated pneumonia and choosing the appropriate antibiotic can be crucial. Endotracheal suction, blind bronchial sampling (BBS), 'blind' bronchoalveolar lavage and FFB assisted BAL are the techniques employed for obtaining the 'secretions' from the lower airways. In a study, we compared these four techniques in children with VAP. Blind bronchoalveolar lavage was the most reliable method followed closely by blind bronchial sampling for the diagnosis of ventilator-associated pneumonia. Considering the difference of the cost in the two procedures, blind bronchial sampling may be the preferred method in the pediatric intensive care unit of a developing country.⁵⁴

FB in Neonates

The first fiberoptic bronchoscope that was useful in neonates was the 3.5 mm Olympus bronchoscope with a 1.2 mm suction channel. Later, even smaller diameter scopes (up to 1.8 mm) with flexible tips have been developed and are being increasingly used in evaluation of pulmonary pathology in newborns.⁵⁵ We have performed bronchoscopy with or without BAL in a fairly large number of newborns using 3.5 mm and 2.8 mm Olympus

bronchoscopes. The smallest size baby was 900 gram pre-term. Taking all the appropriate precautions we have not encountered any major complications. Nor is the rate of minor complications much higher in this age group. Yes, the time for which the bronchoscope can be kept below the glottis in very small babies has to be limited and the bronchoscope withdrawn at the earliest indication of a significant problem, like desaturation on pulse oximeter. Supplemental oxygen is essential in all cases.

Indications of bronchoscopy in newborns are discussed below and the yield of FFB in the common indications from a reported series are summarized in Table 9.⁴¹

Urgent Indications

Suspected airway obstruction in intubated neonate

The obstruction may be in the tube, at its lower end or even beyond. Usually, the cause is thick secretions/mucus plugs. These can be sucked out, thereby obviating the need for tube removal and reintubation.

Suspected dislodgement of the endotracheal tube

This is also best handled with the help of FFB.⁵⁶ In fact, it has been the experience of many at the highly specialized neonatal units that confirmation of the position of lower end of the endotracheal tube by FFB takes less than 60 seconds while a portable X-ray film takes much longer. This time period may be crucial for a newborn with acute severe deterioration. Indeed, Vigneswarm and Whitefield⁵⁷ showed that bronchoscopy resulted in lesser desaturation than radiography and was also more accurate.

Evidence of airway obstruction after extubation

This is a common phenomenon. Quickly performed FFB can detect problems like laryngeal edema, vocal cord paralysis, prolapsing laryngeal structures, mucus plugging or simply posteriorly falling tongue. Fan et al⁵⁸ in 73 consecutive postextubation laryngeal evaluations found a 44 percent incidence of moderate or greater laryngeal injury. Fan et al⁵⁹ and Sherman et al⁶⁰ studied the risk factors for postintubation subglottic stenosis. They suggest that stridor after extubation is a strong indication for bronchoscopy.

Table 9: Diagnostic yield from flexible bronchoscopic procedures in the neonatal period based on indications for bronchoscopy⁴¹

Indication	Diagnosis made/number of procedures (%)
Stridor	52/54 (96)
Acute respiratory distress	9/36 (25)
Congenital anomalies	5/7 (71)
Bleeding	2/2 (100)
Wheezing	24/26 (92)
Atelectasis/Emphysema	28/35 (80)

Vaughy and Reddy

Vaughy and Reddy⁶¹ have pioneered the technique of intubating newborns using the flexible bronchoscope in difficult cases, e.g. hypoplastic mandible or maxilla, hydrocephalus or other malformations.

Such intubations being nasotracheal are more useful. With experience this type of intubation can be done in a very short time.⁵⁶

Elective Indications

- Determination of position of distal tip of an intubated infant has been shown to be reliably confirmed by FFB. The time taken by Dietrich et al⁵¹ was 40 seconds compared to 30 minutes for X-ray
- Stridor or other signs of airway obstruction
- Recurrent atelectasis associated with intubation or following extubation to determine if there are tracheal abnormalities, e.g. tracheomalacia, tracheobronchomalacia
- Persistent localized emphysema
- Focal wheezing
- Wheezing not responding to bronchodilators.

Unusual Indications

- Severe unilateral pulmonary interstitial emphysema
- Persistent unilateral airleaks.

Special Precautions in Preterms and VLBW Newborns

- Avoid disturbing the newborn too much. Perform the procedure in NICU itself
- Oxygenate well throughout the procedure
- When already on ventilator increase FiO₂ to 100%
- Suction very gently and for minimum duration
- Use sedation/analgesia carefully
- Always use adequate local anesthesia
- Use smallest size bronchoscope that will serve the purpose. For most diagnostic work 2.2 mm ultrathin bronchoscope is preferred
- Interrupt the procedure as soon as significant problems like desaturation are noticed
- Perform the procedure in blocks keeping the bronchoscope below the larynx for a maximum of 30 to 40 seconds in one block.

Role of FFB in NICU

We have performed this procedure in a large number of NICU patients, sometimes at the bedside and at other times by shifting them to the bronchoscopy suite.

Age of neonates undergoing the procedure ranged between 1 and 78 days and the weight between 0.9 and 3.6 kg. Unexplained severe stridor, clinical evidence of lower airway obstruction, postintubation/ventilation evaluation of airway, unexplained and persistent pulmonary opacities and atelectasis were the common indications. Evaluation of the airways for a suspected congenital

anomaly is the most frequent indication in the early neonatal period.

Laryngomalacia severely obstructing the airways, tracheobronchomalacia, purulent material in lower airways, mucopurulent plugs, postintubation/endotracheal suctioning granulations and unilateral choanal atresia were the endoscopic findings observed.

Experience of Finer⁵⁶ with neonatal FFB is summarized in Table 10.

FFB with LMA

Laryngeal mask airway (LMA) of pediatric and neonatal sizes have now become available and are proving to be a useful adjunct in FFB. When the size of the endotracheal tube being used for an infant is less than 4 mm, it is not safe to pass a 2.8 mm bronchoscope through it. In such situations, the endotracheal tube can be removed temporarily and replaced by a LMA. The bronchoscope can then be passed through the LMA. When the LMA is properly positioned, entry into the trachea is easily achieved. However, there is some limitation in evaluating the supraglottic structures when the scope is passed through a LMA. We have been very satisfied with LMA in a large number of cases that we have used it. Nussbaum has also found LMA as a good alternative.¹⁶

TYPES OF BRONCHOSCOPIES

Diagnostic Bronchoscopy

Bronchoalveolar Lavage

In 1978, the Olympus company introduced a flexible fiberbronchoscope for use in pediatric patients.⁶² Within the next decade, its use for performing BAL in pediatric patients was described by many pulmonologists.^{32,34,35}

Table 10: Neonatal fiberoptic bronchoscopy⁵⁶

Diagnosis	Number
<i>Upper airway</i> (N = 144)	
• Laryngomalacia	45
• Subglottic narrowing	
– Edema, web, stenosis	16
• Vocal cord paralysis	
– Unilateral or bilateral	11
<i>Lower airway</i> (N = 220)	
• Tracheomalacia	28
• Bronchomalacia	10
• Tracheal/bronchial	
– Granulations	42
Obstructed/dislodged	
– Endotracheal tube	18

N = 220; via endotracheal tube = 76; transnasal, nonintubated = 144; bronchoscopic intubations = 40

BAL can be defined as the instillation into and recovery from the distal airways of a volume of saline sufficient to ensure that the fluid returned contains at least some fluid that was originally present on the alveolar surface.³ Both soluble and cellular constituents of the alveolar (and small airway) surface fluid are contained in the effluent. As an extension of fiberoptic bronchoscopy, bronchoalveolar lavage adds only 3 to 5 minutes to the procedure and has been shown to be relatively safe, with a reported complication rate of <0.4 percent in the largest series of 1095 children described by Wood et al.⁶³ Besides, FFB can be done safely and effectively using topical anesthesia, unlike rigid bronchoscopy for which general anesthesia is virtually mandatory.⁶⁴

BAL^{65,66} yields a specimen that can give representative data from the distal airways and alveolar surfaces. As in adults, BAL has been used in children in the investigation of noninfectious interstitial lung diseases and in the identification of infectious agents.⁶⁷ By far the major application of BAL in the pediatric population has been the diagnosis of infection, particularly in the immunocompromised host.^{32,34-39} Perhaps the best recognized indication is the diagnosis of *Pneumocystis carinii* pneumonia in such children.^{39,68}

The main principle of BAL is to obstruct an airway with catheter and flood the airways and alveolar spaces distal to that site with saline. The airway must be occluded, or the instilled fluid will spill into adjacent airways, resulting in coughing, possible respiratory embarrassment and loss of returned volume. BAL may be performed with a rigid bronchoscope by advancing a catheter beyond the tip of the bronchoscope into the desired location. A flexible bronchoscope, however, is more ideally suited for BAL, since its tip is maneuverable and can be easily directed to and wedged into the desired bronchus. Besides increasing the range of visualization of the peripheral airways, this permits the tip to be wedged in the smaller airways. The volume of lung lavaged will depend on the size of the catheter or bronchoscope in relation to the size of the airway. For example, the standard 3.5 mm pediatric flexible bronchoscope will wedge into a segmental airway in a newborn infant and into a sub-subsegmental airway in an 8-year-old child.⁶⁴

After passage of the bronchoscope intranasally and a general inspection of the airways, a lung subsegment is selected for lavage. In the absence of a localized abnormality in the X-ray or on direct visualization, the right middle lobe or lingular bronchus is usually selected.⁶⁷

Small aliquots 3-4 ml/kg divided into three aliquots with a maximum of 20 ml per aliquot,^{69,70} of sterile normal saline are instilled through the suction channel. The fluid sucked back a little later gets mixed with the secretions and fluids in the wedged area of the lung and is collected in a sterile chamber. This is then analysed in the microbiology and cytopathology laboratories.

Bronchial brushing, commonly used in adults, is not feasible in younger children and infants because of limitations of size of the bronchoscope. However, the microbiology brush can be easily used in children more than 4 years age⁷¹ and sometimes in younger children also.

Bronchial Washings

The utility for bronchial washings is largely for the diagnosis of airway diseases including fungal or mycobacterial infection.¹

Endobronchial Biopsy

This is basically used for lesions directly visualized during bronchoscopy. It provides histological specimens whereas bronchial washing provides only cytological samples.

Indications

- Diagnosis of tuberculosis and other infectious or granulomatous disorders
- To obtain ciliated cells for the diagnosis of primary ciliary dyskinesia
- Research applications include studies on bronchial inflammation in patients with asthma or cystic fibrosis.⁷²⁻⁷⁶

Transbronchial Biopsy

Transbronchial biopsy (TBB) is a technique to obtain peripheral lung tissue for diagnostic studies including histopathological examination and for microbial cultures.

Indications

- TBB has an established place in lung transplant recipients: It has a high sensitivity and specificity, and represents the gold standard for diagnosing acute rejection and delineating opportunistic infection⁷⁷
- It is of less use in diagnosing chronic rejection (bronchiolitis obliterans)⁷⁸
- In patients with human immunodeficiency virus (HIV) infection to delineate noninfective pulmonary pathology
- After bone marrow transplantation to diagnose obliterative bronchiolitis
- In patients with interstitial lung disease.⁷⁹

Fluoroscopy is mandatory for accurate positioning of the biopsy forceps in order to get the maximum yield from sites of radiographic abnormality and to minimize the risk of pneumothorax.

A chest radiograph 2 to 4 hours later is mandatory to rule out a slowly developing pneumothorax. Only one lung should be sampled on a same occasion in order to prevent the occurrence of bilateral pneumothoraces.

Complications

- The major complication of TBB is a pneumothorax with an incidence of ~3% in adults
- Small hemorrhages often occur but resolve either spontaneously or after lavage with saline. If bleeding is

profuse and persistent; instillation of adrenaline solution (1:10,000) may be necessary

- Transient pyrexia
- Transient dyspnea.

Thus, it is recommended that patients should be observed overnight following the procedure.

Transbronchial Needle Aspiration

Transbronchial needle aspiration (TBNA) is a sensitive, accurate, safe, and cost-effective technique in the diagnosis and staging of lung cancer.^{77,80-87} Also used in diagnosis of benign diseases.⁸⁸

Bronchography

Bronchography can be performed by injecting contrast material through the working channel of the flexible bronchoscope in order to delineate anatomic abnormalities.⁸⁹ The flexible instruments can be situated in the area of interest, thus less contrast material is needed. In addition, some of the contrast can be suctioned back at the end of the procedure, thus decreasing the risks of atelectasis and chemical pneumonitis.

Endoscopic Intubation

Intubation of a difficult airway may be accomplished with the aid of a flexible bronchoscope even in preterm neonates (e.g. in patients with Pierre Robin syndrome, craniofacial trauma).⁹⁰ With ultrathin instruments, intubation may be performed with endotracheal tubes as small as 2.5 mm.

Drug Application

Bronchoscopic administration of surfactant may represent an effective method of delivery in acute respiratory distress syndrome.⁹¹ Furthermore, in persistent atelectasis unresponsive to medical therapy bronchoscopic instillation of recombinant human DNAase has been found to be useful.⁹²

Closure of Bronchopleural Fistulae

FB with the delivery of methacrylate adhesive to a bronchopleural fistula may be a reasonable alternative to operative closure when the operative risk is great.⁹³ As the glue should not come into direct contact with the bronchoscope, it should be injected through a catheter placed through the working channel of the instrument.

Ultrathin Bronchoscopy

The ultrathin bronchoscope currently being studied has an outer diameter of 2.8 mm and an inner channel diameter of 1.2 mm and is made up mainly of fiberoptic bundles.

This device has been developed to overcome the low diagnostic yield of FB for small lesions less than 20 mm in

diameter.⁹⁴⁻⁹⁷ Complexities of the distal airway anatomy requires fluoroscopic or CT guidance to maneuver the scope to the peripheral lesions.

Virtual Bronchoscopy

Virtual bronchoscopy (VB) combines multidetector helical CT with computer-assisted image processing to generate high quality intra- and extraluminal views of the airways. Virtual bronchoscopy is a computer-generated, three-dimensional reconstruction technique that simulates a bronchoscopist's view of the airways.⁹⁸

It accurately shows the lumen and the diameter of the trachea, main bronchi, and the bronchial tree down to the fourth order of the bronchial orifices and branches.^{99,100}

According to a study conducted at St Mary's Hospital, London, virtual bronchoscopy is a complementary investigation to conventional bronchoscopy, especially when conventional bronchoscopy is poorly tolerated. Their meta-analysis concluded that though conventional bronchoscopy (FB and rigid bronchoscopy) are the gold standard investigations, VB is accurate in visualizing areas inaccessible to the FB especially bronchial obstructions and endoluminal lesions, and for accessing tracheobronchial tree beyond airway stenosis, bronchoesophageal fistulas, post lung transplantation anastomosis, and suspected foreign body aspiration.

However, it is not reliable in diagnosis of dynamic airway or mucosal lesions.^{101,102}

Hence in selected cases VB can assist and direct FB, but can never replace FB.¹⁰²

Limitations

- Visualization of complex bronchial branching may be complicated by partial volume effects
- Early mucosal or submucosal changes cannot be detected
- A histological tissue sample cannot be obtained, neither can any other therapeutic maneuver be performed
- Very viscous secretions or endoluminal thrombus can simulate an occlusion
- It does not detect any dynamic causes of airway obstruction (e.g. vocal cord paralysis or tracheomalacia) because it is a static technique performed at the end of inspiration
- Exposure to radiation
- It can be created from any routine chest CT on a 16 to 320 MDCT as long as raw data remains available on the scanner to allow thin reconstructions
- Obtaining good quality data to construct VB may not be possible in young infants with fast respiratory rates.

Therapeutic Bronchoscopy

Flexible bronchoscopy has expanded immensely in its therapeutic spectrum since its initial inception. Rigid bronchoscopy has become less popular. Nonetheless, rigid bronchoscopy remains an invaluable tool and should be considered for control of the compromised airway, massive

hemoptysis, silicone stent placement, and removal of large foreign bodies, especially in the pediatric age group.¹⁰³

Indications for Therapeutic Flexible Bronchoscopy

Removal of foreign body, mucus plug, blood clot

When diagnosis of foreign body aspiration is certain, the child can be directly taken up for rigid bronchoscopy under general anesthesia. However, when situation is doubtful (dictum is “Always suspect a foreign body”), FFB is preferred. Similarly, occasionally a foreign body would be found in the airways when it was not the least suspected. Most foreign bodies are left alone on FFB and managed under general anesthesia by rigid bronchoscope.⁴ However, if the foreign body is in small pieces or located in a peripheral airway suction/retrieval by baskets or ureteral forceps externally coated with Teflon, to allow frictionless passage through the narrow suction channel of the FFB, through the flexible scope may be attempted.^{104,105}

Occasionally, the attempt to remove the foreign body by the rigid scope, even in the hands of most competent and experienced bronchoscopist fails. A re-evaluation by FFB in such cases is helpful in planning the further course of management.

Sometimes, even after successful retrieval of the foreign body the clinical and radiological abnormalities do not improve well. This raises the possibility of incomplete removal. Re-evaluation by FFB may show this to be because of another piece of the foreign body or due to granulation, congestion and mucopurulent plugs.

Contraindications: Lack of experience and lack of availability of all necessary endobronchial accessories are the more important contraindications. Removal of a foreign body using FB should be attempted only by or under the supervision of an expert bronchologist.

Procedure: Foreign body removal using FB is carried out in stages:

- Dislodging the foreign body
- Grasping or securing the object
- Removing it along with the flexible bronchoscope as single unit.

A balloon catheter is usually used to dislodge the foreign body from the distal airways and to pull it into the proximal airways. Once the object is grasped and secured with an appropriate accessory, it is kept very close to the tip of the flexible bronchoscope to reduce danger of losing it in the subglottic area or at the level of vocal cords.

A variety of ancillary accessories (forceps, grasping claws, snares, baskets [dormia, fishnet], and magnets) are available for foreign body extraction.¹⁰³ Once the object is in the trachea, the patient can also be asked to cough to expel the foreign body. Lasers and cryoprobes can also be used if a significant amount of granulation tissue is present.

A cryoprobe passed through the flexible bronchoscope can be used to retrieve the foreign body by placing the tip in contact with the object until the point of contact is frozen, leading to adhesion (cryoadhesion). This allows for en bloc removal of the object with the cryoprobe and the flexible bronchoscope.

This approach is especially useful for the removal of blood clots, mucus plugs, friable organic material, and small inorganic objects. Occasionally, laser instruments can assist in the removal of large objects by breaking them up into smaller pieces. Self-expanding metallic stents embedded in the bronchial mucosa can be extracted by fracturing the wires using laser energy.¹⁰³

Complications during foreign body removal:

- Central airway obstruction
- Airway wall perforation
- Flooding of the airways with secretions or blood.
- Hypoxia, bronchospasm, arrhythmias,
- Laryngeal edema
- Bacteremia, fever
- Migration of the object to distal airways
- Object fragmentation
- Loss of the object at the glottis during removal efforts.

The key for the success in foreign body removal is airway protection, an experienced operator, adequate equipment, and availability of a rigid bronchoscope for an emergent situation.¹ There are some drawbacks of the latter technique compared to rigid bronchoscopy:

- The procedure is more time-consuming,
- The inability to perform mechanical resection may result in incomplete resolution of the obstruction and may necessitate more laser energy to vaporise the lesions,
- Complications such as bleeding are difficult to control,
- Flexible endoscopes are easily damaged.

Bronchoalveolar lavage for pulmonary alveolar proteinosis

Aspiration of cysts: mediastinal or bronchogenic

Drainage of lung abscess

Hemoptysis

Pulmonary toilet

Difficult endotracheal intubation

Endoscopy-Assisted Tracheal Intubation and (Selective) Bronchial Intubation—Direct visualization of the airway via a flexible bronchoscope has been reported to be of assistance in the intubation of the patient with a difficult airway and during placement of a bronchial blocker to enable single-lung ventilation during video-assisted thoracoscopic surgery.¹⁰⁴

Percutaneous dilational tracheostomy

Pneumothorax/bronchopleural fistula (fibrin glue therapy)

Gene therapy

Dilation of stricture and stenosis: balloon bronchoplasty

Stent placement

Stents: Stents are devices used for the internal splinting of luminal structures¹⁰⁵ for counteracting extrinsic compression from tumors or lymph nodes. They have been very rarely used in children.

Intralesional injection: *cidofovir, mitomycin, steroid*

Bronchial thermoplasty

Recently, Cox and associates^{106,107} reported their experience with bronchial thermoplasty in asthmatic adults. This novel technique involves treatment of airways with a specially designed, four-wired, thermoplasty probe that ablates airway smooth muscle.

The thermal effect appears to remain confined to the airway wall and the immediate peribronchial area without associated fibrosis. The procedure seems to be well tolerated and patients demonstrate an improvement in airway hyper-responsiveness, quality of life and symptom-free days, and peak flow measurements. However, the technique has not been tried in children.

COMPLICATIONS OF FLEXIBLE BRONCHOSCOPY

FFB is a safe procedure even in the very sick, ventilator dependent children with major complications being uncommon^{17,22,34} and deaths rare (one death having been reported in 1987 by Wagener).¹⁰⁸ Complications in three of the series are listed in Table 11.

Transient dip in arterial oxygen saturation, mild nasal bleed, transient hemoptysis, transient stridor, increased cough for a short while, over-sedation are some of the relatively common complications encountered. All the

possible complications are listed in Table 12. It is important to anticipate problems, monitor the patient closely and take adequate precautions to minimize complications.

Recently, Bar-Zohar and Sivan have reported their experience with FFB in severely sick children in the PICU.⁵² In 155 procedures, no procedure-related death was encountered. Nor did they encounter any significant nasal/airway trauma, stridor, hemoptysis, pneumothorax, septicemia or cardiac arrhythmias. There was no significant reduction in PaO₂/FiO₂ ratio or deleterious effect on blood pH or PaCO₂.

RECOVERY AND POSTPROCEDURE CARE

On completion of the procedure, the child should be awakened whilst still fully monitored. Monitoring of oxygen saturation should continue during the recovery period. An intravenous line should be left *in situ* until the child is fully awake and tolerating oral fluids. Late complications are rare, but have been described, including progressive stridor necessitating intubation.¹⁰⁹ The sedated child should never be left unobserved and may require the same formal recovery facilities as after a general anesthetic.

The child should remain in the recovery area until cardiovascular and respiratory stability are assured and the patient is awake and orientated.

If local anesthetic agents have been applied to the airway then laryngeal reflexes may be depressed for up to an hour after the procedure. Children should not eat or drink during this period as the risk of aspiration may be increased.⁴

Table 11: Complications of FFB^{17,22,34}

	Wood (n = 1095)	GRH (n = 3226)	Reddy and Vauthy (n = over 4000)
<i>Major</i>			
Pneumothorax	2	0	6
Lung abscess	1	0	0
Laryngospasm	1	8	0
Massive hemorrhage			
Prolong hypoxemia requiring intubation	0	3	0
Hypoxemia requiring oxygen/admission	0	6	0
Arrhythmias	nil	nil	nil
<i>Minor</i>			
Minimal nasal bleeding	8	28	5
Mild hemoptysis	0	0	0
Increased cough for up to 1-2 hrs	0	47	0
Transient stridor	2	47	1
Transient O ₂ desaturation		150	
Over-sedation/anesthetic Complication	5	0	
Transient bradycardia	13	34	several

Table 12: Possible complications (all of them are uncommon)^{17,22,34}

Physiological	Hypoxia, hypercapnea, arrhythmias, laryngospasm, bronchospasm
Bacteriological	Transient fever, iatrogenic infection (if standard sterilization techniques not followed), bacterial endocarditis in congenital heart disease patient, cross infection. Bronchoscopist and assistants exposed to patient's infection
Mechanical	Pneumothorax, hemoptysis, epistaxis, laryngeal, trauma, mucosal edema, subglottic edema
Anesthetic complications	Over sedation, apnea

CONTRAINDICATIONS TO BRONCHOSCOPY

FFB should not be performed in the absence of a suitable indication or appropriate equipment and personnel skilled in its use. There are no absolute contraindications. Relative contraindications are those which increase the risk of the procedure. Cardiovascular instability, pulmonary arterial hypertension, bleeding diathesis, severe bronchospasm, hypoxemia are some examples where bronchoscopy is relatively contraindicated.^{3,4,18}

ETHICAL ASPECTS OF BRONCHOSCOPY

Bronchoscopy is unethical in a clinical context unless performed with the maximum attention to safety, and in a context in which the potential benefit to the child justifies the perceived risk of the examination. Fully informed consent, in accord with local and national guidelines, is mandatory.

The ethics of research bronchoscopy have recently been debated.¹¹⁰⁻¹¹² In general, the performance of a bronchoscopy cannot be considered to be of such low risk that it is justified to perform it on a child for research purposes alone.¹¹³

However, if a clinically indicated bronchoscopy is performed, then it is fully justifiable to use clinically gathered material (e.g. BAL fluid, endobronchial biopsy material) for research purposes, provided informed consent has been obtained from the family and age-appropriate assent from the child.¹¹⁴ It may also be legitimate to prolong the procedure for a short time to make extra measurements, for example endobronchial pH.¹¹⁵

RISK/BENEFIT RATIO

The risks involved are minimal except in critically ill child whose hemodynamics are unstable. To keep the risks low oxygenation is continued throughout the procedure. If still the child tends to desaturate the bronchoscope is removed immediately and reinserted again after the child

stabilizes. Care at minor details during the procedure ensures that the mucosa of the nostril, pharynx and lower airways are traumatized the least. Keeping a complete control over the angle of the tip of the bronchoscope and avoiding suctioning when the scope is against the wall is further helpful. Another precaution to minimize suction trauma is to keep the negative suction pressure in the recommended range. Similar precautions are necessary during BAL. Complications encountered during BAL by some workers are summarized in Table 11. When inserting the scope into glottis a careful control over the tip of the scope and adequate local anesthesia of the area allows the skilled bronchoscopist to maneuver the scope into the trachea smoothly. This is helpful in avoiding post bronchoscopy stridor/ laryngeal spasm. The benefits that will accrue to the patient by bronchoscopy should be evaluated carefully before the procedure is undertaken. Since FFB in skilled hands is safe and tolerated well most experts believe that it is an underused procedure and should be undertaken in any puzzling/difficult pulmonary condition.

FLEXIBLE VERSUS RIGID BRONCHOSCOPY

The question now is "Has flexible bronchoscope completely replaced the rigid one?" Most experts agree that the two are complementary with each having its advantages and limitations (Table 13). Overall, for majority of cases FFB is the procedure of choice for diagnosis while rigid bronchoscopy is the procedure of choice for therapeutic indications like removal of foreign body. In general, if a particular function can be performed by either of the two scopes, the flexible one would be preferred by most as FFB has lesser complication rate, improved vision, small size and does not require anesthesia. Most neonatologists, intensivists and pulmonologists in advanced medical centers of the world have now acquired the skills to perform this procedure in their units.

Special Indications of Rigid Bronchoscopy

- Foreign body removal
- Endobronchial procedures
- Evaluation of bronchoesophageal cleft
- Examination of anterior commissure of larynx
- Massive hemoptysis
- Dilatation of stenotic airways.

FUTURE OF PEDIATRIC FFB

Over the past 2 decades applications of pediatric FFB have widened greatly. More and more specialists, pulmonologists, neonatologists, anesthesiologists, ENT surgeons, cardiothoracic surgeons and pediatric surgeons have acquired the skills and the equipment to use this instrument for the benefit of their patients. As subspecialties advance and PICUs and NICUs reach higher levels of sophistication

Table 13: Comparison of rigid and flexible bronchoscopy

	<i>Rigid</i>	<i>Flexible</i>
1. Anesthesia	General	Local + sedation
2. Operation theater	Required	Not required Done in bronchoscopy suite/PICU/NICU/Bedside
3. Nose and nasopharynx	Not seen	Evaluated
4. Upper lobes	Not entered	Entered
5. Distal airway	Not evaluated	Evaluated
6. Beyond a stenosis	Cannot pass	May pass
7. Dynamics of airways	Not visualized	Visualized well
8. Bronchoalveolar lavage (BAL)	Not possible	Ideal
9. Through endotracheal tube	Cannot pass	Can pass
10. Simultaneous ventilator	Cannot work	Can work
11. OPD procedure	No	Can be
12. Aid to difficult endotracheal intubation	No	Yes
13. Aid to extubation	No	Yes
14. Tracheostomy evaluation	Limited value	Valuable
15. In small infants	Possible	Easy
16. In prematures	Not possible	Possible
17. Selective bronchogram	Not possible	Possible
18. Selective bronchial intubation	Not possible	Possible
19. Working channel	Large	Small

in the developing countries FFB will be done more commonly here too.

Newer applications of FFB in both diagnosis as well as in therapy are being explored. The BAL fluid can be analyzed by the sensitive techniques of polymerase chain reaction (PCR) and ELISA to detect organisms like *Mycobacterium*, *Pneumocystis*, CMV, HIV, etc. Delivery of drugs to the targeted parts of lung and airways can be achieved by FFB, especially if the 'drug' cannot be well nebulized. Gene therapy for cystic fibrosis may be possible soon and FFB may be one method by which the gene can be delivered to the respiratory epithelium.⁴¹

A study¹¹⁶ has described a method of quantitatively assessing the degree of airway collapse in infants and children with tracheobronchomalacia. A computer-assisted method is described besides the manual method. This combination of FFB with the computers's help may prove synergistic in future.

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Persistent and Recurrent Pneumonia in Children

Varinder Singh, Rajesh Kumar Meena

INTRODUCTION

Pneumonia is clinically defined as combination of respiratory symptoms (cough, dyspnea or tachypnea) and signs (fever, crepitations, focally-reduced breath sounds, fremitus or wheeze).

Persistent or nonresolving pneumonia is defined as the persistence of symptoms and radiographic abnormalities in a child with lower respiratory tract infections for more than a month despite a course of adequate antibiotic therapy.¹ Documentation of nonresolving abnormal radiographic findings is important for defining a case of persistent pneumonia. Recurrent pneumonia is defined as at least two distinct episodes of radiologically established pneumonia within the same year or three or more such episodes over any time period.² For the diagnosis of recurrent pneumonia, there must be documented complete resolution of clinical and radiological findings between acute episodes. Often distinguishing recurrent and persistent pneumonia is difficult as all the relevant radiographs, particularly those taken after the child gets better, may not be available. As many features of the two might be overlapping both are usually considered together.

ETIOLOGY AND PATHOGENESIS

The presence of abnormal radiographic findings is important for defining an episode of pneumonia in a case of persistent pneumonia. Though radiological lung infiltrates due to acute pneumonia usually resolves within 2 to 4 weeks but a substantial number of children fails to completely clear infiltrates within a period of 4 weeks. The rate of resolution of the radiological shadows depends on the causative agent. Infiltrates caused by common viral agents like respiratory syncytial virus and parainfluenza usually take 2 to 3 weeks to clear while those associated with pneumococcal pneumonia can take up to 6 to 8 weeks and

those associated with adenoviral disease up to 12 months.³ Beside infections, the persistent lung infiltrates can also occur due to a variety of non-infective causes as well.

For the better understanding of the etiology and pathogenesis, the patients with persistent pneumonias are further divided into those who have a single segment/lobe involvement and those in which multiple lobes are involved. Infiltrates that recur in a single lobe or segment of the lung are more likely to be caused by localized pathology like local airway obstruction—intra/extraluminal, structural abnormalities of airway or lung parenchyma. On the other hand, multilobar involvement may be more often a result of a systemic problem. Persistent pneumonias can result from deficiencies in the local pulmonary or systemic host defences or from underlying disorders that modify lung defences. But, majority of children with persistent or recurrent (PRP) have no defect in host defence while few of these children may have transient alteration in their host defences.

Unilobar Persistent Pneumonia

Localized airway narrowing, due either to an intraluminal or an extraluminal compression leads to retained secretions in the area distal to the obstruction. Impaired mucociliary clearance in the involved leads to accumulation of secretions distal to obstruction, in which infection supervenes.

Various causes of unilobar persistent pneumonia are described in Table 1.

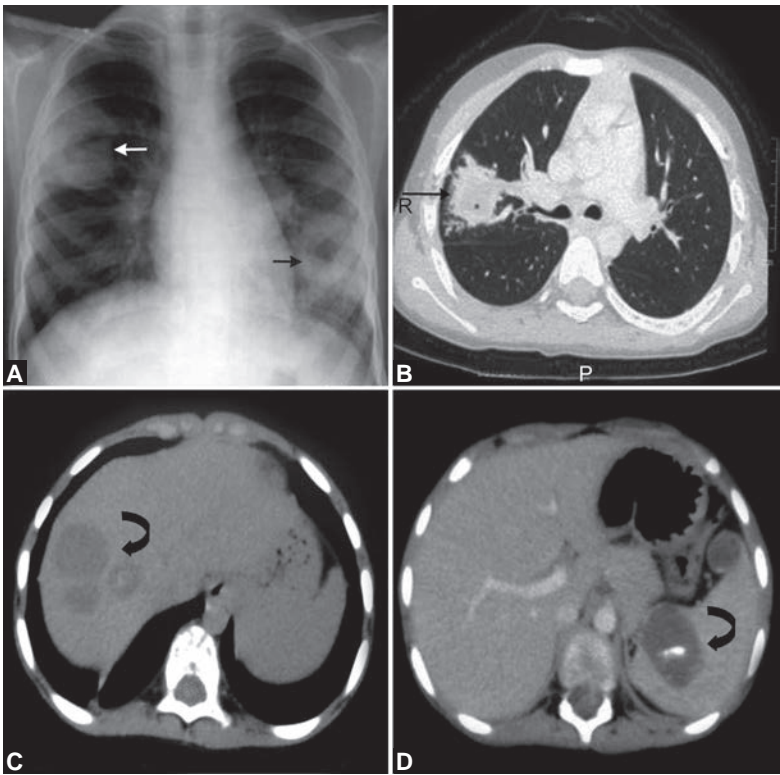
Foreign body aspiration the most frequently leads to intraluminal obstruction in children age 6 months to 3 years. Commonly, foreign bodies impact in the right bronchus because it takes off at a less acute angle from the trachea than the left bronchus. Food or vegetable items such as peanut, gram seed, cashew, etc. are commonly aspirated. It is important to obtain a detailed history of any choking and coughing episodes, but the physician should

maintain a high index of suspicion for foreign body aspiration even in the absence of such history as the choking event may go unnoticed by the care giver. Symptoms are very variable. While in many cases there is a definite history of

choking while eating or playing or mouthing small objects. This is followed by onset of cough and breathlessness instantly or after a variable interval of minutes to hours. Common symptoms include noisy breathing or wheeze, cough, dyspnea, and occasionally hemoptysis. Initial signs of foreign body aspiration include localized wheezing and asymmetry of breath sounds, which are decreased on the side of aspiration.⁴ Sometimes the aspiration episodes are not observed when they occur, and respiratory symptoms may not manifest immediately afterward. As a result, some children are treated for pneumonia and “recover,” only to present later with recurring symptoms. Many a ‘forgotten’ foreign bodies are detected later when the child develops and gets investigated for chronic suppurative lung disease like atelectobronchiectasis. Chest skiagram will often show localized hyperinflation or segmental/lobar collapse. However, in many small children the foreign body may remain in trachea due to its large size and the skiagram may be absolutely normal. Persistent tracheal noises or wheeze on auscultation, particularly when the child is quiet may suggest a tracheal foreign body.

Usual organisms with multidrug resistance to commonly used drugs or unusual organisms can also lead to a non-resolving pneumonia in an immunocompetent as well as an immune-deficient host. Parasites like *Echinococcus* can lead to pulmonary hydatidosis along with liver and kidney involvement (Figs 1A to D).

Table 1: Common causes of unilobar persistent pneumonia	
Intraluminal obstruction	<ul style="list-style-type: none">• Foreign body• Endobronchial granuloma—tuberculoma• Bronchial tumor—hemangioma, lipoma, adenoma, carcinoid, papilloma, etc.
Extraluminal compression	<ul style="list-style-type: none">• Lymphadenopathy:<ul style="list-style-type: none">– Infectious (Tuberculosis)– Noninfectious (Malignancy-Hodgkin’s, sarcoidosis)• Vascular rings and slings• Esophageal foreign body• Cardiomegaly• Inflammatory pseudotumor
Structural abnormalities	<ul style="list-style-type: none">• Congenital anomalies<ul style="list-style-type: none">– Bronchial stenosis– Tracheal bronchus– Congenital cystic adenomatoid malformation– Congenital lobar emphysema– Bronchogenic cyst– Pulmonary sequestration• Right middle lobe syndrome• Bronchiectasis



Figs 1A to D: Hydatid disease of lung (A) Multiple round opacities in right upper and left lower lobe areas (small arrow). Opacity in the left lung field shows cavitation; (B) CT chest showing pneumonic patch around the infected cyst (big arrow); (C and D) and abdomen showing multiple nonenhancing cystic hypodense lesions in liver and spleen hydatid (curved arrows)

Children with active tuberculosis may also present with persistent focal infiltrates or atelectasis caused by endobronchial granulations. Infectious lymphadenopathy is the most common cause of extraluminal compression, leading to chronic or recurrent focal pulmonary disease. Infectious lymph nodes causing airway compression are most commonly caused by infection with *M. tuberculosis*. In active pulmonary tuberculosis, enlarged lymph nodes occur in the perihilar, carinal, and peribronchial regions (Figs 2A to D).

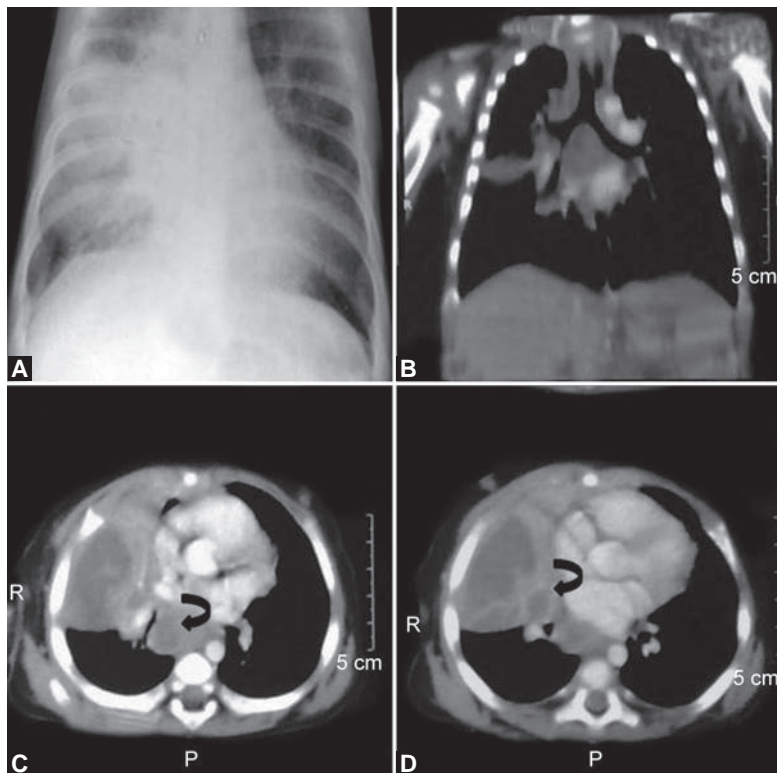
Chronic bacterial infection in cystic fibrosis can lead to lymphadenopathy, pertussis presents with lymphadenopathy in 35 percent of cases. Other less common bacterial causes of lymphadenopathy include—brucellosis, tularemia, and *Mycoplasma* infection (in 34 percent of pediatric cases). However, in most of these situation compression of the airways is not seen.⁵ Tumors are a rare cause of intraluminal obstruction in children but should not be overlooked as a reason for recurrent localized pneumonia. Tumors such as lymphoma, plasma cell granulomas and histiocytomas can also cause extraluminal airway compression. Inflammatory pseudotumors are the most common benign primary pulmonary growths in children. Most patients have no symptoms; those who have, manifestations include fever, cough, chest pain, and recurrent pneumonia.

Congenital anomalies of the heart and great vessels may also cause extrinsic obstruction of the large airways. Children with significant left to right shunt also are more

prone to repeated LRTIs but in that situation the lung involvement is multi focal and bilateral. Vascular rings and slings and esophageal foreign bodies are other causes of extraluminal compression causing unilobar obstruction. Such children more often present with feeding difficulty, noisy breathing and/or stridor.

Right middle-lobe syndrome is the most common recurrent focal finding encountered in clinical practice. It is the atelectasis of the right middle lobe persisting for more than one month or recurring twice or more despite treatment,⁶ a susceptibility attributed to anatomic and physiologic causes. Right middle-lobe syndrome is seen most often in children with asthma. Tuberculosis remains the most common infectious etiology of right middle lobe syndrome. Similarly, the positioning of the right upper lobe bronchus in small infants makes them more prone to collapse of the upper lobe with most LRTIs. This collapse may resolve by chest physiotherapy but can occasionally persist for long times.

Structural abnormalities—either congenital or acquired, can lead to recurrent LRTI. These abnormalities include tracheal bronchus, bronchiectasis, bronchial stenosis, and bronchomalacia. Other congenital anomalies of foregut development, such as congenital cystic adenomatoid malformation (CCAM), congenital lobar emphysema (CLE), bronchogenic cyst, and pulmonary sequestration, can also lead to recurrent pneumonia.⁷ CCAM's represent about 25



Figs 2A to D: Persistent pneumonia due to TB: (A) Consolidation of right lower lobe; (B) Compressed right side lower lobe bronchus; (C and D) Large necrotic mass of lymph nodes (curved arrows) compressing airways

percent of congenital lung abnormalities. Most cases are diagnosed by prenatal ultrasonography or present shortly after birth as respiratory distress. A small number of these present later associated with recurrent pneumonia caused by bronchial compression. However, it must be said that while the congenital anomalies can lead to pneumonia, both recurrently or persistently, but more often these anomalies are unmasked due to a skiagram done for intercurrent respiratory symptoms to which they may not actually be causally related.

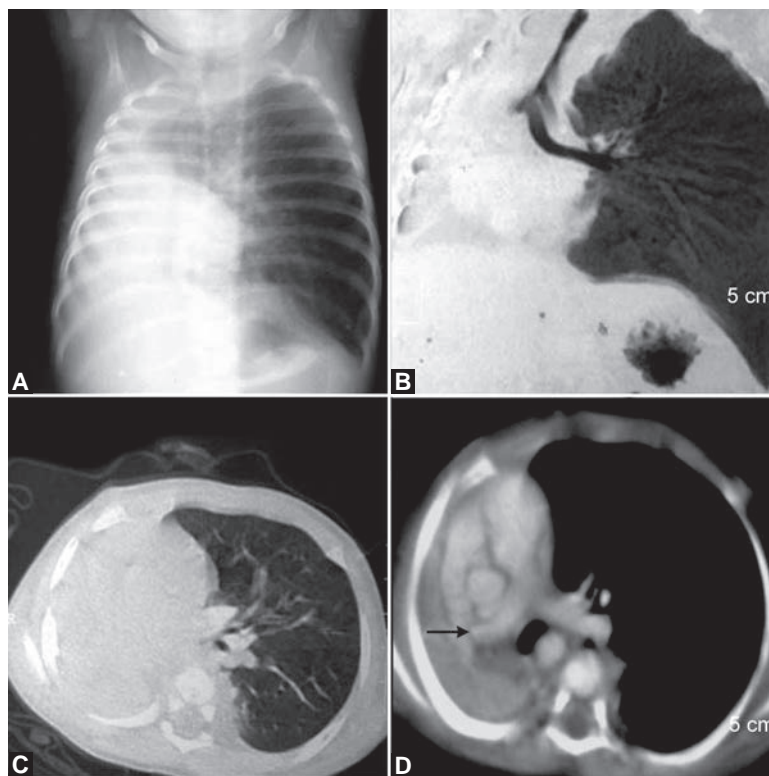
Illustrative Case 1

R, a 5-month-old male, presented with cough for 10 days and fever, fast breathing and difficulty in feeding for 3 days. On examination, there was tachypnea with decreased air entry on right side. The baby had been admitted and treated as right side consolidation about 3-4 weeks back in another hospital. He was discharged when he started feeding and respiratory rate improved. His chest X-ray shows collapsed right lung with hyperinflation of left lung, on detailed history and evaluation, it became evident that in both the episodes child had fever, cough and rapid breathing. The treating pediatrician admitted the patient after the chest skiagram showed significant

shadows. In view of the completely opaque right hemithorax a fiberoptic flexible bronchoscopy was done. It showed inflamed trachea which had a small branch on right side that too tapered off suddenly and was not negotiable further by the bronchoscope. His BAL also showed significant growth of *Acinetobacter* and *Klebsiella* sp., and the patient improved symptomatically with specific therapy though the radiological shadow persisted. CECT chest showed complete lack of pneumatization of right lung with fluid filled nondilated poorly dividing bronchial tree within the non-aerated parenchyma, with significant right sided mediastinal shift and herniation of left lung towards the right side. Proximal part of right main bronchus is aerated but distal part shows smooth tapering with nonvisualization of distal bronchus. Right pulmonary artery was also smaller in size. These findings were suggestive of hypoplasia of right lung.⁸ In this case an intercurrent chest infection unmasked the presence of the underlying lung anomaly to which it was not causally related (Figs 3A to D).

Multilobar Persistent Pneumonia

Pneumonia that occurs in multiple locations or affects more than one lobe indicates a disease process which is more generalized, that a systemic consideration must be taken for



Figs 3A to D: Hypoplasia of right lung: (A) Complete opacification of right hemithorax with hyperinflated left lung cross herniating to the right side with mediastinal shift; (B) Stump like ending of the right main bronchus; (C) Lack of any bronchial tree in the homogeneous hypoplastic right lung; (D) Hypoplastic right pulmonary artery (arrow)

evaluation. Various causes of childhood multilobar persistent/recurrent pneumonia are described in Table 2.

Aspiration is the most common cause of recurrent multifocal pneumonia in children. The location of radiographic infiltrates depends on the position the child was in when aspiration occurred.⁹

Aspiration syndromes can be divided into:

- a. Aspiration from above can occur in cases with impaired swallowing due to central nervous system (CNS)

Table 2: Enumerates some of the common causes of multilobar persistent/recurrent pneumonia

- Aspiration syndromes
 - From above—impaired swallowing
 - CNS or neuromuscular disorders
 - Anatomic abnormalities like cleft palate, laryngeal cleft, etc.
 - Esophageal obstruction or dysmotility
 - Forceful feeding
 - From below—regurgitation
 - Tracheoesophageal fistula (TEF)
 - Gastroesophageal reflux (GER)
- Infections
 - Drug resistant organisms or unusual organisms
 - Fungal pneumonia
 - PCP pneumonia
 - Hydatidosis
- Asthma
- Allergic bronchopulmonary aspergillosis
- Structural abnormalities
 - Tracheobronchomegaly,
 - Cartilage deficiency/incomplete cartilage ,
 - Segmental bronchomalacia
- Congenital heart disease
 - Left to right shunt, e.g. ventricular septal defect, atrial septal defect, patent ductus arteriosus
- Defence mechanism aberrations
 - Cystic fibrosis
 - Primary ciliary dyskinesia
- Immune deficiency disorders
 - Primary: Antibody deficiency, cell-mediated immune deficiency, complement deficiency, phagocytic defect
 - Secondary:
 - HIV
 - Iatrogenic (steroids, immunosuppressive drugs, postradiotherapy, etc.)
 - Malignancy (leukemia and lymphoma, etc.)
- Others
 - Interstitial or diffuse lung disease
 - Pulmonary hemosiderosis (PH)
 - Hypersensitivity pneumonitis (HP)
 - Alpha1-antitrypsin deficiency
 - Pulmonary alveolar proteinosis (PAP)
 - Bronchopulmonary dysplasia

disorders, neuromuscular diseases, structural abnormalities of the oropharynx, forceful feeding, esophageal obstruction—whether extrinsic (vascular rings or mediastinal masses) or intrinsic (foreign bodies or strictures). Esophageal dysmotility caused by achalasia can also lead to repeated aspiration.

Typically, in all these situations there is history of feeding difficulty with cough during feeding due to aspiration, choking like episodes along with recurrent regurgitations and difficulty in weight gain. On examination, child can have tachypnea along with wheeze and or crepts in dependent areas.

- b. Aspiration from below usually occurs in cases with tracheoesophageal fistula and gastroesophageal reflux. Most forms of TEF are diagnosed in the neonatal period, but small, H-type fistulae may not present until later in childhood, when chronic aspiration through the persistent abnormal communication leads to recurrent lower respiratory tract infection. Typically, such children have choking or coughing while drinking liquids though they may be able to accept semi-solids without any symptoms.

Gastroesophageal reflux disease (GERD) can lead to respiratory symptoms due to several mechanisms including repeated aspirations and recurrent pneumonia. Mechanisms which are involved in the respiratory diseases are by direct effect of aspiration leading to tracheitis, bronchitis, pneumonia, atelectasis, or indirectly by provoking airway hyperreactivity in response to inflammation.

There are several methods of studying GER and these include: 24 hours pH monitoring; Gastrointestinal Scintiscan (shows both acid and non-acid reflux, also can detect the pulmonary aspiration of gastric material) and Esophagoscopy (detects esophagitis confirmed by biopsy). Upper GI barium studies are usually not useful though are more sensitive for demonstration of anatomical abnormalities like hiatus hernia along with esophageal motility.

Illustrative Case 2

Patient A, a 2-year-old male presented with complaints of cough and fever for 15 days on presentation with past history of recurrent similar episodes of cough. The cough was more after meals. There were associated complaints of decreased appetite and not gaining height and weight. He had been admitted to hospital 7 times in past since the age of 2 months for treatment of an episode of pneumonia. He had history of regurgitation of feeds in neonatal period which now had decreased. On examination, his breathing was fast. His height and weight both was less than 3rd percentile. Chest examination was unremarkable except for the presence of mild distress and bilateral crackles. The chest skiagram showed bilateral basal pneumonia in lower lobes. In view of the past history of regurgitations and history of cough related to feeds, the

child was investigated for GER. On GER scintiscan there was evidence of significant reflux into the upper part of the esophagus. No tracers were seen in the bronchial tree but microaspiration could not be ruled out. The patient was treated with antireflux therapy and showed a good response in the form of no vomiting, improved appetite and improved respiratory symptoms (Figs 4A and B).

Asthma is the most common cause of recurrent/persistent infiltrate and is often misdiagnosed as recurrent or persistent pneumonia. The pathophysiology of this condition includes mucous plugging and edema of peripheral airways. Such cases can have streaky shadows or small areas of atelectasis appearing as inhomogeneous infiltrates. Collapse of the right middle lobe due to plugging in children with asthma has been well described.

Another set of patients who have recurrent chest infiltrates and respiratory symptoms are those who have allergic bronchopulmonary aspergillosis (ABPA). ABPA is suspected in children with asthma of any severity or children with cystic fibrosis (CF) who have recurrent pulmonary infiltrates, peripheral eosinophilia, and an elevated total serum IgE. A negative immediate-type skin test excludes ABPA, but the diagnosis can be established only by careful serologic studies.

In disorders of the mucociliary system, natural clearance of the airway is compromised. The physician must not overlook disorders such as CF and primary ciliary dyskinesia (PCD) as causes of recurrent lower respiratory infection. Cystic fibrosis is an inherited autosomal recessive disorder recognized by a classic triad of chronic pulmonary disease, pancreatic insufficiency, and elevated sweat chloride concentration. In cystic fibrosis, the inflammatory response initially manifests as chronic bronchiolitis and bronchitis but, ultimately, causes structural changes in the airways and produces bronchiolectasis and bronchiectasis. Sweat chloride estimation is done for establishing the diagnosis of cystic fibrosis. Recurrent pneumonia with chronic sinusitis, steatorrhea, or failure to thrive forms an indication for doing sweat chloride test.

Primary ciliary dyskinesia, another autosomal recessive disorder, is caused by ultrastructural defects in the cilia or abnormal organization of microtubules within each cilium. A child with recurrent pneumonia, chronic otitis media, or sinusitis must be evaluated for PCD, once other diagnoses such as CF and immunodeficiency, have been excluded.

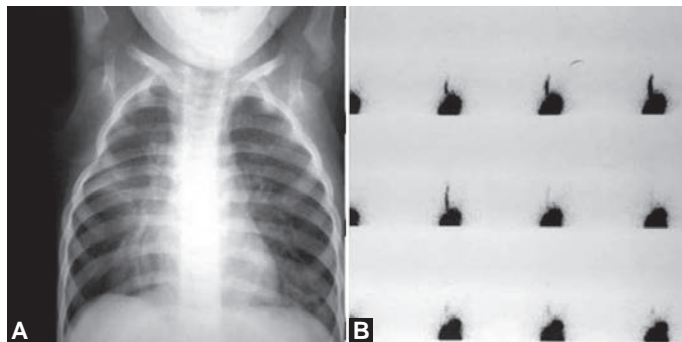
Children with congenital heart disease are predisposed to recurrent pneumonia for various reasons. Those with left to right shunt get repeated infections due to pulmonary congestion while in others an enlarged cardiac chamber and/or pulmonary arteries can cause extrinsic compression of the airway, impairing its drainage. Echocardiography helps to rule out the heart diseases, like congenital heart lesions, vascular slings, abnormally dilated heart chambers, etc. which can lead to persistent or recurrent pneumonias.

Children with BPD have risk factors that predispose them to recurrent pneumonia. These include feeding difficulties that make them susceptible to aspiration, an increased incidence of bronchomalacia, impaired airway clearance mechanisms, focal airway strictures, and a high incidence of GERD.

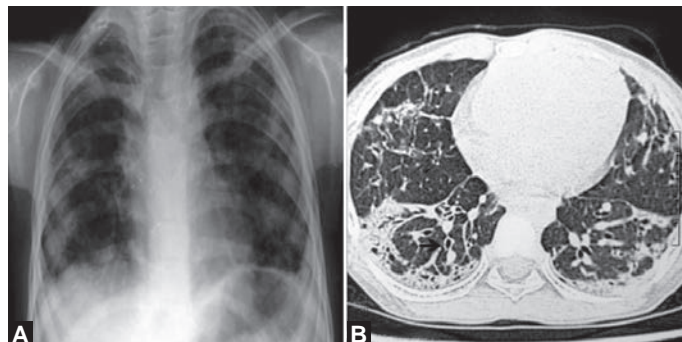
Interstitial or diffuse lung disease is not uncommonly misdiagnosed and treated as persistent pneumonia. Typically these cases do not have significant fever but otherwise have a relentlessly progressive breathlessness with persistent lung shadows.

Illustrative Case 3

Eight-year-old female, A, presented with mildly productive cough and breathing difficulty of 2 months duration. On examination, she had tachypnea and bilateral crepts along with grade 4 clubbing. CBC was unremarkable. Her chest X-ray showed infiltrates in bilateral lung fields with areas of breakdown. Her CECT chest shows interstitial septal thickening with associated ground-glass opacity and traction bronchiectasis in bilateral lungs. Her lung biopsy was done and was reported as non-specific interstitial pneumonitis (Figs 5A and B).



Figs 4A and B: Persistent pneumonia due to gastroesophageal reflux disease: (A) Patchy pneumonia in right lung predominantly in the paravertebral gutter-dependent area for a young child; (B) GER scintiscan showing reflux up to middle of esophagus



Figs 5A and B: Interstitial lung disease: (A) Inhomogeneous opacities in both lung fields with small fibrotic right lung; (B) CT chest showing areas of ground-glass shadowing with fibrosis and development of traction bronchiectasis (arrow)

The primary or secondary immunodeficiency disorders can also lead to recurrent multilobar pneumonia. The primary immunodeficiency diseases, relatively rare disorders may be characterized by severe clinical expression early in life. Primary immunodeficiencies include disorders of antibody, cell-mediated immunity, complement, and phagocytosis. Children with an antibody deficiency present with recurrent sino-pulmonary infections as well as infections outside the respiratory system due to encapsulated bacteria and enteroviruses.¹⁰

Individuals with defects in cell-mediated immunity, such as severe combined immunodeficiency (SCID), DiGeorge syndrome, and Wiskott-Aldrich syndrome (WAS), may have difficulty with recurrent pneumonia due to pyogenic bacteria, *Pneumocystis jiroveci*, and viruses. Patients with complement deficiencies most often present with bacteremia, septic arthritis, and meningitis caused by encapsulated bacteria. Phagocytic disorders such as chronic granulomatous disease (CGD) are characterized by infections of the skin, reticuloendothelial system, and respiratory tract caused by catalase-positive bacteria or fungus. Recurrent pneumonia involving different locations with a residual shadow or incomplete clearance is a hallmark of this disorder of phagocytosis.

Secondary immunodeficiency caused by chemotherapy, steroid therapy, sickle cell disease, diabetes, or human immunodeficiency virus may also presents as recurrent diffuse pneumonia. Risk factors for HIV must be assessed in a child with other recurrent infections, because respiratory infections such as *Pneumocystis jiroveci*

pneumonia are common in acquired immunodeficiency syndrome.¹

EPIDEMIOLOGY

As the etiological agents and causes vary in different regions of the world depending on the industrial development and geographical location, thus the causes and incidence of persistent pneumonia vary in different countries. Although the precise prevalence is not well established but, results of various studies are shown in Table 3.

CLINICAL PRESENTATION

Mostly the parents bring their ward with complaints which are specific for respiratory system like—cough, dyspnea, chest pain and constitutional symptoms like—fever, weight loss, fatigue/malaise, poor appetite; where according to them the condition is persisting for a long time. Presence of persistent fever, limitation of activity, persistent tachypnea and labored breathing, chronic sputum production, digital clubbing, failure to thrive, signs of severe hypoxemia, positive family history—indicates serious lower respiratory tract infection.

APPROACH TO A CASE OF PERSISTENT PNEUMONIA

It includes detailed clinical history and examination. Detailed history includes information regarding the age of onset, frequency, duration and severity of symptoms along with neonatal course, subsequent hospitalizations and

Table 3: Comparison of results of various studies

Etiology	Persistent pneumonia		Recurrent pneumonia		
	Lodha et al ¹¹ n=19	Kumar et al ¹² n=41	Lodha et al ¹³ RP-70	Owayed et al ⁹ n=238	Eigen et al ¹⁴ n=81 (RP-69%)
Bronchiectasis	52.6%	—	7.1%	—	5%
Aspirations	10.5%	29.3%	24.2%	47.9%	40%
Asthma	26.3%	—	14.2%	8%	—
Immunodeficiency	5.2%	7.3%	15.7%	14.3%	5%
Infection		29.3%	—	—	15%
Tuberculosis		19.2%	—	—	—
Structural anomalies		4.9%	8.6%	7.6%	15%
Foreign body	5.2%	2.4%	5.7%	—	—
Ciliary dyskinesia	5.2%	—	7.1%	—	—
Cystic fibrosis		—	—	—	—
Slowly resolving pneumonia		—	—	—	—
Undiagnosed cases	16%	2.4%	15.7%	7.6%	75%

RP—Recurrent pneumonia; PP—Persistent pneumonia

operations. History regarding feeding problems, immunization status, any history suggestive of foreign body aspiration and allergy/atopy; along with this family history of hereditary disorder, allergy/atopy and environmental history is also important. Physical examination includes vitals, detailed anthropometry along with changes in skin and extremities (cyanosis, clubbing, rashes), any signs of pyogenic infections, presence of conjunctivitis, ENT examination, respiratory system examination, cardiovascular system for congenital heart disease, dextrocardia (assoc. with immotile cilia syndrome), nervous system—for swallowing difficulties and neuromuscular diseases, and abdominal examination.

INVESTIGATIONS

These are divided into routine (forms the basic investigations for almost all cases) and advance (done on as indicated basis).

Routine Investigations

These are done as baseline work up in a case of persistent pneumonia, before deciding the specific investigation which helps in final diagnosis and treatment. These include:

1. *Complete hemogram*: A complete blood count is used to assess anemia or polycythemia, abnormal numbers, differential makeup of leukocytes and thrombocytopenia (associated with immunological disorders such as Wiskott-Aldrich syndrome (characterized by recurrent infections and autoimmune disorders), primary hematologic cytopenia's like in aplastic anemia leading to secondary infections or suppression by disseminated virus infection). It also includes absolute eosinophil count (AEC), erythrocyte sedimentation rate (ESR), which are helpful in certain diagnosis like asthma, allergic disorders and tuberculosis, etc. Eosinophilia is

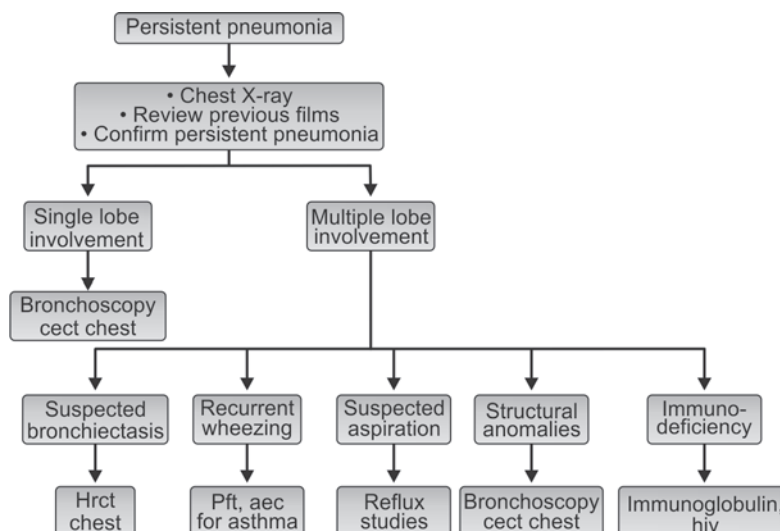
present when absolute eosinophil count (AEC) exceeds $0.4 \times 10^9/L$ and is seen in ABPA, eosinophilic pneumonias, asthma, collagen disorders, etc.

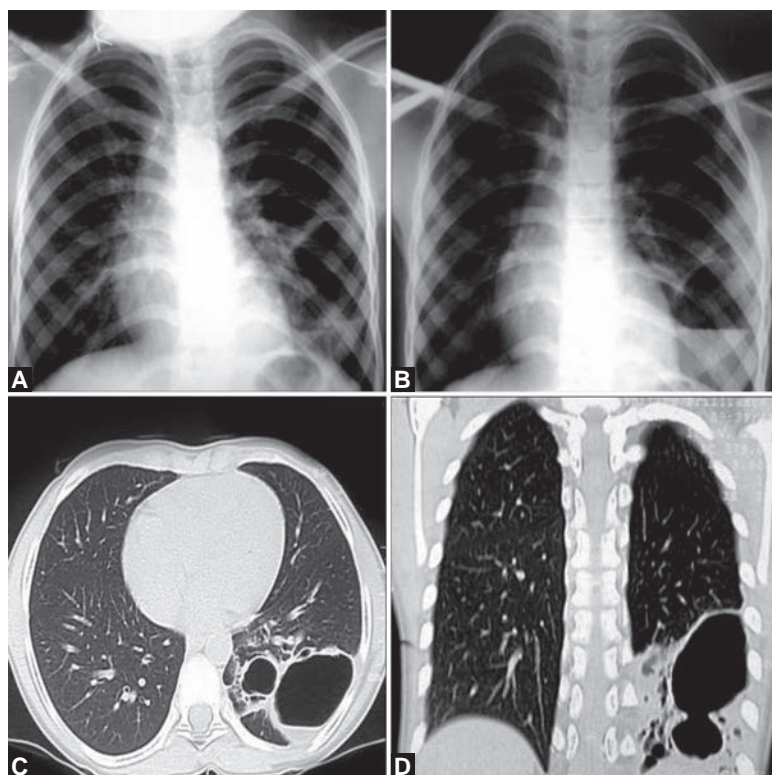
2. *Chest X-ray*: Skiagram of the chest not only forms an important basis of diagnosis and classification of infiltrates while defining disease but also helps in confirming the diagnosis, area involved, suggesting etiology and facilitates follow-up. Often such cases come with several investigations including skiagrams. These films should be arranged in serial order, to decide whether the disease is recurrent or persistent; unilobar or multilobar. Further work-up is planned to make correct diagnosis.
3. Tests for TB including tuberculin skin test and gastric aspirates for acid fast bacilli are commonly used in children with persistent or non-resolving pneumonia who are suspected of tuberculosis.

Special Investigations

The approach of unilobar or multilobar division of persistent/recurrent pneumonia helps in deciding the investigation to be chosen for the diagnosis and then treating the patient as shown in Flow chart 1. In the patients with single lobe involvement, the first in the diagnostic workup is bronchoscopy, as this allows diagnosis- like intraluminal obstructive lesions (bronchial adenoma, lipoma) foreign body, tracheal bronchus, etc. It also provides sample for microbiological investigation for any a resistant bug or unusual organism. This also helps in therapeutic intervention in cases of foreign body aspiration. If bronchoscopy is normal or inconclusive, CECT chest is another investigation which is useful in such situations as it can help find extrabronchial obstruction, bronchiectasis, distal intraluminal obstructions, structural lesions like- sequestrations, CCAM (Figs 6A to D).

Flow chart 1: Diagnostic tests for investigating persistent pneumonia





Figs 6A to D: Sequestration of lung: (A and B) Persistent cystic lesion in left lower lobe with air-fluid level, (C and D) CECT chest confirms a multicystic lesion with systemic blood supply (not seen here) and confirmed on excision

In cases involving multiple lobes and different lobes at different times, a more generalized disease should be suspected- like aspirations due to gastroesophageal reflux, asthma, immunodeficiency, cystic fibrosis, etc. and investigations for them should be planned. Lung biopsy helps in confirming the diagnosis and starting specific therapy in certain diffuse lung diseases like interstitial lung disease, cryptogenic fibrosis, hemosiderosis, etc.

CONCLUSION

Persistent pneumonia though uncommon, can be very distressing both for the patient and the pediatrician. It needs a very detailed work up using a range of investigations of which CECT and bronchoscopy appear to be the mainstay followed by investigations for aspiration. There is an array of investigations available, of which only few may be needed for an individual case. The choice of investigation is predicted by the clinical history, signs, type of radiological shadow, involvement of single/multiple lobes, etc. This can sometimes be very frustrating as no specific diagnosis may be reached in some of the patients.

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Sunil Dutt Sharma, Hina Rizvi

ACUTE SINUSITIS**Abstract**

Sinusitis is a common illness of adolescents and childhood with significant acute and chronic morbidity as well as the potential for serious complications. Therefore, understanding is necessary for the following reason:

- For the efficacy of various antibiotics in children
- For the efficacy of various ancillary, nonantibiotic regimens
- The diagnostic accuracy and concordance of clinical symptoms, radiography (and other imaging methods) and sinus aspirations.

It is recommended that the diagnosis of acute bacterial sinusitis be based on clinical criteria in children 6 years of age who present with upper respiratory symptoms that are either persistent or severe. Although controversial, imaging studies may be necessary to confirm a diagnosis of acute bacterial sinusitis in children >6 years of age.

Computed tomography scans of the paranasal sinuses should be reserved for children who present with complications of acute bacterial sinusitis or who have very persistent or recurrent infections and are not responsive to medical management.

Acute bacterial sinusitis should be treated with antimicrobial therapy to achieve a more rapid clinical cure. Children with complications or suspected complications of acute bacterial sinusitis should be treated promptly and aggressively with antibiotics and, when appropriate, drainage.

Background

The ethmoid and the maxillary sinuses form in the third to fourth gestational month and, accordingly, are present at birth. The sphenoid sinuses are generally pneumatized by 5 years of age; the frontal sinuses appear at age 7 to 8 years

but are not completely developed until late adolescence. The paranasal sinuses are a common site of infection in children and most viral infections of the upper respiratory tract involve the nose and the paranasal sinuses (viral rhinosinusitis). However, bacterial infections of the paranasal sinuses do not usually involve the nose. When the patient with bacterial infection of the paranasal sinuses has purulent (thick, colored and opaque) nasal drainage, the site of infection is the paranasal sinuses; the nose is simply acting as a conduit for secretions produced in the sinuses.

The common predisposing events that set the stage for acute bacterial sinusitis are acute viral upper respiratory infections that result in a viral rhinosinusitis (a diffuse mucositis that predisposes to approximately 80 percent of bacterial sinus infections) and allergic inflammation (that predisposes to 20 percent of bacterial sinus infections). Children have 6 to 8 viral upper respiratory infections each year; it is estimated that between 5 to 13 percent of these infections may be complicated by a secondary bacterial infection of the paranasal sinuses.

Definitions

- *Acute Bacterial Sinusitis*: Bacterial infection of the paranasal sinuses lasting less than 30 days in which symptoms resolve completely
- *Subacute bacterial sinusitis*: Bacterial infection of the paranasal sinuses lasting between 30 and 90 days in which symptoms resolve completely
- *Recurrent acute bacterial sinusitis*: Episodes of bacterial infection of the paranasal sinuses, each lasting less than 30 days and separated by intervals of at least 10 days during which the patient is asymptomatic
- *Chronic sinusitis*: Episodes of inflammation of the paranasal sinuses lasting more than 90 days. Patients have persistent residual respiratory symptoms such as cough, rhinorrhea or nasal obstruction

- *Acute bacterial sinusitis superimposed on chronic sinusitis:* Patients with residual respiratory symptoms develop new respiratory symptoms. When treated with antimicrobials, these new symptoms resolve, but the underlying residual symptoms do not.

Etiology

- *Streptococcus pneumoniae* (30%), *Haemophilus influenzae* (20%), *Moraxella catarrhalis* (20%) are major causes. Uncommon causes include *Staphylococcus aureus*, other streptococci, and anaerobes. *H. influenzae*, β -hemolytic streptococci, *M. catarrhalis*, *S. pneumoniae* and coagulase -ve staph are commonly recovered from children with chronic sinus disease
- Predisposing factors are viral upper respiratory infection, allergic rhinitis, cigarette smoke exposure, immune deficiencies (particularly IgG), cystic fibrosis, abnormalities of phagocyte function, GE reflux, anatomic defects (cleft palate), nasal polyps and nasal foreign bodies. Immunosuppression for bone marrow transplantation or malignancy with profound neutropenia and lymphopenia predisposes to severe fungal (*Aspergillus*, mucor) sinusitis, often with intracranial extension. Patients with nasotracheal intubation and nasogastric tubes may have obstruction of the sinus ostia and develop sinusitis with multiple drug resistant organisms of ICU.

Clinical Manifestations

Children with severe onset of acute bacterial sinusitis may have an intense headache that is above or behind the eye; in general, they seem to be moderate. Unfortunately, the physical examination does not generally contribute substantially to the diagnosis of acute bacterial sinusitis. This is explained by the similarity of physical findings in the patient with an uncomplicated viral rhinosinusitis and the patient with acute bacterial sinusitis. In both instances, examination of the nasal mucosa may show mild erythema and swelling of the nasal turbinates with mucopurulent discharge.

Facial pain is an unusual complaint in children. Facial tenderness is a rare finding in small children and may be unreliable as an indicator of acute bacterial sinusitis in older children and adolescents. Reproducible unilateral pain, present on percussion or direct pressure over the body of the frontal and maxillary sinuses, may indicate a diagnosis of acute bacterial sinusitis. Likewise, observed or reported periorbital swelling is suggestive of ethmoid sinusitis. Low-grade fever may be periodic but is usually not prominent.

Diagnosis

For children 6 years of age or younger, because a positive history predicts the finding of abnormal sinus radiographs so frequently (and because history plus abnormal

radiographs results in a positive sinus aspirate in 75% of cases), radiographs can be safely omitted and a diagnosis of acute bacterial sinusitis can be made on clinical criteria alone.

In children older than 6 years the American College of Radiology has taken the position that the diagnosis of acute uncomplicated sinusitis should be made on clinical grounds. They support this position by noting that plain radiographs of the paranasal sinuses are technically difficult to perform, particularly in very young children alone. It is essential to recognize that abnormal images of the sinuses (either radiographs, CT scan or magnetic resonance imaging) cannot stand alone as diagnostic evidence of acute bacterial sinusitis under any circumstances.

Images can serve only as confirmatory measures of sinus disease in patients whose clinical histories are supportive of the diagnosis. Numerous investigations have demonstrated the high frequency of abnormal images in the paranasal sinuses of children undergoing imaging for indications other than suspected sinusitis. <http://aappolicy.aappublications.org/cgi/content/full/pediatrics;108/3/748-838>. Computed tomography scans are indicated in children who present with complications of acute bacterial sinus infection or those who have very persistent or recurrent infections that are not responsive to medical management. In these instances, the image, preferably a complete CT scan of the paranasal sinuses, is essential to provide precise anatomic information to the clinician. These are instances in which the physician may be contemplating surgical intervention, including aspiration of the paranasal sinuses.

Patients with recurrent acute bacterial sinusitis are defined as having had 3 episodes of acute bacterial sinusitis in 6 months or 4 episodes in 12 months. The response to antibiotics is usually brisk and the patient is completely free of symptoms between episodes.

Persistent symptoms are those that last longer than 10 to 14, but less than 30 days. Such symptoms include nasal or postnasal discharge (of any quality), day time cough (which may be worse at night), or both.

Severe symptoms include a temperature of at least 102°F (39°C) and purulent nasal discharge present concurrently for at least 3 to 4 consecutive days in a child who seems ill.

The child who seems toxic should be hospitalized and is not considered in this algorithm. It is the concurrent presentation with high fever and purulent nasal discharge for at least 3 to 4 consecutive days that helps to define the severe presentation of acute bacterial sinusitis.

Sinus aspirate culture is the only accurate method but is not practical for routine use of immunocompetent patients. It may be necessary for immunocompromised patients with suspected fungal sinusitis. To promote the judicious use of antibiotics, it is essential that children diagnosed as having acute bacterial sinusitis meet the

defining clinical presentations of “persistent” or “severe” disease as described previously.

Transillumination of the sinus cavities may demonstrate the presence of fluid but cannot reveal whether it is viral or bacterial in origin. In children it is difficult to perform and unreliable.

Treatment

American Academy of Pediatrics (AAP) recommends antimicrobial treatment for acute bacterial sinusitis to promote resolution of symptoms and prevent suppurative complications, although 50 to 60 percent of children recover without antimicrobial therapy. To promote the judicious use of antibiotics, it is essential that children diagnosed as having acute bacterial sinusitis meet the defining clinical presentations of “persistent” or “severe” disease as described previously (Flow chart 1). Currently, approximately 50 percent of *H. influenzae* and 100 percent of *M. catarrhalis* are likely to be β -lactamase positive nationwide. Upper respiratory tract isolates of *S. pneumoniae* are not susceptible to penicillin in 15 to 38 percent (average 25%) of children; approximately 50 percent are highly resistant to penicillin and the remaining half are intermediate in resistance. The mechanism of penicillin resistance in *S. pneumoniae* is an alteration of penicillin binding proteins. The desire to continue to use amoxicillin as first-line therapy in patients suspected of having acute bacterial sinusitis relates to its general effectiveness, safety, and tolerability; low cost, and narrow spectrum.

For children younger than 2 years of age with uncomplicated acute bacterial sinusitis that is mild to moderate in degree of severity, who do not attend day care, and have not recently been treated with an antimicrobial, amoxicillin is recommended at either a usual dose of 45 mg/kg/d in 2 divided doses or a high dose of 90 mg/kg/d in 2 divided doses. If the patient is allergic to amoxicillin, either cefdinir (1 mg/kg/d in 1 or 2 doses), cefuroxime (30 mg/kg/d in 2 divided doses), or cefpodoxime (10 mg/kg/d once daily) can be used (only if the allergic reaction was not a type 1 hypersensitivity reaction). In cases of serious allergic reactions, clarithromycin (15 mg/kg/d in 2 divided doses) or azithromycin (10 mg/kg/d on day 1, 5 mg/kg/d \times 4 days as a single daily dose) can be used in an effort to select an antimicrobial of an entirely different class.

The food and drug administration has not approved azithromycin for use in patients with sinusitis. Alternative therapy in the penicillin-allergic patient who is known to be infected with a penicillin-resistant *S. pneumoniae* is clindamycin at 30 to 40 mg/kg/d in 3 divided doses.

Most patients with acute bacterial sinusitis who are treated with an appropriate antimicrobial agent respond promptly (within 48-72 hours) with a diminution of respiratory symptoms (reduction of nasal discharge and cough) and an improvement in general well-being. If a patient fails to improve, either the antimicrobial is ineffective or the diagnosis of sinusitis is not correct.

If patients do not improve while receiving the usual dose of amoxicillin (45 mg/kg/d), have recently been treated with an antimicrobial, have an illness that is moderate or more severe, or attend day care, therapy should be initiated with high-dose amoxicillin-clavulanate (80-90 mg/kg/d of amoxicillin component, with 6.4 mg/kg/d of clavulanate in 2 divided doses). This dose of amoxicillin will yield sinus fluid levels that exceed the minimum inhibitory concentration of all *S. pneumoniae* that are intermediate in resistance to penicillin and most, but not all, highly resistant *S. pneumoniae*. There is sufficient potassium clavulanate to inhibit all β -lactamase producing *H. influenzae* and *M. catarrhalis*. Alternative therapies include cefdinir, cefuroxime, or cefpodoxime.

A single dose of ceftriaxone (at 50 mg/kg/d), given either intravenously or intramuscularly, can be used in children with vomiting that precludes administration of oral antibiotics. Twenty-four hours later, when the child is clinically improved, an oral antibiotic is substituted to complete the therapy.

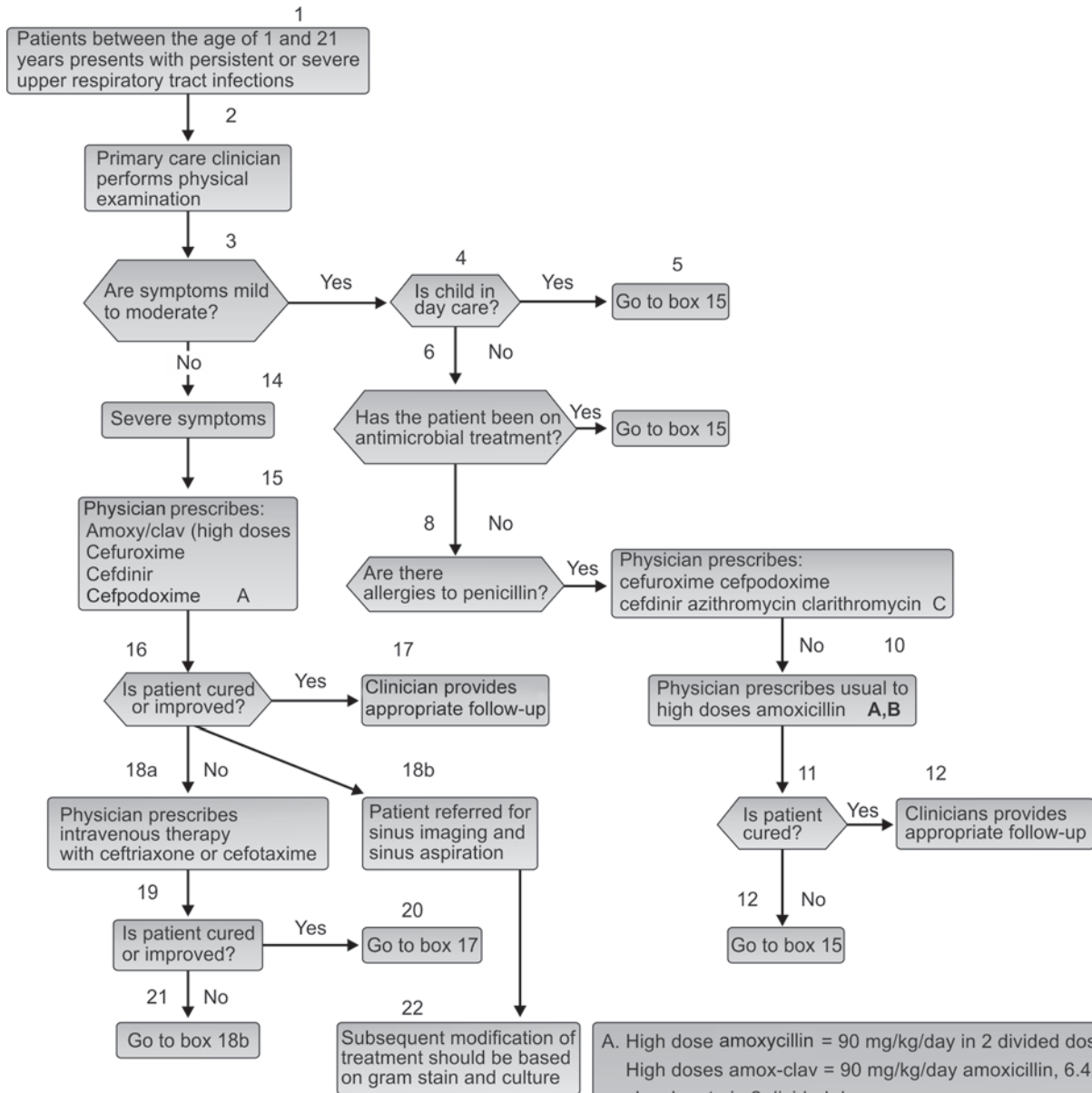
For patients who do not improve with a second course of antibiotics or who are acutely ill, there are 2 options. It is appropriate to consult an otolaryngologist for consideration of maxillary sinus aspiration to obtain a sample of sinus secretions for culture and sensitivity so that therapy can be adjusted precisely. Alternatively, the physician may prescribe intravenous cefotaxime or ceftriaxone (either in hospital or at home) and refer to an otolaryngologist only if the patient does not improve on intravenous antibiotics. Some authorities recommend performing cultures of the middle meatus instead of aspiration of the maxillary sinus to determine the cause of acute bacterial sinusitis. However, there are no data in children that have correlated cultures of the middle meatus with cultures of the maxillary sinus aspirate. <http://aapolicy.aappublications.org/cgi/content/full/pediatrics;108/3/798-854>.

The optimal duration of therapy for patients with acute bacterial sinusitis has not received systematic study. Often empiric recommendations are made for 10, 14, 21, or 28 days of therapy. An alternative suggestion has been made that antibiotic therapy be continued until the patient becomes free of symptoms and then for an additional 7 days. This strategy, which individualizes treatment for each patient, results in a minimum course of 10 days and avoids prolonged courses of antibiotics in patients who are asymptomatic and thereby unlikely to be compliant.

The use of decongestants, antihistaminics, mucolytics and intranasal corticosteroids have not been adequately studied in children and are not recommended for the treatment of acute uncomplicated bacterial sinusitis.

Complications

The complications of acute bacterial sinusitis usually involve either the orbit, the central nervous system, or both. Although rare, complications can result in

Flow chart 1: Management of a child between 1 year and 21 years with source acute upper respiratory tract infection

- A. High dose amoxycillin = 90 mg/kg/day in 2 divided doses.
High doses amox-clav = 90 mg/kg/day amoxicillin, 6.4 mg/kg/day clavulanate in 2 divided doses.
- B. Usual doses amoxicillin=45 mg/kg/day in 2 divided doses
- C. Most patients with allergy to penicillin will tolerate cephalosporins.
If allergy manifests as anaphylaxis, macrolides should be prescribed instead of cephalosporins:
1. Cefuroxime 30 mg/kg/day in 2 divided doses
 2. Cefpodoxime 10 mg/kg/day once daily
 3. Cefdinir 14 mg/kg/day once daily
 4. Azithromycin 10 mg/kg/day on day 1; 5mg/kg single daily dose for 4 days
 5. Clarithromycin 15 mg/kg/day in 2 divided doses

permanent blindness or death if not treated promptly and appropriately.

Periorbital and intraorbital inflammation and infection are the most common complications of acute sinusitis and most often are caused by acute ethmoiditis. These disorders are commonly classified in relation to the orbital septum. The orbital septum is a sheet of connective tissue continuous with the periosteum of the orbital bones that separates tissues of the eyelid from those of the orbit. Preseptal inflammation involves only the eyelid, whereas postseptal inflammation involves structures of the orbit. Complications can be classified as 1) periorbital (or preseptal) cellulitis or sympathetic edema (periorbital cellulitis is not a true orbital complication. The periorbital swelling is attributable to passive venous congestion; infection is confined to the paranasal sinuses, 2) subperiosteal abscess, 3) orbital abscess, 4) orbital cellulitis, or 5) cavernous sinus thrombosis.

Mild cases of periorbital cellulitis (eyelid <50% closed) may be treated with appropriate oral antibiotic therapy as an outpatient with daily patient encounters. However, if the patient has not improved in 24 to 48 hours or if the infection is progressing rapidly, it is appropriate to admit the patient to the hospital for antimicrobial therapy consisting of intravenous ceftriaxone (100 mg/kg/d in 2 divided doses) or ampicillin-sulbactam (200 mg/kg/d in 4 divided doses). Vancomycin (60 mg/kg/d in 4 divided doses) may be added in children in whom infection is either known or likely to be caused by *S. pneumoniae* that are highly resistant to penicillin. If proptosis, impaired visual acuity, or impaired extraocular mobility are present on examination, a CT scan (preferably coronal thin cut with contrast) of the orbits/sinuses is essential to exclude a suppurative complication. In such cases, the patient should be evaluated by an otolaryngologist and an ophthalmologist.

Suppurative complications generally require prompt surgical drainage. An exception to this is the patient with a small subperiosteal abscess and minimal ocular abnormalities for whom intravenous antibiotic treatment for 24 to 48 hours is recommended while performing frequent visual and mental status checks. Patients who have changes in visual acuity or mental status or who fail to improve within 24 to 48 hours require prompt surgical intervention and drainage of the abscess. Antibiotics can be altered, if inappropriate, when results of culture and sensitivity studies become available.

In patients with altered mental status, neurosurgical consultation is indicated. Signs of increased intracranial pressure (headache and vomiting) or nuchal rigidity require immediate CT scanning (with contrast) of the brain, orbits, and sinuses to exclude intracranial complications such as cavernous sinus thrombosis, osteomyelitis of the frontal bone (Pott's puffy tumor), meningitis, subdural empyema, epidural abscess and brain abscess. Central

nervous system complications, such as meningitis and empyemas should be treated either with intravenous cefotaxime or ceftriaxone and vancomycin pending the results of culture and susceptibility testing.

Other complications include osteomyelitis of the frontal bone (*Pott puffy tumor*), which is characterized by edema and swelling of the forehead and *mucoceles*, which are chronic inflammatory lesions commonly located in the frontal sinuses that can expand, causing displacement of the eye with resultant diplopia. Surgical drainage is usually required.

Conclusion

This clinical practice guideline provides evidence-based recommendations for the management of bacterial rhinosinusitis in children ages 1 to 21 years. The guideline emphasizes

- Appropriate diagnosis in children who present with persistent or severe upper respiratory symptoms
- The utility of imaging studies to confirm a diagnosis
- Treatment therapies such as antibiotic use including prophylaxis, adjuvant treatment, and alternative interventions
- Management of complications.

The guideline provides decision-making strategies for managing sinusitis to assist primary care providers in diagnosing and treating children with this common health problem.

OTITIS MEDIA

Otitis media (OM) figures importantly in differential diagnosis of fever in children. Its peak incidence and prevalence is from 6 to 20 months of age. An important characteristic of OM is its propensity to become chronic and recur. The earlier in life a child experiences the 1st episode, the greater the degree of subsequent difficulty in terms of frequency of recurrence, severity and persistence of middle ear effusion.

The term *otitis media* has 2 main components: acute or suppurative otitis media (AOM); and inflammation accompanied by effusion termed nonsuppurative or secretory otitis media or otitis media with effusion (OME). These two are interrelated. Middle ear effusion is a feature of both AOM and OME.

Definition

- A diagnosis of AOM requires
 - A history of acute onset of signs and symptoms,
 - The presence of MEE, and
 - Signs and symptoms of middle-ear inflammation
 Elements of the definition of AOM are all of the following
- Recent, usually abrupt, onset of signs and symptoms of middle-ear inflammation and MEE

The presence of MEE that is indicated by any of the following

- Bulging of the tympanic membrane
- Limited or absent mobility of the tympanic membrane
- Air-fluid level behind the tympanic membrane
- Otorrhea
- Signs or symptoms of middle-ear inflammation as indicated by either
 - Distinct erythema of the tympanic membrane or
 - Distinct otalgia (discomfort clearly referable to the ear[s] that results in interference with or precludes normal activity or sleep).

Epidemiology

Age highest rates during the ages of 6 to 20 months. After 2 years of age the incidence and prevalence of OM decline progressively although the disease remains relatively common into the early school age years. The most likely reasons for higher rates in infants and younger children include less well developed immunologic defenses and less favorable eustachian tubal factors involving both structure and function of the tube. The incidence is greater in boys than girl. Otitis media has a heritable component. There is higher degree of concordance among monozygotic twins than among dizygotics. Poverty, crowding, limited hygienic facilities, suboptimal nutritional status, limited access to medical care, limited resources for complying with prescribed medical regimens are predisposing factors. Breast milk has a protective effect as compared to formula feed. There is a significant link between tobacco smoke and OM. Many studies give a positive correlation between the occurrence of OM and extent of repeated exposure to other children whether at home or out of home day care. The highest rates of occurrence are observed in cold weather and the lowest during warm weather, in keeping with the pattern of URTIs.

Otitis media is universal among infants with unrepaired palatal clefts and also highly prevalent among children with submucous cleft palate, other craniofacial anomalies and Down syndrome. It is due to deficiency in functioning of the eustachian tube.

Vaccination of infants with a conjugate pneumococcal vaccine leads to the modest reduction in the incidence of otitis media.

Etiology

Numerous studies have shown that the common pathogens in AOM are *Streptococcus pneumoniae*, nontypeable *H. influenzae*, and *M. catarrhalis*. *S. pneumoniae* has been recovered from the middle-ear fluid of approximately 25 to 50 percent of children with AOM, *H. influenzae* from 15 to 30 percent, and *M. catarrhalis* from approximately 3 to 20 percent. There is some evidence that the microbiology of AOM may be changing as a result of routine use of the

heptavalent pneumococcal vaccine. Block et al. showed an increase in *H. Influenzae* from 39 to 52 percent of isolates in children 7 to 24 months of age with AOM and a decrease in *S. pneumoniae* from 49 to 34 percent between 1992 to 1998 and 2000 to 2003. Viruses, including respiratory syncytial virus, rhinovirus, coronavirus, parainfluenza, adenovirus, and enterovirus, have been found in respiratory secretions and/or MEE in 40 to 75 percent of AOM cases and in MEE without bacteria in 5 to 22 percent of cases and may be responsible for many cases of apparent antibacterial agent “failure.” In approximately 16 to 25 percent of cases of AOM, no bacterial or viral pathogen can be detected in MEE pathogens typically found in AOM can be recovered in approximately 30 percent of children with OME using standard culture techniques.²

Pathogenesis

In relation to middle ear, eustachian tube has 3 main functions: ventilation, protection and clearance, most important being ventilation. Middle ear mucosa depends on a continuous supply of air from the nasopharynx via eustachian tube. Interruption of this ventilator process by tubal obstruction initiates a complex inflammatory response that includes secretory metaplasia, compromise of mucociliary transport system and effusion of liquid into the tympanic cavity. Impaired middle ear ventilation is an important contributing factor to both AOM and OME.

Eustachian tube obstruction may result extraluminally from hypertrophied nasopharyngeal adenoid tissue, or tumor; or intraluminally, from inflammatory edema of tubal mucosa; most commonly as a consequence of viral URTI; or from impairment of the opening mechanism of tube attributable to abnormal tubal muscular function or excessive tubal wall compliance, or both. Progressive reduction in tubal wall compliance with increasing age may help explain the decline in the occurrence of OM as children grow older. The shorter and more horizontal orientation of the tube in infants and young children may increase the likelihood of reflux from the nasopharynx and impair passive gravitational drainage through the eustachian tube. Another possible explanation for improved eustachian tube function and decreased OM incidence as infants mature is that the luminal diameter increases, reducing the opportunity for tubal obstruction and dysfunction.

In children with cleft palate, where OM is a nearly universal finding, the main factor underlying the chronic middle-ear inflammation is impairment of the opening mechanism of the eustachian tube, due perhaps to greater-than-normal compliance of the tubal wall. Another possible factor is defective velopharyngeal valving, which may result in disturbed aerodynamic and hydrodynamic relationships in the nasopharynx and proximal portions of the eustachian tube. In children with other craniofacial anomalies or with down syndrome, the high prevalence of OM is

attributed to structural and/or functional eustachian tubal abnormalities; histologic evaluation of the eustachian tube in these patient populations demonstrates such abnormalities. Many, if not most, episodes are initiated by a viral or bacterial upper respiratory tract infection. In a study of children in group day care, IgA deficiency is found in some children with recurrent AOM, but its significance is questionable, because IgA deficiency is not uncommon in children without recurrent AOM. Selective IgG subclass deficiencies (despite normal total serum IgG) may be found in children with recurrent AOM in association with recurrent sinopulmonary infection; these deficiencies probably underlie the susceptibility to infection.

Evidence that respiratory allergy is a primary etiologic agent in OM is not convincing, however, in children who have both allergies and OM, it seems possible that the otitis may be aggravated by the allergy.

Ample evidence exists that children with frequent exposure to other children have an increased risk of both nasopharyngeal colonization and acute OM pathology with bacterial types with multiple antimicrobial resistances, making treatment more difficult and prolonged pathology more likely.

Clinical Manifestations

Signs and symptoms of AOM are highly variable, especially in infants and young children. There may be evidence of ear pain, often manifested by irritability, a change in sleeping or eating habits, and, occasionally, holding or tugging at the ear. Pulling at the ear, however, has a low sensitivity and specificity. Fever also may be present and, rarely, rupture of the tympanic membrane with purulent otorrhea. Systemic symptoms and symptoms associated with upper respiratory tract infections also occur, and occasionally there may be no symptoms, with AOM discovered at a routine health examination. OME often is not accompanied by overt complaints of the child but usually is accompanied by hearing loss. This hearing loss may manifest as changes in speech patterns but often goes undetected if it is unilateral or mild, especially in younger children. Balance difficulties or dysequilibrium also can be associated with OME, and older children may complain of mild discomfort or a sense of fullness in the ear (Flow chart 2).

Diagnosis

The presence of MEE is commonly confirmed with the use of pneumatic otoscopy but can be supplemented by tympanometry and/or acoustic reflectometry. MEE also can be demonstrated directly by tympanocentesis or the presence of fluid in the external auditory canal as a result of tympanic membrane perforation.

Visualization of the tympanic membrane with identification of an MEE and inflammatory changes is necessary to establish the diagnosis with certainty. To visualize the

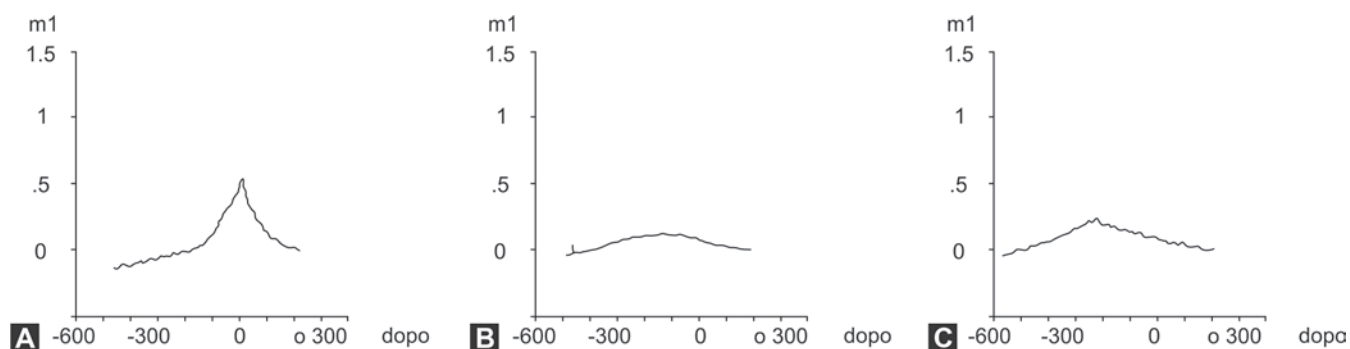
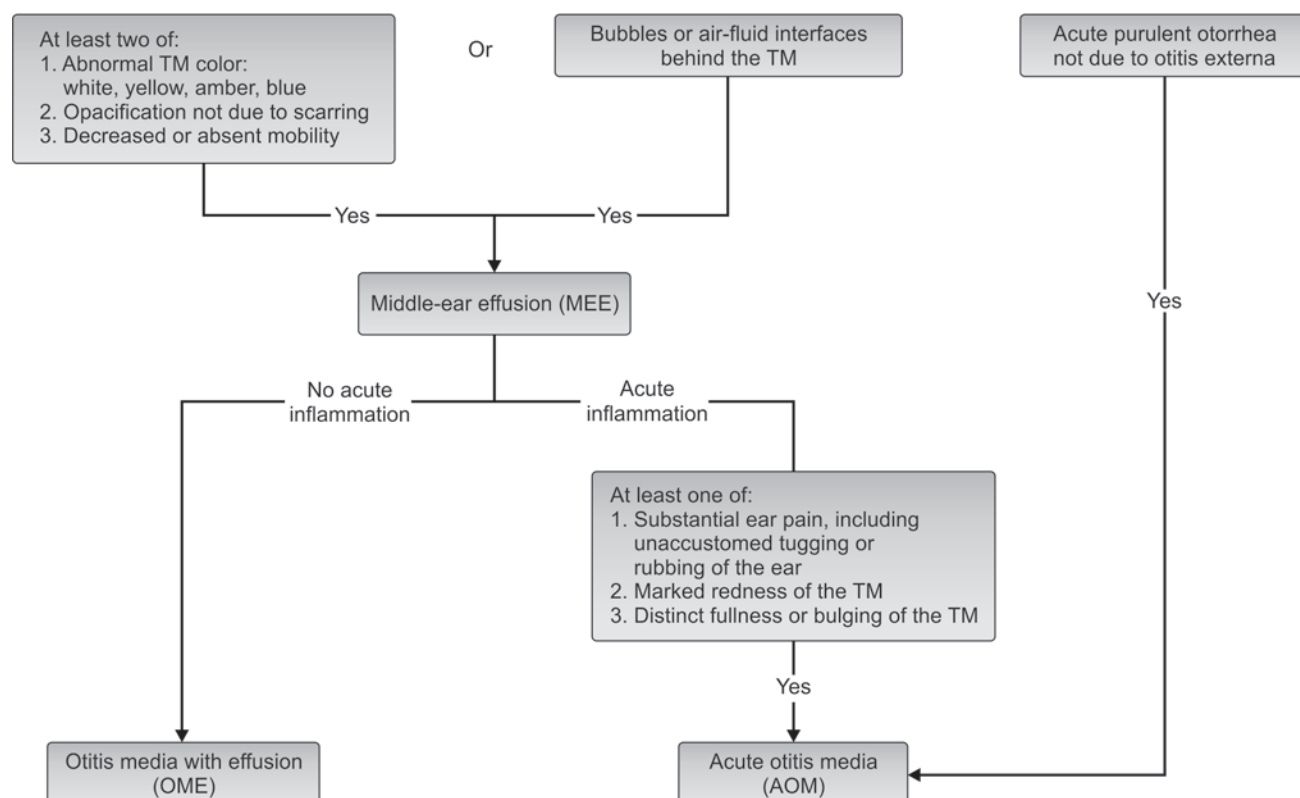
tympanic membrane adequately it is essential that cerumen obscuring the tympanic membrane be removed and that lighting is adequate. For pneumatic otoscopy, a speculum of proper shape and diameter must be selected to permit a seal in the external auditory canal. Appropriate restraint of the child to permit adequate examination may be necessary.

The findings on otoscopy indicating the presence of MEE and inflammation associated with AOM have been well defined. Fullness or bulging of the tympanic membrane is often present and has the highest predictive value for the presence of MEE. When combined with color and mobility, bulging is also the best predictor of AOM. Reduced or absent mobility of the tympanic membrane during performance of pneumatic otoscopy is additional evidence of fluid in the middle ear. Opacification or cloudiness, other than that caused by scarring, is also a consistent finding and is caused by edema of the tympanic membrane. Redness of the tympanic membrane caused by inflammation may be present and must be distinguished from the pink erythematous flush evoked by crying or high fever, which is usually less intense and remits as the child quiets down. In bullous myringitis, blisters may be seen on the tympanic membrane. When the presence of middle-ear fluid is difficult to determine, the use of tympanometry or acoustic reflectometry can be helpful in establishing a diagnosis.

Correct diagnosis of AOM is important to guide clinical treatment decisions. Although in many instances an accurate diagnosis can be made easily, this can be a challenging task, especially with an uncooperative patient. Consensus guidelines defining the required elements for a diagnosis of OM include all of the following elements: (1) recent and usually acute onset of illness, (2) presence of MEE, and (3) signs and symptoms of middle-ear inflammation, including erythema of the tympanic membrane or otalgia. A simplified differentiating schema establishes a diagnosis of AOM when, in addition to having MEE, a child gives evidence of recent, clinically important ear pain or the tympanic membrane shows marked redness or distinct fullness or bulging.

Tympanograms may be grouped into 1 of 3 categories (Figs 1A to C). Tracings characterized by a relatively steep gradient, sharp-angled peak, and middle-ear air pressure (location of the peak in terms of air pressure) that approximate atmospheric pressure (Fig. 1A) (type A curve) are assumed to indicate normal middle-ear status. Tracings characterized by a shallow peak or no peak and by negative or indeterminate middle-ear air pressure, and often termed flat or (type B curve) (Fig. 1B), usually are assumed to indicate the presence of a middle-ear abnormality that is causing decreased tympanic membrane compliance. The most common such abnormality, by far in infants and children, is MEE. Tracings characterized by intermediate findings—a somewhat shallow peak, often in association

Flow chart 2: Distinguishing between acute otitis media (AOM) and otitis media with effusion (OME). Tympanic membrane (TM).



Figs 1A to C: Tympanograms obtained with a Grason-Stadler GSI 33 Middle Ear Analyzer, exhibiting (A) high admittance, steep gradient (i.e. sharp-angled peak), and middle-ear air pressure approximating atmospheric pressure (0 decaPascals [daPa]); (B) low admittance and indeterminate middle-ear air pressure; and (C) somewhat low admittance, gradual gradient, and markedly negative middle-ear air pressure

with a gradual gradient (obtuse-angled peak) or negative middle-ear air pressure, or combinations of these features (Fig. 1C), may or may not be associated with MEE, and must be considered nondiagnostic or equivocal. In general, the more shallow the peak the more gradual the gradient, and the more negative the middle-ear air pressure, the greater the likelihood of MEE.

When reading a tympanogram it is important to look at the volume measurement also provided. A patient with a tympanic membrane perforation or patent tympanostomy tube will have a flat, type B tympanogram and a “high volume.” The tympanometer measures and records the volume of the external auditory canal, and if a tympanic membrane perforation or a patent tympanostomy tube is

present, the volume of the middle ear and mastoid air cells as well. A volume reading of >1.0 ml should suggest the presence of either a perforation or a patent tympanostomy tube. Therefore, in a child with a tympanostomy tube present, a flat tympanogram with a volume <1.0 ml would suggest a plugged or nonfunctioning tube and middle-ear fluid, whereas a flat tympanogram with a volume >1.0 ml would suggest a patent tympanostomy tube.

Although tympanometry is quite sensitive in detecting MEE, it can be limited by patient cooperation, the skill of the individual administering the test, and the age of the child, with less reliable results in very young children. Use of tympanometry may be helpful in office screening, both by obviating the need for routine otoscopic examination in difficult-to-examine patients whose tympanic membranes have been visualized previously, who are asymptomatic, and whose tympanograms are classified as normal, and by identifying patients who require further attention because their tympanograms are abnormal. Tympanometry also may be used to help confirm, refine, or clarify questionable otoscopic findings; to objectify the follow-up evaluation of patients with known middle-ear disease; and to validate otoscopic diagnoses of MEE. Importantly, even though tympanometry can predict the probability of MEE, it cannot distinguish the effusion of OME from that of AOM.

Treatment

Individual episodes of AOM customarily have been treated with antimicrobial drugs. Concern about increases in bacterial resistance has prompted some authors to recommend withholding antimicrobial treatment in some cases unless symptoms persist for 2 to 3 days, or worsen (Table 1).

From subcommittee on management of acute otitis media: Diagnosis and management of acute otitis media (Flow chart 3).

The management of AOM should include an assessment of pain. If pain is present, the clinician should recommend treatment to reduce pain (Table 2). (This is a strong recommendation based on randomized, clinical trials with limitations and a preponderance of benefit over risk.)

First Line Treatment

If a decision is made to treat with an antibacterial agent, the clinician should prescribe amoxicillin for most children. (This recommendation is based on randomized, clinical trials with limitations and a preponderance of benefit over risk.)

When amoxicillin is used, the dose should be 80 to 90 mg/kg per day. (This option is based on extrapolation from microbiologic studies and expert opinion, with a preponderance of benefit over risk.) In patients who have severe illness (moderate to severe otalgia or fever of 39°C or higher) and in those for whom additional coverage for β -lactamase-positive *Hemophilus influenzae* and *Moraxella catarrhalis* is desired, therapy should be initiated with high-dose amoxicillin-clavulanate (90 mg/kg per day of amoxicillin component, with 6.4 mg/kg per day of clavulanate in 2 divided doses). This dose has sufficient potassium clavulanate to inhibit all β -lactamase-producing *H. influenzae* and *M. catarrhalis*.

Currently approximately 50 percent of isolates of *H. influenzae* and 100 percent of *M. catarrhalis* derived from the upper respiratory tract are likely to be β -lactamase-positive nationwide. Between 15 percent and 50 percent (average: 30%) of upper respiratory tract isolates of *S. pneumoniae* are also not susceptible to penicillin; approximately 50 percent of these are highly resistant to penicillin (minimum inhibitory concentration: $2.0\text{ }\mu\text{g/mL}$ or higher), and the remaining 50% are intermediate in resistance (minimum inhibitory concentration: between 0.1 and $1.0\text{ }\mu\text{g/mL}$). The mechanism of penicillin resistance among isolates of *S. pneumoniae* is not associated with β -lactamase production but rather an alteration of penicillin-binding proteins. This phenomenon, which varies considerably according to geographic location, results in resistance to penicillins and cephalosporins. The patient is allergic to amoxicillin and the allergic reaction was not a type I hypersensitivity reaction (urticaria or anaphylaxis), cefdinir (14 mg/kg per day in 1 or 2 doses), cefpodoxime (10 mg/kg per day, once daily), or cefuroxime (30 mg/kg per day in 2 divided doses) can be used. In cases of type I reactions, azithromycin (10 mg/kg per day

Table 1: Criteria for initial antibacterial-agent treatment or observation in children with AOM

Age	Certain Diagnosis	Uncertain Diagnosis
<6 months	Antibacterial therapy	Antibacterial therapy
6 months–2 years	Antibacterial therapy	Antibacterial therapy if severe illness; observation option* if nonsevere illness
≥ 2 years	Antibacterial therapy if severe illness; observation option* if nonsevere illness	Observation option*

*Observation is an appropriate option only when follow-up can be ensured and antibacterial agents started if symptoms persist or worsen. Nonsevere illness is mild otalgia and fever $<39^{\circ}\text{C}$ in the past 24 hours. Severe illness is moderate to severe otalgia or fever $\geq 39^{\circ}\text{C}$. A certain diagnosis of AOM meets all 3 criteria: (1) rapid onset, (2) signs of MEE, and (3) signs and symptoms of middle-ear inflammation.

Table 2: Methods of handling pain in AOM

<i>Modality</i>	<i>Comments</i>
Acetaminophen, ibuprofen	Effective analgesia for mild to moderate pain, readily available, mainstay of pain management for AOM
Home remedies (no controlled studies that directly address effectiveness)	May have limited effectiveness
Distraction	
External application of heat or cold	
Oil	
Topical agents	
Benzocaine (auralgan, americaine otic)	Additional but brief benefit over acetaminophen in patients >5 y
Naturopathic agents (otikon otic solution)	Comparable with ametocone/ phenazone drops (Anesthetic) in patients >6 y
Homeopathic agents	No controlled studies that directly address pain
Narcotic analgesia with codeine or analogs	Effective for moderate or severe pain; requires prescription; risk of respiratory depression, altered mental status, gastrointestinal upset, and constipation
Tympanostomy/ myringotomy	Requires skill and entails potential risk

on day 1 followed by 5 mg/ kg per day for 4 days as a single daily dose) or clarithromycin (15 mg/ kg per day in 2 divided doses) can be used in an effort to select an antibacterial agent of an entirely different class. Other possibilities include erythromycin-sulfisoxazole (50 mg/kg per day of erythromycin) or sulfamethoxazole-trimethoprim (6–10 mg/kg per day of trimethoprim). Alternative therapy in the penicillin-allergic patient who is being treated for infection that is known or presumed to be caused by penicillin-resistant *S. pneumoniae* is clindamycin at 30 to 40 mg/kg per day in 3 divided doses. In the patient who is vomiting or cannot otherwise tolerate oral medication, a single dose of parenteral ceftriaxone (50 mg/kg) has been shown to be effective for the initial treatment of AOM.

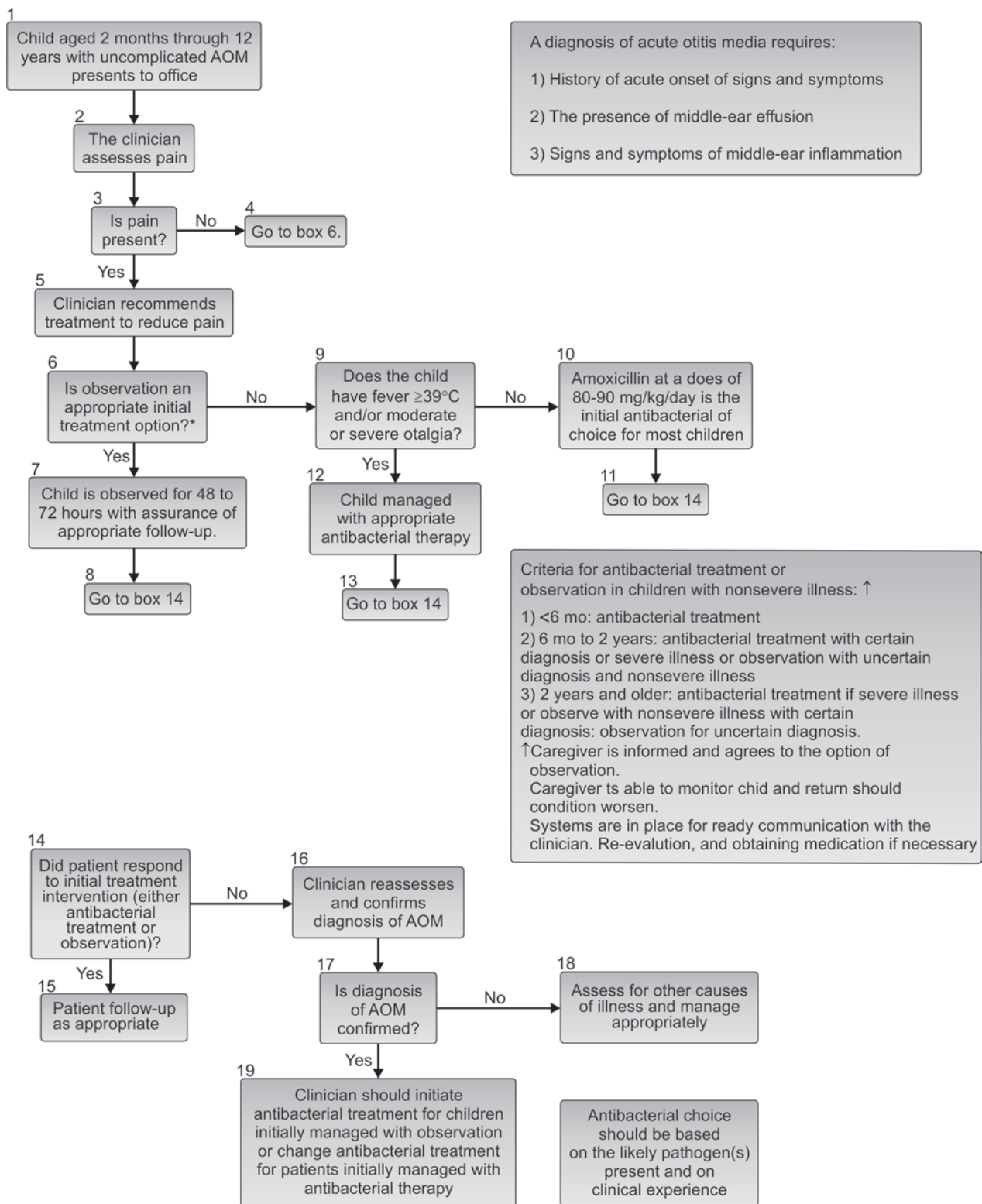
The optimal duration of therapy for patients with AOM is uncertain. Studies comparing standard duration of treatment (10 days) to short-duration treatment (1–7 days) were often characterized by limitations including inadequate sample size (therefore, having low or limited statistical power), few or no children younger than 2 years, exclusion of otitis-prone children, lack of standardized or stringent criteria for the diagnosis of AOM or for improvement or cure, use of an antibacterial medication that had less than optimal efficacy against common middle-ear pathogens, use of lower than recommended dosage of a medication, and lack of analysis of outcome by age. Not surprisingly, the results of these studies were variable. Several more recent studies have been reported that addressed the issue of duration of therapy. The results favoring standard 10-day therapy have been most significant in children younger than 2 years and suggestive of

increased efficacy in those 2 to 5 years of age. Thus, for younger children and for children with severe disease, a standard 10-day course is recommended. For children 6 years of age and older with mild to moderate disease, a 5 to 7 days course is appropriate.

Second-Line Treatment

If the patient fails to respond to the initial management option within 48 to 72 hours, the clinician must reassess the patient to confirm AOM and exclude other causes of illness. If AOM is confirmed in the patient initially managed with observation, the clinician should begin antibacterial therapy. If the patient was initially managed with an antibacterial agent, the clinician should change the antibacterial agent.

Antibacterial agent choice after initial failure of observation or first-line antibacterial therapy should be based on the likely pathogen(s) present and on clinical experience. If the patient was treated with initial observation, amoxicillin should be started at a dose of 80 to 90 mg/ kg per day. For patients who have severe illness (moderate to severe otalgia or temperature of 39°C or higher), in those for whom additional coverage for β -lactamase-positive *H. influenzae* and *M. catarrhalis* is desired, and for those who had been treated initially with amoxicillin and did not improve, high-dose amoxicillin-clavulanate (90 mg/kg per day of amoxicillin component, with 6.4 mg/ kg per day of clavulanate in 2 divided doses) should be used. Alternatives in patients with a history of a non-type I allergic reaction to penicillins are cefdinir, cefpodoxime, or cefuroxime. In cases of type I reactions, alternatives are

Flow chart 3: Management of AOM: Diagnosis and management of Acute Otitis Media. Pediatrics 2004;113:1451-1465.

azithromycin, clarithromycin, erythromycin-sulfisoxazole, or sulfamethoxazole-trimethoprim. Ceftriaxone (50 mg/kg per day), given for 3 consecutive days either intravenously or intramuscularly, can be used in children with vomiting or in other situations that preclude administration of oral antibacterial agents. In the treatment of AOM unresponsive to initial antibacterial therapy, a 3-day course of ceftriaxone has been shown to be better than a 1-day regimen. Although trimethoprim-sulfamethoxazole and erythromycin-sulfisoxazole have traditionally been useful as first- and second-line therapy for patients with AOM, recent pneumococcal surveillance studies indicate that resistance to these 2 combination agents is substantial. Therefore, when patients fail to improve while receiving amoxicillin, neither trimethoprim-sulfamethoxazole nor erythromycin-sulfisoxazole is optimal for antibacterial therapy.

- A patient who fails amoxicillin-potassium clavulanate should be treated with a 3-day course of parenteral ceftriaxone because of its superior efficacy against *S. pneumoniae*, compared with alternative oral antibacterials. If AOM persists, tympanocentesis should be recommended to make a bacteriologic diagnosis. If tympanocentesis is not available, a course of clindamycin may be considered for the rare case of penicillin-resistant pneumococcal infection not responding to the previous regimens. If the patient still does not improve, tympanocentesis with gram-stain, culture, and antibacterial-agent sensitivity studies of the fluid is essential to guide additional therapy.

Indications for myringotomy in children with AOM include severe, refractory pain, hyperpyrexia, complications of AOM such as facial paralysis, mastoiditis, labyrinthitis, or central nervous system infection; and immunologic compromise. Myringotomy should be considered as third-line therapy in patients who have failed 2 courses of antibiotics for an episode of AOM. In children with AOM in whom clinical response to vigorous, second-line treatment has been unsatisfactory, either diagnostic tympanocentesis or myringotomy is indicated to enable identification of the offending organism and its sensitivity profile.

When a patient requires 3 to 4 courses of antibiotics for episodes of AOM in a 6-months period or 5 to 6 episodes in a 12-months period, potential surgical management of the child's AOM should be discussed with the parents.

Management of Otitis Media with Effusion

To determine the course of an episode of OME, and to distinguish between persistence and recurrence, examination should be conducted monthly until resolution, and hearing should be assessed if effusion has been present for >3 months. Although hearing loss may be of primary concern, OME causes a number of other difficulties in children that also should be considered. These include predisposition to recurring AOM, pain, disturbance of

balance, and tinnitus. Long-term sequel that have been demonstrated to be associated with OME include pathologic middle-ear changes; atelectasis of the tympanic membrane and retraction pocket formation, adhesive OM, ossicular discontinuity, cholesteatoma, and conductive and sensorineural hearing loss. Long-term adverse effects on speech, language, and cognitive and psychosocial development also are noted. Children with OME persisting >3 months deserve close monitoring of their hearing levels with skilled audiologic evaluation; frequent assessment of developmental milestones, including speech and language assessment; and attention paid to their rate of recurrent AOM.

Medical Treatment

Antimicrobials have definite but limited efficacy in resolving OME, presumably because they help eradicate nasopharyngeal infection or inapparent middle-ear infection, or both. However, mainly because of the short-term nature of their benefit and because of the contribution of antimicrobial usage to the development of bacterial resistance, routine antimicrobial treatment of OME, previously recommended by some authorities, no longer seems wise. Instead, treatment should be limited to cases in which there is evidence of associated bacterial upper respiratory tract infection or untreated middle-ear infection. For this purpose, the most broadly effective drug available should be used, as recommended for AOM.

The efficacy of oral corticosteroids in the treatment of OME is probably short-term at best, and guidelines for the treatment of OME have determined that the risk-benefit ratio for these medications would argue against their use. Antihistamine-decongestant combinations are not effective in treating children with OME, but their efficacy has not been tested in children with environmental allergies. Antihistamines alone, decongestants alone, and mucolytic agents are unlikely to be effective.

Myringotomy and Insertion of Tympanostomy Tubes

When OME persists despite an ample period of watchful waiting, usually 3 to 6 months or perhaps longer in children with unilateral effusion, the question arises as to surgical intervention. Myringotomy alone, without tympanostomy tube insertion, permits evacuation of middle-ear effusion and sometimes is effective; often, because the incision heals before the middle-ear mucosa returns to normal the effusion soon reaccumulates. Inserting tubes offers the likelihood that middle-ear ventilation will be sustained for at least as long as the tube remains in place and functional, about 12 months on average, and nearly uniformly reverses the conductive hearing loss associated with OME. Occasional episodes of obstruction of the tube lumen and premature tube extrusion may limit the effectiveness of tympanostomy

tubes, and tubes also can be associated with otorrhea. However, placement of tympanostomy tubes usually is effective in providing resolution of OME in children. Sequel following tubal extrusion include residual perforation of the eardrum, tympanosclerosis, localized or diffuse atrophic scarring of the eardrum that may predispose to the development of atelectasis or a retraction pocket or both, residual conductive hearing loss, and cholesteatoma. Fortunately, the more serious of these sequel occur infrequently.

Complications of Acute Otitis Media

Intratemporal Complications

Infectious dermatitis

Infectious dermatitis is an infection of the skin of the external auditory canal resulting from contamination by purulent discharge from the middle-ear. The skin often is erythematous, edematous, and tender. Management consists of proper hygiene combined with systemic antimicrobials and ototopical drops as appropriate for treating AOM and tube otorrhea.

Tympanic membrane perforation

Rupture of the tympanic membrane can occur with episodes of either AOM or OME. Although damage to the tympanic membrane from these episodes usually heals spontaneously, chronic perforations can develop in a small number of cases and require further surgical intervention.

Chronic suppurative otitis media

Chronic suppurative OM consists of persistent middle-ear infection with discharge through a tympanic membrane perforation. The disease is initiated by an episode of AOM with rupture of the membrane. The mastoid air cells always are involved. The most common etiologic organisms are *P. aeruginosa* and *S. aureus*. Treatment is guided by the results of microbiologic investigation. If an associated cholesteatoma is not present, parenteral antimicrobial treatment combined with assiduous aural cleansing is likely to be successful in clearing the infection, but in refractory cases, tympanomastoidectomy can be required.

Acute mastoiditis

Technically, all cases of AOM are accompanied by mastoiditis by virtue of the associated inflammation of the mastoid air cells. However, early in the course of the disease no signs or symptoms of mastoid infection are present, and the inflammatory process usually is readily reversible, along with the AOM, in response to antimicrobial treatment. Spread of the infection to the overlying periosteum, but without involvement of bone, constitutes *acute mastoiditis with periosteitis*. In such cases, signs of mastoiditis usually are present, i.e., inflammation in the postauricular area, often with displacement of the pinna inferiorly and

anteriorly. Treatment with myringotomy and parenteral antibiotics, if instituted promptly, usually provides satisfactory resolution. In acute mastoid osteitis, or coalescent mastoiditis, infection has progressed further, causing destruction of the bony trabeculae of the mastoid. Frank signs and symptoms of mastoiditis usually, but not always, are present. In acute petrositis, infection has extended further to involve the petrous portion of the temporal bone. Eye pain is a prominent symptom, due to irritation of the ophthalmic branch of the cranial nerve V; cranial nerve VI palsy later develops. *Gradenigo syndrome* is the triad of suppurative OM, paralysis of the external rectus muscle, and pain in the ipsilateral orbit. Rarely, mastoid infection spreads to the neck muscles that attach to the mastoid tip, resulting in an abscess in the neck, termed a *Bezold abscess*. When mastoiditis is suspected or diagnosed clinically, CT scanning of the temporal bone should be carried out to further clarify the nature and extent of the disease. Bony destruction of the mastoid must be differentiated from the simple clouding of mastoid air cells that often is found in uncomplicated cases of OM. The most common causative organisms in all variants of acute mastoiditis is *S. pneumoniae*, nontypable *H. influenzae*, and *P. aeruginosa*. Children with acute mastoid osteitis require intravenous antimicrobial treatment and mastoidectomy, with the extent of the surgery depending on the extent of the disease process:

- Each of the variants of mastoiditis also may occur in subacute or chronic form. Symptoms are correspondingly less prominent. Chronic mastoiditis always is accompanied by chronic suppurative OM, and occasionally will respond to the conservative regimen recommended for that condition. In most cases, however, mastoidectomy also is required.

Facial paralysis

The facial nerve, as it traverses the middle-ear and mastoid bone, may be affected by adjacent infection. Facial paralysis as a complication of AOM is uncommon, and often resolves after myringotomy and parenteral antibiotic treatment. Facial paralysis in the presence of AOM requires urgent attention, because prolonged infection can result in permanent facial paralysis, which, when it occurs, can have a devastating affect on a child. If facial paralysis develops in a child with mastoid osteitis or with chronic suppurative OM, mastoidectomy should be undertaken urgently.

Acquired cholesteatoma

Cholesteatoma is a cyst like growth within the middle-ear or other pneumatized portions of the temporal bone, lined by keratinized, stratified squamous epithelium and containing desquamated epithelium and/or keratin. Acquired, as distinct from congenital, cholesteatoma most often develops as a complication of long-standing chronic OM. However, the condition also may develop from a

deep retraction pocket of the tympanic membrane or as a consequence of epithelial implantation in the middle-ear cavity from traumatic perforation of the tympanic membrane or insertion of a tympanostomy tube. Cholesteatomas tend to expand progressively, causing bony resorption, and may extend intracranially, with potentially life-threatening consequences. Cholesteatoma should be suspected if otoscopy shows a discrete, whitish opacity of the eardrum or a polyp protruding through a defect in the eardrum; or white caseous debris persistently overlies the eardrum, especially its superior portion; or persistent malodorous aural discharge is present. When cholesteatoma is suspected, consultation with an otolaryngologist should be sought immediately. Delayed recognition and treatment can have significant long-term consequences, including the need for more extensive surgical treatment, permanent hearing loss, facial nerve injury, labyrinthine damage with loss of balance function, and intracranial extension. Tympanomastoid surgery is required for treatment of cholesteatoma.

Labyrinthitis

Labyrinthitis occurs uncommonly as a result of the spread of infection from the middle-ear and/or mastoid to the inner-ear. Cholesteatoma or chronic suppurative OM is the usual source. Symptoms and signs include vertigo, tinnitus, nausea, vomiting, hearing loss, nystagmus, and clumsiness. Treatment is directed at the underlying condition and must be undertaken promptly to preserve inner-ear function and prevent the spread of infection.

Intracranial Complications

Meningitis, epidural abscess, subdural abscess, focal encephalitis, brain abscess, lateral sinus thrombosis (also called sigmoid sinus thrombosis), and otitic hydrocephalus each may develop as a complication of acute or chronic middle-ear or mastoid infection, through direct extension, hematogenous spread, or thrombophlebitis. Bony destruction adjacent to the dura often is involved, and a cholesteatoma may be present. In a child with middle-ear or mastoid infection, the presence of any systemic symptom, such as fever, headache, or lethargy, of extreme degree, or a finding of meningismus or of any central nervous system sign on physical examination should prompt suspicion of an intracranial complication.

When an intracranial complication is suspected, lumbar puncture should be performed only after imaging studies establish that there is no evidence of mass effect or hydrocephalus. In addition to examination of the cerebrospinal fluid, culture of middle-ear exudate obtained via tympanocentesis may identify the causative organism, thereby helping guide the choice of antimicrobial drugs, and myringotomy should be performed to permit middle-ear drainage.

Intravenous antibiotic treatment of all intracranial complications, including surgical drainage of any abscess, is required urgently. If mastoiditis is present, mastoidectomy should be undertaken as soon as feasible. When meningitis develops as a complication of AOM, investigation should be directed at the possible presence of a perilymphatic fistula.

Lateral sinus thrombosis may be complicated by dissemination of infected thrombi with resultant development of septic infarcts in various organs. Diagnosis is facilitated through MRI. Mastoidectomy may be required even in the absence of osteitis or coalescent mastoiditis, especially in the case of propagation or embolization of infected thrombi. However, mastoiditis sometimes can be treated with tympanostomy tube placement and intravenous antibiotics. Anticoagulation therapy also may be considered in the treatment of lateral sinus thrombosis; however, an otolaryngologist should be consulted before initiating this therapy to coordinate the possible need for surgical intervention prior to anticoagulation.

Otitic hydrocephalus, also termed *benign intracranial hypertension* (pseudotumor cerebri), is an uncommon condition that consists of increased intracranial pressure without dilatation of the cerebral ventricles, occurring in association with acute or chronic OM or mastoiditis. The pathogenesis is uncertain, but the condition commonly is associated with lateral sinus thrombosis, and the pathophysiology may involve obstruction by thrombus of intracranial venous drainage into the neck, producing a rise in cerebral venous pressure and a consequent increase in cerebrospinal fluid pressure. Symptoms are those related to increased intracranial pressure. Signs may include, in addition to evidence of OM, paralysis of 1 or both lateral rectus muscles and papilledema. MRI can confirm the diagnosis. Treatment measures include the use of antimicrobials and drugs such as acetazolamide or furosemide to reduce intracranial pressure, mastoidectomy, repeated lumbar puncture, lumboperitoneal shunt, and ventriculoperitoneal shunt. If left untreated, otitic hydrocephalus may result in loss of vision secondary to optic atrophy.

Physical Sequel

The physical sequel of OM consists of structural middle-ear abnormalities resulting from long-standing middle-ear inflammation. In most instances, these sequel are consequence of severe and/or chronic infection, but some also may result from the presumably noninfective inflammation of long-standing OME. The various sequel may occur singly, or inter relatedly in various combinations.

Tympanosclerosis consists of whitish plaques in the tympanic membrane and nodular deposits in the submucosal layers of the middle ear. The changes involve hyalinization with deposition of calcium and phosphate crystals. There may be associated conductive hearing loss, but this

is uncommon. In developed countries, probably the most common cause of tympanosclerosis is tympanostomy tube insertion.

Atelectasis of the tympanic membrane is a descriptive term applied to either severe retraction of the tympanic membrane caused by high negative middle-ear pressure or loss of stiffness and medial prolapse of the membrane, presumably as a consequence of long-standing retraction or severe or chronic inflammation. A retraction pocket is a localized area of atelectasis. Atelectasis often is transient and usually is not accompanied by symptoms, but a deep retraction pocket may lead to erosion of the ossicles and adhesive otitis, and may serve as the nidus of a cholesteatoma. For a deep retraction pocket, and for the unusual instance in which atelectasis is accompanied by symptoms such as otalgia, tinnitus, or conductive hearing loss, tympanostomy tube insertion is necessary.

Adhesive OM consists of proliferation of fibrous tissue in the middle-ear mucosa, which may in turn result in impaired movement of the ossicles, rarefying osteitis and ossicular discontinuity, conductive hearing loss, and cholesteatoma. The hearing loss may be amenable to surgical correction.

Cholesterol granuloma is an uncommon condition in which the tympanic membrane appears to be dark blue, reflecting the presence of thick, granulomatous material in the middle-ear cavity. The condition appears to result more often from long-standing OME than from frank middle-ear infection. Tympanostomy tube insertion alone does not provide satisfactory relief, and the required treatment is middle-ear and mastoid surgery.

Chronic perforation may develop after spontaneous rupture of the tympanic membrane during an episode of AOM, as sequel of chronic suppurative OM, from trauma, or as a result of failure of closure of the tympanic membrane following extrusion of a tympanostomy tube. A chronic perforation almost always is amenable to surgical repair, usually after the child has been free of OM for an extended period.

Permanent *conductive hearing loss* may result from any of the conditions just described. Rarely, permanent sensorineural hearing loss may occur in association with acute or chronic OM, presumably from the spread of infection or products of inflammation through the round window membrane, or as a consequence of suppurative labyrinthitis.

POSSIBLE DEVELOPMENTAL SEQUEL

Permanent hearing loss in children has a significant negative impact on development, particularly delays in speech and language. The degree to which OM impacts long-term development in children is difficult to assess, and there have been conflicting studies examining this question. However, the developmental impact is most likely to

be significant in children with greater levels of hearing loss, hearing loss that is sustained for longer periods of time, and hearing loss that is bilateral, and in those children who have other developmental difficulties or risk factors for developmental delay.

Prevention

- Encouraging breast-feeding
- Feeding child upright if bottle fed
- Avoiding exposure to passive smoke
- Tobacco cessation counseling
- Limiting exposure to numbers of children to the extent possible
- Teaching adults and children careful hand washing technique
- Limiting exposure to viral upper respiratory infections
- Avoid pacifier use beyond 10 months of age
- Ensure immunizations are up-to-date; including influenza and 13 valent conjugated polysaccharide vaccine (PCV13).

SUMMARY

This clinical practice guideline provides evidence-based recommendations for the definition and management of AOM in children from 2 months through 12 years of age without signs or symptoms of systemic illness unrelated to the middle-ear. It emphasizes accurate diagnosis and adherence to a consistent definition of AOM. Management of the pain associated with AOM is identified as an essential aspect of care. An option to observe a select group of children with AOM with symptomatic therapy for 48 to 72 hours is supported by evidence and may potentially lead to decreased use of antibacterial agents. If a decision is made to treat with an antibacterial agent, amoxicillin at a dose of 80 to 90 mg/kg per day is recommended as the initial antibacterial agent of choice for most children. Additional guidance is given for choosing an antibacterial agent when an alternative to amoxicillin is indicated. Also addressed is evidence related to the prevention of AOM and the role of CAM in the treatment of AOM. The recommendations are summarized.

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Assessment of Critically Ill Child in the PICU

Kundan Mittal

AIM

The aim of initial assessment of critically ill patient is to identify physiological abnormalities, appropriate measures to correct these physiological abnormalities, and to diagnose the underlying etiology of the critical illness. Both acute illness and injury result in alteration in nearly all bodily physiological system (altered vital parameters, immunity response, coagulation system, metabolism of glucose, fat and protein, and psychological response). Prompt and early recognition of these altered physiological parameters in critically ill will make it easier for the physician to manage the child with simple interventions and prevent further harm. Children may not show signs and symptoms of acute illness at early stage due to their greater tendency to compensate.

Children are different anatomically, physiologically and developmentally from adults and their psychomotor skills and social skills depend on the developmental stage of life. The appearance and expected behavior to illnesses also varies with age. Despite having similar genetic make-up their expressions are different from adults. Children also have certain anatomical and physiological differences from adults. Moreover, children depend on care-givers for their needs. It is also important to know weight and height of different age group.

- Age distribution
 - Newborn: From birth to 28 days
 - Infant: up to one year
 - Toddler: 1 to 3 years
 - Preschool: 3 to 6 years
 - School age child: 6 to 12 years
 - Adolescent: 12 to 18 years
- Calculation of weight
 - 1 to 6 years = $\text{Age} \times 2 + 8$
 - 7 to 12 years = $\text{Age} \times 7 - 5/2$

- Calculation of height (2-12 years)
- $\text{Age in year} \times 6 + 77 = \text{cm}$

Initial or general assessment of acutely ill child helps to evaluate physiological abnormality, severity of illness and stabilization of child. Systematic approach has been developed for the assessment of critically ill. There are four components for assessment:

- General assessment
- Primary assessment
- Secondary assessment
- Tertiary assessment

The routine systematic approach of taking full history, conducting complete physical examination and investigation, making correct diagnosis and planning treatment cannot be followed in emergency situation. “*Time is of essence*” In assessing critically ill, all the above steps should be carried simultaneously, i.e. in parallel. The best guess diagnosis should be made and patient should be reassessed after every intervention. In acute illness, we should restrict ourselves only to the information required for immediate intervention rather eliciting detailed history. Background health information/status and hospital record/charts/information from paramedics are also necessary in many situations especially in ICU. Assessment may also be required for specific situations like nutritional assessment, preoperative or postoperative assessment, neurological assessment, organ transplant decision, during transport, DNAR and brain death issues. We will primarily focus on our assessment in critically ill who are first seen or encountered in ICU. Sequence assessment is same in whatever conditions we are assessing the critically ill child. Various conditions requiring immediate assessment in ICU’s are given below (Table 1).

Quick assessment is done using pediatric assessment triangle (Fig. 1) to know whether child is stable or severely ill. Accordingly child is stated to be having either

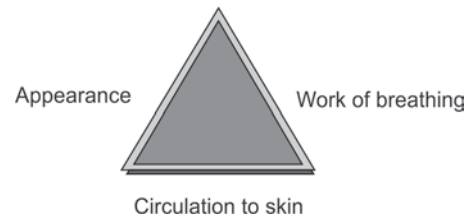
Table 1: Conditions requiring immediate assessment in ICU

System(s)	Clinical features
Cardiovascular system	Supraventricular tachycardia, symptomatic bradycardia, tension pneumothorax, severe hypotension
Respiratory system	Tachypnea, increased work of breathing, bradypnea, oxygen saturation <94% in room air, asynchrony with ventilator, cyanosis
Nervous system	Acute deterioration in consciousness level, agitation, aggressive behavior, seizures
Renal	Decreased urine output <0.5 ml/kg/hr over a period of 6 hrs
Gastrointestinal system	Hematemesis (bleeding from upper gut), severe jaundice, melena (black color stool)
Metabolic	Metabolic acidosis, symptomatic hypoglycemia (low blood sugar), electrolyte disturbances

life-threatening problem where immediate resuscitation is started using BLS/PALS guidelines or categorized according to illness (respiratory and or cardiovascular). Neurological disorders can be primary or secondary to hypoperfusion or hypoxemia. PAT is a rapid way to assess physiological abnormalities by visual and auditory clues within few seconds. The three components of pediatric assessment triangle (appearance, work of breathing, and circulation to skin) are interdependent and reflect child's physiological status. The three components of the PAT reflects general status, oxygenation and ventilation status, perfusion, and brain functions of the child.

COMPONENTS OF PEDIATRIC ASSESSMENT TRIANGLE

- *Appearance:* It reflects the adequacy of ventilation, oxygenation, brain perfusion, homeostasis, and brain

**Fig. 1:** Pediatric assessment triangle

functions. Remember that appearance does not reflect etiology of disease. Various components of appearance are tone, interactiveness, consolability, gaze, speech and cry.

- *Work of breathing:* It primarily reflects oxygenation and ventilation status of the child. Visual and auditory clues for increased work of breathing are; *abnormal sounds, head bobbing, abnormal position, retractions, nasal flaring, and tachypnea.*
- *Circulation:* Aim is to assess the adequacy of cardiac output and perfusion of vital organs. Pallor, mottling, abnormal behaviour, tachypnea and cyanosis are features of inadequate circulation. Also see exposed part of body for any injury and evidence bleed.

Three components when combined can give an idea of likelihood physiological abnormalities, severity of illness, and define life threatening conditions (Tables 2 to 4). This also gives an idea that how quickly one should intervene and what type of management to be instituted.

Once the general assessment has been done, life-threatening problem has been dealt then secondary and tertiary assessment is done. In the mean while, child is also attached to monitor. The primary assessment includes assessment of airway, breathing, circulation, disability, and exposure or environment. The problem identified should be classified according to type and severity and interventions are done accordingly to stabilize the child. One may take the appropriate blood samples simultaneously.

Table 2: Categorization of severity of illness using PAT

Appearance	Work of breathing	Circulation	Physiological status
Abnormal	Normal	Normal	Primary brain dysfunction
Normal	Abnormal	Normal	Respiratory distress
Abnormal	Abnormal	Normal	Respiratory failure
Normal	Normal	Abnormal	Compensated shock
Abnormal	Normal	Abnormal	Hypotensive shock
Abnormal	Abnormal	Abnormal	Cardiorespiratory failure

Table 3: Categorization of patients after initial assessment

1. Stable: These patients need minimal monitoring and have no abnormality in appearance (level of consciousness), work of breathing and circulation to skin
2. Stable with risk of deterioration
3. Respiratory distress/failure
4. Cardiovascular compromise
5. Neurological compromise
6. Cardiopulmonary failure/arrest

Table 4: Life-threatening conditions required immediate attention

1. Complete or partial airway obstruction
2. Apnea, bradypnea, tachypnea, increased work of breathing
3. Signs of poor perfusion, symptomatic bradycardia, hypotension, tachycardia, ventricular fibrillation or tachycardia, supraventricular tachycardia, symptomatic complete heart block
4. Unresponsiveness, decreased response or abnormal motor response to pain
5. Hypothermia, bleeding consistent with septic shock, acute abdominal distension
6. In PICU child fighting with ventilator, acute fall in oxygen saturation, ET blockade, status epilepticus, coning of brain

Secondary assessment done includes SAMPLE history and focussed examination including vital parameters. After you have detected the problem, the ancillary studies are carried out according to system. Blood sugar and arterial

blood gas analysis are two most important investigations to be carried out in ICU and emergency. The important physiological parameters of clinical significance are given in Tables 5 to 7.

Table 5: Normal respiratory rate in children

Age	Breaths/min
Infant (<1 year)	30–60
Toddler (1–3 years)	24–40
Preschool (4–5 years)	22–34
School age (6–12 year)	18–30
Adolescent (13–18 year)	12–16

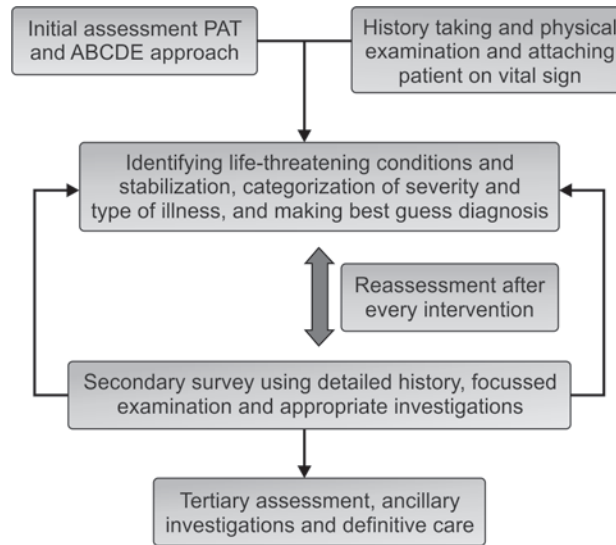
Table 6: Normal heart rate in children

Age	Awake	Mean	Sleeping
Newborn to 3 months	85–205	140	80–160
3 months to 2 year	100–190	130	75–160
2 years to 10 years	60–140	80	60–90
> 10 years	60–100	75	50–90

Table 7: Normal blood pressure in children

Age	SBP (mm Hg)		DBP (mm Hg)	
	Female	Male	Female	Male
Neonate (1st day)	60–76	60–74	31–45	30–44
Neonate (4th day)	67–83	68–84	37–53	35–53
Infant (1 month)	73–91	74–94	36–56	37–55
Infant (3 months)	78–100	81–103	44–64	45–65
Infant (6 months)	82–102	87–105	46–66	48–68
Infant (1 year)	68–104	67–103	22–60	20–58
Child (2 years)	71–105	70–106	27–65	25–63
Child (7 years)	79–113	79–115	49–77	38–77
Adolescent (15 years)	93–127	95–131	47–85	45–85
Mean blood pressure = $55 + (\text{age in years} \times 1.5)$ mm Hg				

SUMMARY OF ASSESSMENT OF ACUTELY/CRITICALLY ILL



Section 6

Neurology

Editors
RK Sabharwal
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*Ravindra Arya, Puneet Jain***STORY**

The story of development of drug therapy for epilepsy has all the ingredients of romantic fiction: mystery, jealousy, serendipity and genuine hard work. In May 1857, Dr Edward Sieveking presented before Royal Medical and Chirurgical Society an 'analysis of 52 cases of epilepsy'. During discussion, Sir Charles Locock, obstetrician to Queen Victoria, shared his experience with potassium bromide in young women with 'hysterical epilepsy connected with the menstrual period'; and, thus, began the pharmacotherapy of epilepsy. The story moves from Victorian academics to a young resident psychiatrist, Alfred Hauptmann, who lived above an epilepsy ward and was frequently woken up when these patients kept falling out of bed during their seizures. To ensure a good night's sleep, he tried sedating these patients with phenobarbital and noticed that not only they had fewer seizures in night, but they did have reduced seizures the next day also. He recorded and published his observations and the modern drug therapy of epilepsy started. The next breakthrough came with the development of a feline model of epilepsy by Tracy Putnam and Fredric Gibbs; supply of non-sedative phenyl compounds by a pharmaceutical company and clinical testing of the relatively non-toxic one (phenytoin) by Houston Merritt. In the mid-1960s, a pharmaceutical company tried to develop a competitor for recently marketed chlorpromazine and thus came the carbamazepine. Simultaneously in 1963, Pierre Eymard realized that valproic acid, which he was using for dissolving his insoluble khallins, was probably the active ingredient and not the solutes, all of which surprisingly acquired anti-seizure property. Concurrently, Leo Sternbach developed benzodiazepines and their clinical use was pioneered by Henri Gastaut with the seminal paper on the use of diazepam for the treatment of status epilepticus in 1965. In 1975, National Institute of Neurological Disorders and Stroke

established the Anticonvulsant Drug Development program which resulted in screening of >28,000 chemical compounds. Emphasis on target-oriented design, structural modification of existing chemical compounds and development of rodent seizure models has resulted in licensure and clinical use of several 'newer' antiepileptic drugs (AEDs) in last 4 decades, many of which have truly novel mechanisms and have contributed to increasing understanding of neurochemistry.

NEWER ANTIEPILEPTIC DRUGS**Gabapentin**

Gabapentin (GBP) is a structural but not functional analogue of γ -amino-butyric acid (GABA). It neither interacts with GABA receptors nor affects GABA reuptake, synthesis or metabolism. GBP binds to $\alpha 2$ - δ subunit of L (large conductance) type voltage-gated calcium channels, leading to reduced transmitter release and attenuation of post-synaptic excitability. The oral bioavailability of GBP varies inversely with dose. It is excreted unchanged in urine.

It is licensed for adjunctive treatment of partial seizures with or without secondary generalization in patients 6 years or older. Clinically, GBP is a narrow spectrum AED with poor efficacy and seldom offers substantial therapeutic benefit. There is risk of exacerbation of generalized seizures and caution must be exercised when using it in patients with mixed seizure types.

Overall, GBP has low prevalence of adverse effects. Behavioral manifestations are common including emotional lability, aggressiveness, hostility, hyperactivity and attention deficit. Other reported adverse effects are fatigue, somnolence, nausea, dyspepsia, rash and weight gain. GBP is initiated at 15 to 20 mg/kg/day in 3 divided doses and up-titrated to a usual maintenance dose of 35 to 40 mg/kg/day (maximum 3600 mg/day).

Lacosamide

Lacosamide (LAC) was licensed for clinical use in 2008. It acts by enhancing slow inactivation of voltage-gated sodium channels resulting in stabilization of hyperexcitable neuronal membranes. It is unique in this regard, since other sodium channel blockers modulate fast inactivation. It is known to bind to collapsing response mediator protein-2, a phosphoprotein involved in neuronal differentiation and control of axonal outgrowth. This action is supposedly neuroprotective; however, its relevance to antiseizure efficacy is undefined. It has 100 percent oral bioavailability unaffected by food co-ingestion, with <15 percent plasma protein binding. It is metabolized in liver, 30 percent by demethylation to inactive metabolites. Forty percent of administered dose is excreted unchanged in urine.

LAC is licensed for adjunctive treatment of partial onset seizures with or without secondary generalization in patients 17 years and older. Since an intravenous formulation is available, it has also been used for non-convulsive status epilepticus.

Common adverse effects involve nervous system particularly the vestibulo-cerebellar structures: dizziness, vertigo, balance and coordination difficulties, memory impairment, somnolence, tremor, nystagmus, diplopia, blurred vision, headache, nausea, vomiting, and depression. Hence, patients should be warned against increased risk of accidental injury or falls. Other adverse effects include constipation, flatulence, and pruritus. LAC is known to increase PR interval, therefore, patients with known second- or third-degree atrioventricular block may be at risk of myocardial infarction or heart failure. Also, caution should be exercised when co-prescribing with other AED known to prolong PR interval, e.g. carbamazepine, lamotrigine, and pregabalin.

LAC is usually initiated at 50 mg twice daily for 1 week, increasing by 100 mg/day in 2 divided doses at weekly intervals to a maximum of 400 mg/day. Intravenous solution (10 mg/ml) is bioequivalent and hence infused in same doses over 15 to 30 minutes. Optimal therapeutic plasma levels have been determined to be 10 to 20 mg/L (40–80 $\mu\text{mol/L}$). Interestingly, LAC can be monitored using salivary level which represent the free non-protein bound plasma concentration and is pharmacologically relevant. The syrup formulation of LAC contains fructose and aspartame, contraindicating it for patients with hereditary fructose intolerance and phenylketonuria respectively. LAC requires dose modification in patients with renal impairment with a total maximum dose of 250 mg/day in patients with creatinine clearance <30 ml/min.

Lamotrigine

Lamotrigine (LTG) inhibits voltage gated sodium channels in a voltage-, frequency- and use-dependent manner

by interacting with open conformation of the channels at α -pore forming subunit. It is also known to inhibit release of glutamate and increase the activity of dendritic hyperpolarization activated cation channels, increasing the excitatory threshold. LTG has a high oral bioavailability (~98%) with roughly 50 percent plasma protein binding. It is glucuronized to inactive metabolites which are eliminated in urine along with some unchanged dose. LTG is the only newer AED to show auto-induction of its metabolism. It has a long $t_{1/2}$ - β (~30 hours) which can double with valproate co-therapy.

LTG is approved monotherapy in patients aged >12 years for treatment of partial seizures and primary or secondarily generalized tonic-clonic seizures; as adjunctive therapy for the same indication in patients aged 2 to 12 years; and, adjunctive therapy of LGS in patients 2 years or older. It is also used for treatment of absence seizures where valproate and/or ethosuximide have failed. LTG is known to exacerbate myoclonic seizures in JME, Dravet syndrome or progressive myoclonus epilepsy. Children with cryptogenic perisylvian epilepsy have been reported to develop negative myoclonus, atypical absence or electrical status epilepticus with LTG. Some of these cases probably represent atypical benign partial epilepsy or pseudo-Lennox syndrome (personal experience).

The major adverse effect with LTG is the erythematous rash appearing 2 to 8 weeks after initiation of therapy. There is a huge variation in the reported incidence of LTG-induced rash (0.5-10%). Our viewpoint is that the incidence of rash does not differ significantly from conventional AED like carbamazepine, but, a disproportionately higher proportion of patients develop toxic epidermal necrolysis or Stevens-Johnson syndrome. Higher doses, rapid titration and concomitant valproate use increases the risk. Clinically, any child on LTG who develops a rash should be promptly evaluated. Other adverse effects include somnolence, headache, diplopia, ataxia, increased appetite, anxiety, tics and tremors. Clinically, most relevant drug interaction of LTG is with valproate which inhibits its metabolism and decreases its clearance. LTG is prescribed in 2 divided doses as per the schedule given in Table 1.

Levetiracetam

Levetiracetam (LEV) has a unique antiepileptic mechanism. It binds to a specific synaptic vesicle protein (SV2A) which is probably involved in the vesicle fusion and exocytosis, thus affecting release of multiple neurotransmitters. Other postulated mechanisms include partial inhibition of N (neuronal) type voltage gated calcium channels, reduction of GABA and glycine mediated inhibition; and, decreased voltage-gated potassium currents. LEV has high oral bioavailability (>95%) unaffected by food and low protein binding (<10%). It has minimal hepatic metabolism and primarily renal excretion.

Table 1: Dosing schedule for lamotrigine

	<i>Monotherapy</i>	<i>With enzyme inducers</i>	<i>With valproate</i>
Initiation	0.3 mg/kg/day	0.6 mg/kg/day	0.15 mg/kg/day
Increment (1-2 weekly)	0.3 mg/kg/day	0.6 mg/kg/day	0.15 mg/kg/day
Maintenance	2-8 mg/kg/day	5-15 mg/kg/day	1-5 mg/kg/day
Maximum dose	400 mg/day	800 mg/day	200 mg/day

LEV has a fairly broad range of efficacy and represents a first or second choice for idiopathic generalized epilepsies (IGE) with primary generalized or myoclonic seizures; and, for partial seizures with or without secondary generalization where it is the main challenger for carbamazepine. It is approved for use in partial seizures (+/- secondary generalization) as monotherapy in patients 16 years or older and as adjunct in those 4 years and above. It is also licensed for adjunctive treatment of myoclonic seizures in patients 12 years or older with juvenile myoclonic epilepsy (JME); and, of primary generalized tonic-clonic seizures (GTCS) in patients above 6 years with idiopathic generalized epilepsy; where it is a contender of valproate. Other indications include absence seizures, benign rolandic epilepsy, post-anoxic myoclonus, progressive myoclonic epilepsy (Unverricht-Lundborg syndrome), and, severe polymorphic epilepsy of infancy (Dravet syndrome).

Adverse effects are infrequent and usually include somnolence, asthenia, dizziness and headache. Behavioral effects like aggression, emotional lability or oppositional tendency is particularly problematic in children.

The initial oral dose is 10 mg/kg/day with bi-weekly increases of 20 mg/kg/day to the maximum maintenance dose of 60 mg/kg/day. The maximum dose is 3000 mg/d. In children, it is prescribed in 3 divided doses. Optimal therapeutic plasma concentration is 12 to 46 mg/L (70–270 µmol/L). For status epilepticus, the loading dose is 20 mg/kg infused over 15 to 20 minutes. Repeat mini-bolus with 10 mg/kg may be followed by usual maintenance dose.

Brivaracetam is the S enantiomer of LEV with 13-fold higher binding affinity for SV2A. It is expected to share broad antiepileptic efficacy and has shown increased potency than LEV against secondarily generalized seizures, in preclinical efficacy. It is likely to have more favorable adverse effect profile in children.

Rufinamide

Rufinamide (RUF) acts on inactivated voltage-sensitive sodium channels and blocks their return to activated state thereby preventing the generation of sustained bursts of high frequency action potentials. Its oral bioavailability has not been determined but probably varies inversely with dose, having nonlinear pharmacokinetics at a dose >1600 mg/day. More importantly, food co-ingestion substantially increases the rate and extent of absorption. It is 35 percent protein bound in plasma. RUF is metabolized

primarily by CYP independent hydrolysis. The resulting inactive metabolite is primarily excreted in urine along with a minor acyl-glucuronide.

RUF is licensed for adjunctive treatment of Lennox-Gastaut syndrome (LGS) in patients 4 years and older. It is efficacious against multiple seizure types in LGS.

Common adverse effects include dizziness, diplopia, somnolence, nausea, vomiting and fatigue. It is known to decrease QTc interval. Hence, it should be avoided in patients with congenital short QT syndrome or a family history of such disorder. There are reports of increased frequency of status epilepticus in patients on RUF, but the significance of this phenomenon in clinical decision-making requires further data. Conventional enzyme inducers and vigabatrin are known to decrease the plasma level of RUF, whereas, valproate can increase it. On the other hand, RUF can increase plasma levels of carbamazepine and lamotrigine; and, decrease those of phenytoin, phenobarbital and triazolam. Also, RUF enhances the metabolism of hormonal contraceptives, leading to reduced efficacy and breakthrough bleeding.

For children 4 years or older, weighing <30 kg and not receiving valproate, RUF is started at 100 mg/day increasing every 2 to 3 days by 200 mg/day to a usual maintenance dose of 1000 mg/day. If the child is on valproate, the dosing schedule remains the same but the typical maintenance dose is decreased to 400-600 mg/day. For adults and children >30 kg, treatment is started at 200 mg/day with every 2 day increase by 400 mg/day to a usual maintenance dose of 1800 mg/day (30-50 kg), 2400 mg/day (50-70 kg) and 3200 mg/day (>70 kg) respectively. It is prescribed in 2 daily divided doses, along with food. It is advisable to obtain liver and renal function tests and electrocardiogram before starting and yearly during treatment. Therapeutic plasma concentrations are determined to be 10-25 mg/L (42-105 µmol/L). The commercial formulation of RUF contains lactose; hence it should be avoided in patients with lactose intolerance.

Stiripentol

Stiripentol (STP) increases GABA levels in the nervous system by inhibition of synaptic uptake and inhibition of GABA-transaminase. It also enhances GABA-A receptor-mediated transmission and increases the mean-duration (but not the frequency) of GABA-A receptor chloride channels by a barbiturate-like mechanism. STP has significant

(99%) plasma protein binding. It is metabolized in the liver, primarily by desmethylation and glucuronidation, mediated by CYP1A2, CYP2C19, and CYP3A4, to 13 different inactive metabolites. It has a saturable kinetics with elimination half-life and clearance inversely varying with dose. About 73 percent of an administered dose is excreted in urine as metabolites.

It has been authorized under a “conditional approval” scheme by the European Medicines Agency for adjunctive treatment of seizures in children with severe polymorphic epilepsy of infancy (Dravet syndrome). However, it has also been used as adjunctive treatment with carbamazepine in children with refractory focal seizures. Importantly, carbamazepine, phenytoin and phenobarbital should not be combined with STP in the management of Dravet syndrome.

Common adverse effects include mild-moderate gastrointestinal symptoms: anorexia, loss of appetite, nausea or vomiting. Weight gain is common when it is co-administered with valproate. Less commonly STP causes drowsiness, ataxia, hypotonia, dystonia, hyperkinesias insomnia, aggressiveness, irritability, or hyperexcitability. Rarely, cutaneous photosensitivity has been reported.

STP is known to have numerous drug interactions. Conventional enzyme inducers are known to decrease plasma levels of STP. Contrarily, STP is a potent inhibitor of CYP2C19, CYP3A4, and CYP2D6; and, increases plasma levels of carbamazepine, phenobarbital, valproic acid, clobazam and its pharmacologically active metabolite N-desmethyloclobazam; and, numerous other drugs viz. citalopram, omeprazole [CYP2C19]; astemizole, chlorpheniramine, calcium channel blockers, statins, codeine [CYP3A4]; propranolol, fluoxetine, sertraline, haloperidol, and tramadol [CYP2D6]. Because of this interaction STP enhances anorexia associated with valproic acid; risk of polymorphic ventricular tachyarrhythmia with cisapride, halofantrine, pimozide, quinidine, and bepridil; risk of extremity necrosis with ergot alkaloids; nephrotoxicity with tacrolimus, sirolimus and cyclosporine; and, rhabdomyolysis with statins.

It is usually initiated at a dose of 50 mg/kg/day in 2 to 3 divided doses, increasing every 3 days by 100 mg/kg/day to a maximum of 4 g/day. Clinically, the regimen would almost always include a co-prescription of valproate and clobazam; hence, upward titration should be cautious once the dose exceeds 3 g/day. Weight gain becomes an important issue with this regimen, so, it is good to obtain baseline fasting blood glucose and serum lipids (personal practice). STP is rapidly degraded by gastric acid, hence, it must always be ingested with food, but co-ingestion of milk or dairy products and carbonated drinks should be avoided. It should be remembered that STP was evaluated for the treatment of Dravet syndrome in children >3 years or age. Thus, the decision to prescribe it to younger children should be made on an individual basis.

Topiramate

Topiramate (TPM) is a sulfamate-substituted monosaccharide derivative of D-enantiomer of fructose. The proposed mechanisms for TPM include inhibition of AMPA or kainate subtype of glutamate receptors, augmentation of GABA-A receptor mediated chloride currents, inhibition of sodium and L (large conductance) type voltage gated calcium channels, increased potassium channel conductance and weak carbonic anhydrase inhibition. It has high oral bioavailability (80%) and the absorption is not significantly affected by food. It has minimal liver metabolism and mainly renal excretion.

It is approved as monotherapy (age >10 years) or adjunctive therapy (age >2 years) of partial seizures with or without secondary generalization; and, for adjunctive therapy of seizures associated with LGS (age >2 years). Other indications include absence seizures, infantile spasms, JME, and, myoclonic-astatic epilepsy (MAE, Doose syndrome). Clinically, it is mostly used as add-on in patients with focal epilepsy failing adequate monotherapy and in children with LGS.

Adverse effects commonly affect cognition and include impaired expressive language function, impaired verbal memory, dysnomia and decline in word fluency. Other adverse effects include somnolence, fatigue, ataxia, angle closure glaucoma, weight loss, metabolic acidosis, renal stones, hypohidrosis and paresthesias. Higher dose, rapid titration and poly-therapy contribute to increased propensity for adverse effects. Children on ketogenic diet should specially be monitored for metabolic acidosis and nephrolithiasis. Concurrent administration with valproate is known to increase the risk of hyperammonemic encephalopathy and such children should be screened for inborn urea cycle disorders.

TPM is started at 0.5 to 1 mg/kg/day with slow titration to usual maintenance dose of 5 to 9 mg/kg/day (maximum 500 mg/d), given in 2 divided doses. Renal impairment with creatinine clearance <70 ml/min/1.73 m² warrants dose adjustment. There is a report of using TPM for refractory status epilepticus with nasogastric bolus dose of 10 mg/kg for 2 days followed by 5 mg/kg/day.

Vigabatrin

Vigabatrin (VGB) exists as a racemic mixture with both an active S(+) enantiomer and inactive R(-) enantiomer. It is an irreversible inhibitor of GABA-transaminase, the major GABA degradation enzyme. Hence, the pharmacologic action of VGB lasts typically for 4 to 6 days, until inactivated enzymes are re-synthesized. It may also stimulate GABA release. It has good oral bioavailability (>90%), negligible protein binding and minimal liver metabolism. Renal excretion of unchanged drug is the major route of elimination.

VGB is the drug-of-choice for treatment of infantile spasms associated with tuberous sclerosis complex. It is licensed for monotherapy of other cryptogenic infantile spasms and for adjunctive therapy of resistant focal epilepsy. Clinically, VGB is also used as first or second line treatment of symptomatic infantile spasms. Importantly, VGB can aggravate atypical absence seizures in LGS where it can provoke absence status epilepticus; and, myoclonic seizures in static encephalopathy and progressive myoclonus epilepsy syndromes.

The major adverse effect of VGB is irreversible visual field constriction which starts as a bilateral nasal defect and may progress to a bilateral concentric field defect. The central visual acuity and color vision are always preserved. It is recommended that patients should undergo testing at treatment initiation, then at 3-month intervals for the first 18 months of treatment, and every 6 months thereafter. Static or kinetic perimetry is suitable for patients aged >9 years of age. Field-specific visual evoked potentials are sensitive and specific for identifying the VGB-induced defect in children aged >2 years. Full-field or multifocal electroretinogram may be useful to evaluate infants and developmentally delayed children. The next common group of adverse effects includes behavioral changes: hyperactivity, irritability, aggression, self-injurious behavior and self-defiance. Other reported undesirable effects are weight gain, facial edema, headache, insomnia, ataxia, tremor, somnolence and stupor. VGB does not have significant drug interactions except that it may decrease phenytoin levels. The recommended dose of VGB is 20-150 mg/kg/day in 2 divided doses (maximum 3000 mg/day).

Zonisamide

Zonisamide (ZNS) is a sulfonamide with several proposed mechanisms including partial blockade of activity-dependent sodium channels, blockade of the T (transient opening)-type voltage gated calcium channels, and, inhibition of potassium-mediated glutamate release. It has other molecular effects whose relevance to antiseizure efficacy is not exactly defined, including, increase in extracellular levels of dopamine and serotonin, upregulation of excitatory amino acid carrier-1, downregulation of the expression of GABA transporter-1, and weak carbonic anhydrase inhibition.

It has >90 percent bioavailability after oral administration. Co-ingestion of food may delay but does not decrease the absorption. It is metabolized by successive acetylation, reduction and glucuronidation, the intermediate step being mediated by CYP3A4 iso-enzyme. The metabolites are not pharmacologically active. It excreted by kidney, 35 percent unchanged and 65 percent as metabolites. At a creatinine clearance of <20 ml/min, the clearance of ZNS is reduced by 35 percent. Hence, it requires a proportional dose modification in patients with renal compromise.

ZNS is licensed for adjunctive therapy for partial and secondarily generalized seizures in adults. However, it is a broad spectrum AED with efficacy in several seizure types and epilepsy syndromes including childhood onset focal seizures with or without secondary generalization, absence seizures, infantile spasms and myoclonic seizures occurring in the context of JME, LGS, MAE (Doose syndrome) and some progressive myoclonus epilepsy syndromes.

Common adverse effects include neuropsychiatric symptoms like drowsiness, fatigue, ataxia, reduced spontaneity and psychomotor slowing or transient impairment in verbal learning. Contrarily, sometimes there may be aggression, agitation, irritability, poor attention, hyperactivity, dysphoria, paranoia or even frank psychosis. The next common adverse events involve gastrointestinal system, e.g. anorexia, nausea, abdominal discomfort, vomiting and weight loss. Although ZNS is chemically similar to sulfonamide antibiotics, it does not contain an arylamine group at N4 position, hence, the risk of allergic reactions is substantially lower. Less commonly, metabolic and autonomic adverse effects have been reported including metabolic acidosis, nephrolithiasis, paresthesias and hypohidrosis. Because of 65 percent hepatic metabolism it is susceptible to a decrease in plasma levels when administered concurrently with cytochrome inducers. Risperidone is also known to decrease plasma levels, however, the mechanism is not known.

Children are typically started on 1 to 2 mg/kg/day with upward titration every 1 to 2 weeks to a usual maintenance dose of 8 mg/kg/day. If concurrent enzyme inducers are used, a higher maintenance dose of 12 mg/kg/day may be required. Rarely, in young children, very high doses of up to 20 mg/kg/day are required and well tolerated. ZNS is prescribed in 1 to 2 divided doses. Slow titration probably prevents some of the neurobehavioral adverse effects. If feasible, ZNS should be avoided in patients on acetazolamide, topiramate or ketogenic diet, because of increased risk of metabolic acidosis and nephrolithiasis. Adequate fluid intake is prudent in all patients on ZNS. Children are susceptible to hyperthermia due to decreased sweating and may require palliative measures.

ISSUES

Basic Science: Response and Resistance

Epileptogenesis has never been understood in terms of individual patient, thus, application of the understanding of AED mechanisms to customize drug therapy for every patient has not been possible. Of late, the importance of host factors in drug treatment of epilepsy is being realized. Patients who do not respond to AED may be inherently 'resistant' to them from the outset or may become 'refractory' to them because of multiple concurrent genetic or acquired factors. Recent research has focused on changes which prevent optimal drug-receptor interaction (target

hypothesis) and failure to attain sufficient levels inside the nervous system at the site of action (transporter hypothesis). Other emerging mechanisms for epileptogenesis include autoimmunity, inflammation, mitochondrial oxidative stress and electrical coupling in neurons or glial cells via gap junctions. These mechanisms represent potential targets for development of newer AED.

CLINICAL TRIALS

Most patients with new-onset epilepsy have a 50 percent likelihood of being controlled with their first AED at moderate dose. Additional 10 percent would attain seizure freedom with second monotherapy or add-on. Newer AED are, perhaps, unlikely to offer a huge advantage in terms of this 'efficacy'. However, it is expected that they offer substantial benefit in terms of 'effectiveness' which is a combined measure of efficacy and tolerability. However, most of the newer AED have not been evaluated as monotherapy in clinical trials. Since placebo-controlled design would be unethical, they are usually tested with alternative active-control designs like pseudo-placebo (lowest dose of standard treatment) or add-on-taper-to-monotherapy.

The duration of such trials is very short, e.g. presurgical withdrawal design. Further, failed superiority trials are taken to imply non-inferiority without any further analysis. Thus, the existing evidence for newer AED does not reflect clinical decision-making and there is need to design more representative studies, e.g. newer monotherapy versus conventional polytherapy. Overall, newer AED have not changed the prognosis for the whole epileptic population vastly; but have certainly improved outcome in selected patients. There are very few AED in phase III trials at present, and the wise thing as a clinician is to choose judiciously both the regimen and the patient to whom it is prescribed.

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Febrile Seizures: Revisited

Amitava Sengupta

BACKGROUND

Febrile convulsions are the most common type of seizure disorder observed in the pediatric age group. They generally have a very good prognosis but may also indicate an acute critical infectious disease such as bacterial meningitis or sepsis.¹

Historically, febrile seizures were first described by the ancient Greeks. However, it was not until this century that febrile seizures were recognized as a distinct syndrome separate from epilepsy. In 1980, a consensus conference held by the National Institutes of Health (NIH) described a febrile seizure as, “An event in infancy or childhood usually occurring between three months and five years of age, associated with fever, but without evidence of intracranial infection or defined cause”.² It does not exclude children with prior neurological impairment and neither provides specific temperature criteria at which a seizure is considered febrile.

As per consensus of present day updates, febrile seizures are defined as seizures during fever, between six months and five years of age in the absence of intracranial infection.³

DEFINITIONS

Febrile seizures can be classified as simple, complex or atypical.

Simple febrile seizures are defined as seizures in neurologically healthy infants and children between six months and five years of age whose seizure is brief (<15 minutes), generalized, and occurs only once during a 24-hour period. This practice parameter excludes children whose seizures are attributable to a central nervous system infection (symptomatic febrile seizures) and those who have had a previous afebrile seizure or central nervous system abnormality (secondary febrile seizures).⁴

Complex febrile seizures are prolonged (last >15 minutes), have a focal onset and recur more than once in 24 hours. Complex febrile seizures may indicate a more serious disease process, such as meningitis, encephalitis, or cerebral abscess.⁵

Atypical febrile seizures vary from the above mentioned criteria, with features like unusual age of presentation or lower temperature than usual. The more the seizure differs from the classical syndrome; it is preferable to classify the event as “seizures with fever”. Febrile seizures should rarely be diagnosed in children who have afebrile seizures.⁶

Late onset febrile seizure, persistent febrile seizure, generalized epilepsy and febrile seizure (GEFS) and febrile status epilepticus (one seizure lasting 30 minutes or multiple seizures during 30 minutes) are special entities that need to be considered in the spectrum of febrile seizures.³

During the past two decades, the discussion on febrile seizures has moved from their natural history to their treatment. Now that we recognize that the majority of febrile seizures are benign, the aim of ideal management is to reassure parents. Knowledge of epidemiology, causes, and prognosis of febrile seizures will help us treat children and advise the parent’s rationally.⁷

EPIDEMIOLOGY

The prevalence rate of febrile seizures in young children is three to four percent.⁸ They are age dependent and are rare before nine months and after five years of age. The peak age of onset is 14 to 18 months of age.¹ Febrile seizures frequently recur, with recurrence rate of about 33 percent. Increased rates of recurrence ranging up to 50 percent are seen in first febrile seizures that occur below 12 months of age,⁸ seizures with low-grade fevers, when there is positive family history for febrile seizure and complex

features. Febrile seizures occur in all races and some studies demonstrate a slight male predominance. Remission is usually seen by the age of five years.³

Children with febrile seizures have a slightly higher incidence of epilepsy compared with the general population (2% versus 1%). Risk factors for epilepsy later in life include complex febrile seizure or neurologic abnormality prior to first febrile seizure, developmental delay and family history of epilepsy/febrile seizures.^{9,10} In patients with several risk factors, the incidence of epilepsy rises to nine percent as compared to one percent in children having febrile seizures with no risk factors.¹

PATHOPHYSIOLOGY

Febrile seizures occur in young children during a period in their development when the seizure threshold is low. This is a time when they respond with comparably higher temperatures. Animal studies suggest a possible role of endogenous pyrogens, such as interleukin 1 beta that, by increasing neuronal excitability, may link fever and seizure activity.¹¹ Preliminary studies in children appear to support the hypothesis that the cytokine network is activated and may have a role in the pathogenesis of febrile seizures, but the precise clinical and pathological significance of these observations is not yet clear.^{12,13}

The most commonly associated illnesses are upper respiratory infection, gastrointestinal infections, otitis media and roseola. Viral illnesses are the predominant cause of febrile seizures. In recent literature, the human herpes virus types six and seven have been implicated as possible specific causal agents. *Shigella* gastroenteritis also has been associated with febrile seizures. A direct toxicity affecting the central nervous system has been linked with this association.⁷ One study suggests a relationship between recurrent febrile seizures and influenza A.¹⁴

Febrile seizures tend to occur in families. In a child with febrile seizure, the risk of febrile seizure is 10 percent for the sibling and almost 50 percent for the sibling if a parent has history of febrile seizures as well.¹⁵

While polygenic inheritance is likely, a small number of families are identified with an autosomal dominant pattern of inheritance of febrile seizures, leading to the description of a “febrile seizure susceptibility trait”. Although the exact molecular mechanisms of febrile seizures are yet to be understood, underlying mutations have been found in genes encoding the sodium channel and the gamma amino-butyric acid A receptor.¹⁶⁻¹⁸ Studies have linked the febrile seizure gene to chromosomes 19p and 8q 13-21.¹

RISK FACTORS FOR DEVELOPING FEBRILE SEIZURES¹⁹⁻²²

- Family history of febrile seizures (first- or second-degree relative)

- History of developmental delay
- Preterm birth and low-birth weight
- Neonatal discharge at an age greater than 28 days (suggesting perinatal illness requiring hospitalization)
- Daycare attendance
- Maternal alcohol intake and smoking during pregnancy has a 2-fold increased risk.

Surprisingly there is no data to support the theory that a rapid rise in temperature is a cause of febrile seizures.

Presence of 2 of the above risk factors increases the probability of a first febrile seizure to about 30 percent.

RISK FACTORS FOR RECURRENT FEBRILE SEIZURES^{23,24}

About one-third of all children with a first febrile seizure experience recurrent seizures.

- Young age at time of first febrile seizure (less than 12 months of age)
- Relatively low-grade fever at time of first seizure
- Family history of a febrile seizure in a first-degree relative
- Brief duration between fever onset and initial seizure (less than one hour)
- Multiple initial febrile seizures during same episode (complex features).

EPILEPSY AND COGNITIVE OUTCOME

The greatest concern for the family following their child's febrile seizure is the risk of developing epilepsy (defined as two unprovoked seizures) in future. Children with febrile seizures have only a minimally greater risk of epilepsy in later life as compared to the general pediatric population. Risk factors for developing epilepsy in later life have been already enumerated in the section of epidemiology.

The effects of febrile seizures on developmental milestones and behavior appear to be limited. There is no evidence of brain damage, motor or intellectual compromise following simple febrile seizures.²⁵ Even febrile status epilepticus does not appear to affect long-term neuropsychological outcome. Literature does not reveal any difference between controls and children with febrile seizures on IQ testing and academic performance.⁷

Although usually benign, experiencing febrile seizures in their child is very frightening for all parents. Reassurance is the most important key-both by careful medical evaluation and proper counseling of the family.

HISTORY

The type of seizure (generalized or focal) and its duration should be described in order to help differentiate between simple and complex febrile seizures. Focus on the history of fever, duration of fever, and potential exposures to illness must be noted. A history of the cause of fever (e.g.

viral illnesses, gastroenteritis) should be elucidated. Some children may be suffering from a chronic seizure disorder and have aggravation of seizure episodes during fever. These are not febrile seizures and are termed as “seizures with fever.”

Recent antibiotic use is particularly important because partially treated meningitis must be kept in mind. A history of seizures, neurologic problems, developmental delay, or other potential causes of seizure (e.g. trauma, ingestion of any poisons) should be sought.

Physical

A clinician's initial prime approach should be to determine the cause of fever and to rule out meningitis, encephalitis or evidence of any other intracranial infection and pathology. A careful physical examination and evaluation often reveals otitis media, pharyngitis, or a viral exanthem. Serial monitoring of the patient's neurologic status is important. Focused clinical examination for meningeal signs as well as for signs of trauma or toxic ingestion is essential.

Differentials

A rationale list of possibilities should be entertained while working up a case of seizure associated with fever. These may include illnesses like: Meningitis and encephalitis, bacteremia and sepsis, epidural and subdural infections epidural hematoma and brain abscess.

Laboratory Studies

Variability exists in the approach to optimal management of patients with complex febrile seizures. Routine laboratory studies such as complete blood counts, cultures and routine chemistries including electrolytes are performed as part of a search for the source of fever and evaluation of the patient; in view of history and clinical findings. Patients with febrile seizures have an incidence of bacteremia similar to patients with fever alone.

Imaging Studies

Neuroimaging is not recommended in the evaluation of a neurologically healthy child with a first simple febrile seizure. They may be considered, if the seizures are complex or atypical, the child is neurologically abnormal, or if there are multiple febrile seizures.⁶

Electroencephalogram

The value of an electroencephalogram (EEG) in the evaluation of febrile seizure has not been promising. It shows deviation from normalcy in the early phase in one-third of affected children. Both focal and generalized abnormalities have been described in the immediate postictal period. However, these abnormalities do not predict the risk of a recurrence or risk of epilepsy in the future.⁷

An EEG is not necessary in the routine evaluation of a child with a first febrile seizure. It may be considered in the work-up of children with complex or atypical seizures or with additional risk factors for epilepsy in future.¹

EEG is useful in ruling out possibility of encephalitis in a child with complex febrile seizures or prolonged postictal period.⁷

Lumbar Puncture

Lumbar puncture is usually not recommended for children with first simple febrile seizure.²⁶ Meningitis can present with a seizure. However, the seizure usually is not the only sign of meningitis. Patients who have a first-time febrile seizure and have an unusually prolonged postictal period should be evaluated for meningitis. Reviews of the medical literature report less than 5 percent incidence of meningitis in children presenting with seizures and fever.

Risk factors for meningitis in patients presenting with seizure and fever include the following:

- Visit to a healthcare facility, 48 hours prior to the seizure episode
- Seizure activity at the time of arrival in the emergency
- Focal seizures with suspicious clinical features relating to meningitis
- Prolonged postictal period 1996, American Academy of Pediatrics (AAP) recommendations for lumbar puncture
- Strongly considered in infants younger than 12 months presenting with fever and seizure
- A lumbar puncture is considered in patients aged 12 to 18 months, if seizures are complex with prolonged postictal phase
- Lumbar puncture should not routinely be done in children older than 18 months, unless there is history or clinical features suggestive of intracranial infection.

Clinicians must be sensitive to the fact that often, recognizing meningitis in infants and young children may be difficult and the range of experience in the evaluation of pediatric patients among attending physicians is crucial. We should never assume that a child with a previous febrile seizure will not develop meningitis. Children with persistent fever should be closely monitored, even if the initial CSF examination is normal.

MANAGEMENT

This primarily includes rationale approach towards investigations with restraint, treatment of the acute episode and prophylaxis for future episodes with adequate and proper family counseling.³

Antipyretics do not prevent recurrences, however, controlling the fever with antipyretics does give comfort to the child and reassurance to the family.¹ Acetaminophen (15 mg/kg/dose), ibuprofen (5-10 mg/kg/dose) or mefenamic acid (3-5 mg/kg/dose) are preferred medications.

Acute Management

Termination of active seizures lasting two to five minutes.

Benzodiazepines are rapidly absorbed and have a short, effective half-life. Hence, they are used as first line drugs of choice for aborting acute seizures. However, the clinician must be aware of side effects, such as somnolence, lethargy, irritability, ataxia and deal with them accordingly. The two drugs most widely used in this group are midazolam and diazepam.

Home Therapy

Rectal diazepam has been well documented in literature for treatment of acute seizures.²⁷

Studies comparing efficacy of intranasal midazolam to diazepam for acute treatment of prolonged acute febrile seizures, found both drugs to be equally effective.²⁸

Further, some studies from the year 2000 onwards have reported that intranasal midazolam was effective in ending acute seizures within ten minutes.²⁹⁻³¹ Intranasal midazolam is a reasonably safe and preferred route for terminating acute seizures in childhood. It has a rapid onset of action, no significant effects on respiration, is easy to administer and is more socially acceptable.³²

Dosages

- Midazolam – buccal/nasal spray (0.2-0.4 mg/kg/dose). During nasal instillation, the dosage is to be divided equally into each nostril. Intranasal midazolam is available in an atomizer which contains 50 metered doses of 0.5 mg/ metered dose. Intranasal midazolam solution contains 5 mg/ml. The preparation is available with the brand name of “INSED”.
- Rectal diazepam (0.5 mg/kg/dose), buccal (0.4-0.5 mg/kg/dose), intranasal (0.2 mg/kg/dose). Rectal diazepam is available in the form of gel, and also the injectable preparation of the drug can be given rectally.

Hospital Therapy

Active seizures should be treated with airway management, high-flow oxygen, supportive care and anticonvulsants as necessary.

- Midazolam (0.1-0.2 mg/kg/dose intravenous bolus)
- Diazepam (0.2-0.5 mg/kg/dose intravenous bolus).

Infusions may be used when indicated in situations such as status epilepticus.

Intermittent Prophylaxis

In majority of children who experience febrile seizures in early life and their good outcomes make it unfeasible to justify long-term administration of anticonvulsants.²⁸ However, intermittent prophylaxis, administered when children at risk for febrile seizures have fever is prudent.

The ideal approach to prevent recurrence of febrile seizures is to intervene at the onset of febrile illness by initiating the recommended anticonvulsant.

Intermittent diazepam therapy for the prevention of recurrence of febrile seizures has been well documented in literature and shown to be effective.³³

Intermittent clobazam therapy is also as effective in the prevention of recurrence of febrile seizures. Clobazam induced ataxia is much lower than that reported with diazepam.³⁴ As per present day recommendations, oral clobazam is the preferred drug in intermittent prophylaxis for preventing recurrence.³

Dosages

- Clobazam
The therapeutic dosage of clobazam ranges from 0.3 to 1 mg/kg/day.
Recommendation for Intermittent Prophylaxis:
 - (0.75 mg/kg/24 hours) in 2 divided doses, for two to three days.³
 - Doses as per weight category³⁴
 - Up to 5 kg – 5 mg/day
 - 6 to 10 kg – 5 mg/twice daily
 - 11 to 15 kg – 7.5 mg/twice daily
 - >15 kg 10 mg/twice daily
 Duration two to three days.
- Diazepam
Oral diazepam at the onset of each febrile illness-0.3 mg/kg/dose every eight hours (1 mg/kg/24 hours) for two to three days duration.¹

Prolonged Prophylaxis

Continuous anticonvulsant prophylaxis for preventing recurrent febrile seizures is no longer recommended for most children. Phenobarbitone usage decreases recurrence of febrile seizures but also results in compromise of cognitive function in treated children as compared with untreated children.¹

Special Circumstances for Consideration of Continuous Prophylaxis³

- Febrile seizure recurrence more than six per year, in spite of regular intermittent prophylaxis
- Severe cases of febrile status epilepticus

Age group less than one year- phenobarbitone as per recommended doses: for a period of one to two years

Older children- sodium valproate as per recommended doses: for a period of one to two years

In this regards, a discussion with the parents about the harms and benefits of prolonged anticonvulsant therapy should have a holistic approach along with proper counseling.

INPATIENT CARE

The decision to admit should be individualized. Most patients should be observed in the emergency room (ER) until awake and alert.

Conditions requiring admission of the patient include the following:

- More than one seizure within 24 hours
- Unstable clinical status
- Lethargy beyond the postictal period
- Uncertain home situation
- Unclear follow-up care.

FOLLOW-UP ADVICE

Medical re-evaluation of discharged patients and parental education should be arranged in a follow-up appointment within 24 to 48 hours. Discharge medications include antipyretics and antibiotics, if indicated (e.g. otitis media, pneumonia).

PATIENT EDUCATION

Parents should be taught what to do if their child has another seizure. They should be counseled on the benign nature of febrile seizures and educated about the role of Intermittent prophylaxis therapy. Also, parents should be reassured that simple febrile seizures do not lead to neurologic problems or developmental delay.

SPECIAL CAUTIONS

- 2008 Clinical Practice Guideline for the Long-term Management of the Child with Simple Febrile Seizures:
 - Evidence shows preponderance of harm over benefit with continuous or intermittent use of anticonvulsants for children with one or more simple febrile seizures.³⁵
 - The AAP guideline released in 2008 does not recommend prophylactic use of diazepam as the risk outweighs the benefits.³⁵
- Studies report that diazepam, given orally or rectally every eight hours during febrile illnesses, is effective in preventing recurrence of febrile seizures.^{36,37} However, these benzodiazepines can cause lethargy, drowsiness, and ataxia, and sedation, which could mask an evolving central nervous system infection.
- A strong association exists between febrile status epilepticus or febrile seizures characterized by focal symptoms and later development of temporal lobe epilepsy.^{38,39}

PREVENTION

Influenza A is now having a more established role in the etiology of febrile seizure, both acute and recurrent.

Vaccination against influenza A in the flu season may have a role in preventing development of both acute and recurrent febrile seizures.⁴⁰

CONCLUSION

Febrile seizures are a frequent and benign disorder of infancy and early childhood. In a majority of children, they represent the expression of a genetically inherited response to fever. For these children, usually no treatment is required and parents and family should be reassured and adequately counseled. It is rare that febrile seizures represent early evidence for later epilepsy. Electroencephalography is not predictive of epilepsy in the future in children with febrile seizures.

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Intractable Epilepsy in Children and Adolescents

Nandan Yardi

INTRODUCTION AND EPIDEMIOLOGY

Epilepsy is one of the important public health problems in developing¹ and developed countries accounting for a prevalence (active cases, with at least one seizure in the last 5 years) of 0.5 to 1 percent of the general population while incidence (occurrence of new cases, usually in 1 year) is higher in developing countries at 70-100/100,000 population per year. A treatment gap of 85 to 90 percent, defined as the percentage of persons with active epilepsy, who at any given time, are not receiving treatment, has been found in most developing countries including India in urban, rural and tribal populations.^{2,3}

Five community-based surveys from India have revealed prevalence rates per thousand population of 2.5 for Kashmir,⁴ 3.6 for Parsis of Mumbai,⁵ 4.5 for tribals of western Maharashtra,³ 4.4. for Karnataka⁶ and 4.9 for Kerala.⁷ Age specific prevalence of epilepsy was higher in the first three decades of life.

Although believed to be intractable and progressive in the past two centuries by many authors, it has become evident in the present century with advances in various treatment options, that a few unfortunate individuals have intractable epilepsy. The challenges for this century are reduction of the treatment gap and management of intractable cases. When misdiagnoses, misclassification, occasional seizures, pseudoepileptic seizures and noncompliance are excluded, the true intractability of epilepsy is less than 20 to 30 percent and not more than 5 to 10 percent of patients on optimal and appropriate antiepileptic therapy will prove to be truly intractable, when these factors and surgery are ruled out.¹⁴ The most common misdiagnoses are vascular collapse and arrhythmias, psychiatric causes, breath holding spells day dreaming and other sleep disorders (parasomnias, night terrors) and migraine or vertigo that need to be carefully ruled out at the outset by a careful history and documentation by video-EEG.

DEFINITION OF INTRACTABILITY

The concept of intractability has to take into account not only the seizure frequency, but also severity based on severity rating systems, circadian variations, and most importantly the impact of the disorder on the persons well-being and level of scholastic and social functioning and is usually graded according to how aggressively previous treatment has been pursued. Several population based studies have shown that 70 to 80 percent of persons with newly diagnosed epilepsy have a 1 year remission⁸ that most remissions occur early.⁹ Still we are left with 20 to 30 percent of patients with difficult to treat seizures and are intractable.

There is a cluster of intractable seizures in infancy and early childhood. In infancy the immature brain is especially susceptible to seizures due to, among other things, enhanced excitation, diminished inhibition and underdeveloped nigral seizure control.¹⁰ These and other susceptibility factors predispose to many intractable syndromes, peculiar to infancy and early childhood, such as early infantile epileptic encephalopathy (Ohtahara's syndrome), West syndrome, Lennox-Gastaut syndrome, epilepsia partialis continua (Kojewnikow syndrome and Rasmussen's encephalitis) and the Dravet syndrome. In adolescence, partial seizures, progressive myoclonic epilepsies and lesion epilepsies tend to be associated with intractability.

Predictors of Intractability

The predictors of intractability for seizures in children were symptomatic etiology of seizures, occurrence of status epilepticus, high initial seizures frequency and poor short-term outcome of therapy.¹¹ Early onset of epilepsy in infancy, abnormal neurological status, neurotic or psychotic comorbidity, a grossly abnormal EEG, presence of

multiple seizure types are other predictors. Individual seizure types such as tonic, atonic or myoclonic have a different outcome on long-term follow-up. There is a marked overlap between individual risk factors necessitating a multivariate analysis.

Two classical population based studies^{12,13} have suggested that most patients that achieve seizure control do so in the first-two years of the onset of epilepsy. This knowledge has been utilized to make the working definition of intractable epilepsy—patients who continue to have two or more disabling seizures per month for a period of two years or more in spite of adequately monitored and supervised antiepileptic drugs, appropriate for the seizure type and syndrome, using two monotherapies (some include one polytherapy) are said to be intractable and need evaluation in a comprehensive epilepsy care program from an epileptologist and his team. Depending on individual situations and substrates (in this post-MRI era), this period is sometimes shortened before presurgical evaluation is conducted, as some conditions like mesial temporal sclerosis or certain hamartomas that are highly epileptogenic such as a dysembryoplastic neuroectodermal tumor, cause disruption of the quality of life and learning, needing early surgical attention.

Conditions Likely to be Associated with Intractability

In childhood and adolescence, the following conditions are likely to be resistant to therapy and have a peculiar natural course with and without antiepileptic medication.

These are progressive myoclonic epilepsies and other progressive metabolic encephalopathies.

- The triad of age dependent epileptic encephalopathies—West syndrome, Ohtahara's syndrome, Lennox-Gastaut syndrome.
- Rasmussen encephalitis and infantile hemiplegia.
- Neurocutaneous syndromes like tuberous sclerosis and Sturge-Weber syndrome.
- Cerebral malformations and disorders of neuronal migration.
- Granulomas—Neurocysticercal and tubercular.
- Cerebral palsy and hypoxic ischemic encephalopathy.
- Localization related epilepsies, both symptomatic and cryptogenic.
- Hippocampal or mesial temporal sclerosis, sometimes seen in childhood but the commonest structural cause in adolescence and early adulthood.
- Vascular malformations including cavernomas and AVMs.
- Indolent tumors like gliomas, meningiomas, dysembryoplastic neuroectodermal tumors (DNETs).
- Scars—postmeningitic, vascular damage, hypoxic ischemic damage associated with difficult childbirth or otherwise, hypoglycemic damage, traumatic damage.

Investigation of Intractable Epilepsy

The objectives of investigation are to confirm that the person has epilepsy and to rule out nonepileptic conditions masquerading as episodic seizure like events, to clarify the nature of the seizure type and to make a syndromic diagnosis if possible, so as to treat generalized epilepsies and idiopathic partial epilepsies with appropriate antiepileptic medication. At this point, it is an opportunity to re-evaluate the past antiepileptic drugs used and ensure that therapeutic use has been documented to determine pharmacoresistance to various drugs used,¹⁷ preferably taking into account the past drug levels findings, if available. It is important to localize focal nonidiopathic epilepsies, to confirm lateralization of the seizure focus, and to determine the operability of the focal lesion. This determines ideal selection of surgical candidates with concordance for seizure semiology, imaging, and electrographic and neuropsychological tests. It ensures that the surgery will not result in untoward disabling neuropsychological deficits.

All these are part of the presurgical evaluation indicated in all patients with difficult to treat seizures.

Protocol for Presurgical Evaluation

A protocol for presurgical evaluation may need to be extensive depending on what epilepsy syndrome we are dealing with and as it becomes apparent whether it is a defined temporal lobe syndrome, the evaluation may be discontinued so as to have a low cost of presurgical evaluation.^{15,16} In extratemporal lesions, especially localized to eloquent areas, usually the evaluation needs to be more extensive, so as to evaluate the safe operability of the lesion.

The protocol we follow at the yardi epilepsy clinic, Pune and comprehensive epilepsy center at Jehangir Hospital, Pune consists of:

Detailed medical history—evaluate the past treatments, drug levels, seizure type, frequency, EEGs, medical and neurological examinations.

Sixteen channel wake and sleep scalp EEG with activating procedures—hyperventilation and photic stimulation.

MRI scans—epilepsy profile 1.5 T or 3 T MRI study for hippocampal volume and sclerosis. Use of coils brings out cortical malformations better and can be effectively used with 1.5 T MRI and review of previous CT and screening MRI studies:

- Neuropsychological evaluation
- Psychosocial evaluation
- Psychiatric evaluation
- Visual field testing
- Ictal video scalp EEG recording to characterize the seizures, and lateralize the seizures and to rule out psychogenic seizures (3-5 days or till adequate habitual seizures are recorded)

- Intracarotid amobarbital (Wada) test for evaluation of language and memory lateralization may be done but depends on availability of the medication. Alternatively, if MRI scan may help to localize the eloquent areas such as speech and memory using special protocols for evaluation
- Single photon emission spectrophotometry (SPECT) scan, SISCOM and positron emission tomography (PET) using radiolabelled ligands to define various areas of brain by imaging techniques have been useful in recent times
- Magnetoencephalography (MEG) and use of intracranial or depth electrodes need to be used judiciously to define the epileptogenic cortex.

All findings are discussed in a multidisciplinary case conference by concerned specialists to decide the feasibility and planning of the surgical procedure planned and the expected outcome.

HISTORY

Obtaining a detailed history from the patient and relatives who have been onlookers, for the habitual seizures, is very important to determine auras, and automatisms, (oroalimentary or gestural), events like ictal paretic posturing of the upper limb, ictal dysphasia, spitting, and postictal Todd's palsy that help in localization. A detailed neuropsychiatric and psychological evaluation may help to rule out nonepileptic pseudoseizures in most patients especially when both true and nonepileptic-seizures exist in the same patient.

Clinical Examination

Often unrewarding in patients with focal epilepsies, it may yield useful information at times in the form of mild hemiparesis, visual fields defects, and mimic facial palsy, to help lateralize the focus.

Scalp EEG

Awake and sleep-deprived sleep studies have a higher positive yield than a wake record which depends on the strict protocol followed in recording and interpretation of EEGs that is critical to tailor the further evaluations in the protocol. The most reliable EEG findings in intractable patients are interictal spike or spike wave discharges from one temporal lobe and temporal intermittent rhythmic delta activity (TIRDA) but bitemporal spikes or spike wave activity is commonly seen in one-third of patients. Tandem sleep and wake records are important to rule out ESES (electrical status epilepticus in slow wave sleep).

Benign epileptiform variants such as wicket waves, 14 Hz spikes, and mu rhythm have to be carefully ruled out.

Prolonged Video EEG using Scalp Electrodes by Digitized Monitoring

A continuous digitized video EEG monitoring of habitual seizures is required for localization of electro-graphic abnormality and to correlate for semiologic concordance. Often when the seizure frequency is not very high, step-wise reduction of AEDs is done in admitted patients to allow seizures to be recorded. A handycam imaging for studying semiology and time locking with digital EEG is an adequate improvised tool for low cost presurgical evaluation, in straight forward temporal lobe cases showing unilateral hippocampal sclerosis and volume loss, when correlated with a good MRI study, in start up centers in developing countries.¹⁵ At this point of time, one can confidently rule out pseudoseizures and nonepileptic events.

In persons with unilateral temporal interictal abnormalities, it is mandatory to record at least 2 to 3 habitual seizures with concordant electrographic onset but with bitemporal interictal abnormalities, at least 5 to 7 seizures need to be recorded to make the decision about lateralization of the electrographic abnormality to determine the side of resection.

Semiological correlation is looked for in the analysis of these seizures. Features such as early head turning, unilateral limb automatisms, unilateral blinking and ictal nose wiping automatisms indicate ipsilateral localization while dystonic limb posturing, late head turning localize to the opposite hemisphere. Speech arrest and prolonged postictal dysphasia localize to dominant hemisphere while ictal spitting, ictal vomiting and ictal speech localize to nondominant hemisphere.

Neuroimaging: CT scan is not the modality of choice in epilepsy except when one looks for calcification in lesions such as DNET, neurocysticercosis or tumors or there is a discrete abnormality in a CT scan. A screening MRI scan is usually done in persons with epilepsy and may provide information about focal lesions but may not contain critical information about cortical dysplasia and hippocampal sclerosis or volume loss unless specific sequences are ordered as in an epilepsy profile MRI study. Angled coronal FLAIR sequences and spoiled gradient imaging are a must in each epilepsy profile study with Hippocampal volumes following thin sections to determine subtle abnormalities. Problems arise when there are bilateral Hippocampal abnormalities and dual lesions consisting of neocortical lesions with secondary hippocampal lesions.

MRI imaging and V EEG have revolutionized epilepsy presurgical evaluation and are the mainstays of evaluation, in experienced hands to give a cost effective yield and need to be ordered with great care at centers with good machines and experienced neuroradiologists to avoid repetitive costs from poorly ordered MRI studies.³¹

Neuropsychological assessment: Neuropsychological tests are the mainstay to determine the cognitive abilities of the brain and psychological state of the person with resistant epilepsy. It tells us about the dominance of the hemispheres, the various functions of various lobes from lobe function tests and chances of postresection memory loss. It is important to evaluate the quality of life issues pre and postresection.

Therapeutic drug monitoring: Plasma drug monitoring is important because of the large interindividual variation in blood levels of various antiepileptic drugs¹⁷ and interaction especially as resistant seizures are associated with polytherapy. The monitoring of drug levels has to be used and interpreted with great care to get maximum benefit for optimum seizure control.

Functional mapping: Noninvasive functional procedures such as SPECT, PET, functional MRI scans (fMRI), MR spectroscopy (MRS) and magnetoencephalography (MEG) with dipole localization, are some of the tests that may have to be used for difficult cases, especially extratemporal, neocortical epilepsies, to provide additional information regarding functional areas like memory, speech, language to avoid unacceptable neurological deficit following resection and to determine the appropriate type of resective procedure.^{18,19}

Invasive monitoring: Whenever the results of noninvasive monitoring (scalp EEG, video EEG and MRI and neuropsychological tests) are conflicting one may have to resort to invasive monitoring to get additional information. Mesiotemporal onset seizures may be missed on these tests or are poorly localized and need sphenoidal electrode placement below the foramen ovale to detect the ictal and interictal spike discharges.^{20,21} For extratemporal neocortical lesions, grids or strips or epidural pegs or intracerebral depth needle electrodes are used singly or in combination to obtain maximum information about interictal and ictal events and for functional mapping. These are associated with higher morbidity than the noninvasive monitoring and the results of resection of extratemporal lesions are not as good as temporal resections²²⁻²⁴ and noneloquent areas may be resected with limited presurgical investigation, if cases are chosen carefully, with fairly good results, especially if guided by intraoperative corticography.¹⁵

Intracarotid Amytal Test (Wada's Test)

The Wada's test is used in children above the age of 12 years and adults to determine the lateralization of language to one of the other hemisphere. The injection of amobarbital dose in one carotid is made to anesthetize each hemisphere in turn and language and memory are assessed for the nonanesthetized hemisphere using a standardized protocol for carefully assessing and interpreting the findings.²⁵ Amobarbital is not easily available in India.

Clinical Approach to Intractable Epilepsy

The first step in evaluation of intractable epilepsy is to determine if the seizures exist and therefore to rule out nonepileptic events. Then one determines the seizure type and treats generalized seizures and idiopathic focal seizures using appropriate antiepileptic drugs in therapeutic range guided by antiepileptic drugs where possible. Newer antiepileptic medications may be tried in polytherapy taking great care to avoid interactions. Alternative therapies may be tried. Polytherapy may be tried in a rational manner using drug combinations with different mechanisms of action based on the recent developments in receptor understanding. Many times, monotherapies is better than polytherapy in achieving an acceptable level of seizures with minimal side effects that may sometimes occur with polytherapy and may be more disabling than the seizure themselves.

However, nonidiopathic focal (lesional) epilepsies need to be picked up early and subjected to appropriate presurgical evaluation to determine respectability of the electrographic focus. Appropriate counseling of the patient and parents/relatives needs to be done from time to time as the presurgical evaluation progresses. Questions related to quality of life issues such as schooling, employment, driving, marriage, parenting and costs of medical and surgical therapy need to be discussed. Often, the direct and indirect costs of medical therapy are more in the long-term, especially if expensive new antiepileptic medications are used, as against resectable lesions where surgery may offer cure and an improved quality of life.

EPILEPSY SURGERY

Surgical treatment should be considered and performed before the negative consequences of the epilepsy have become destructive and irreversible, and before spread of the epileptogenicity has made the person inoperable. Yet surgical therapy should not be considered unless there is a reasonably good chance of improving the patient's quality of life (QOL). Establishment of the general and specific criteria for surgery is a process, which takes some time. For proper timing, it is preferable that a multiprofessional team headed by the epileptologist evaluates the patient at regular intervals, at a comprehensive epilepsy care center—it should not be considered as the last resort after AED's in all combinations have been tried for adequate periods—a process that may, mathematically, take up most of the patients and physicians lifetime.

CANDIDATE FOR EPILEPSY SURGERY

- Persistent intractable seizures inspite of maximally tolerated AEDs—the period of observation depends on the seizure type, frequency, type of epilepsy and etiology-usually 2 years

- Evidence of medical, social and educational disability due to seizures. Poor QOL which is likely to improve after surgery.
- Diagnostic evidence points to a common and single epileptogenic focus by EEG, imaging, neuropsychology and seizure semiology.
Discordant results are associated with poor surgical outcome.
- Intracarotid amytal test (Wada's test) shows that the contralateral temporal lobe can sustain memory and speech independently, usually after 10 years of age.

Surgical Procedures for Epilepsy

The various surgical procedures for intractable epilepsy carried out are:

- Resective procedures
- Removal of a mass of epileptogenic tissue:

Standard anterior temporal lobectomy in cases of intractable partial epilepsy with onset in temporal lobe and normal memory function in contralateral temporal lobe.

Selective Amygdalohippocampectomy—intractable partial epilepsy with seizure onset in medial temporal lobe with contralateral borderline memory function.

Removal of an epileptic focus or discrete lesion—lesionectomy where there is gross removal of malfunctioning brain tissue.

Focal Corticectomy

Functional Procedures

Disconnection procedures—corpus callosotomy—when there is unilateral cerebral.

Pathology causing focal plus secondary generalized seizures and especially with frequent atonic seizures in mentally retarded children.

Separation of epileptogenic cortex from the rest of the brain—multiple subpial transactions: When there are intractable partial seizures originating in unresectable foci in primary cortices especially eloquent areas serving the functions of motor, speech, language and memory.

Hemispherectomy: When there is evidence of major lesions involving one hemisphere and there is no useful opposite hand, being involved in a hemiparesis.

Anterior Temporal Lobectomy and

Amygdalohippocampectomy: En Bloc Resection

The most common surgical procedure for epilepsy is the anterior temporal lobectomy with en bloc removal of amygdala and hippocampus (ATL). It is performed by standard temporal craniotomy under propofol or pentobarbital anesthesia and consists of resection of 5 to 6 cm block of temporal neocortex along with the superior temporal gyrus, and anterior two-thirds of the hippocampus

lateral two-thirds of the Amygdala along with the uncus and the parahippocampal gyrus.

With proper selection of concordant cases having MTS, nearly 60 to 70 percent may become seizure free after ATL, while 80 to 85 percent cases may have substantial reduction in seizure frequency. Most patients have a significantly improved quality of life and some may improve their verbal and performance IQ by up to 10 percentage points. Indicators of good long-term seizures free outcomes are—a lesion detected in mesial temporal lobe, unilateral temporal interictal EEG spike focus, presence of abnormal pathology in the resected surgical specimen and absence of disabling seizures in the first year of resection.^{26,27} Absence of pathology in the resected specimen is a negative prognostic factor.

Extratemporal Resection

Surgery of extratemporal epilepsy is both difficult and has a poor outcome than that for temporal lobe epilepsy. The reasons being that it is difficult to define the epileptogenic zone with certainty and to do so requires much noninvasive and invasive investigation that is both cumbersome and expensive, there is rapid spread of the seizures discharge to contiguous regions and along long association fibers to distant regions causing varied and confusing manifestations and difficult electrographic localization, possibly more diffuse epileptogenesis and dual pathology, more frequent overlap with adjacent eloquent areas limiting resectability. The outcomes do not differ much from frontal to parietal to occipital lobe and range from 45 to 55 percent of seizure reduction and lower figures for seizure freedom and better outcomes have been associated with MRI detectable lesions than just electrographic localization without discrete MRI lesion, and when there is a single epileptogenic lesion.^{28,29}

Corpus Callosotomy

It is the surgery of choice in mentally retarded children or adolescents with frequent drop attacks as seen in Lennox-Gastaut syndrome and multifocal epilepsy from both hemispheres with frequent generalized seizures. It has an outcome for reducing disabling drop attacks of nearly 80 percent and greatly improves the QOL in this subgroup of patients. Usually the anterior two-thirds of the corpus callosum are adequately resected to avoid a disconnection syndrome.

Hemispherectomy

The classical hemispherectomy, with complete disconnection of one hemisphere from the rest of the brain, was recommended for the children who have multiple or large epileptogenic areas localized to one hemisphere and there is no useful hand control of the opposite side, being

involved in a hemiparesis. Recently variations of the procedure have been more commonly used in various centers, to avoid late complications arising from superficial cerebral hemosiderosis. These are modified hemispherectomy, functional hemispherectomy, shunted hemispherectomy and hemidecortication. It improves the QOL in children with Rasmussen's encephalitis, HHE syndrome. Sturge-Weber syndrome and hemimegalencephaly, also reducing the spread of seizures, although the patient may still get partial seizures.

Multiple Subpial Transactions (MST)

Lesions located in the vicinity of eloquent areas such as motor and speech areas, it is mandatory to minimize the excised volume without compromising seizure control due to the fact that epileptic discharges propagate tangentially throughout the cortex while impulses controlling voluntary movements propagate in a radial direction, a series of vertical cuts can be made to control the epilepsy and yet preserve normal function using special instruments (Morrell's procedure). It is a safe option to reduce seizures without causing neurological deficits.

Stereotactic Procedures

Stereotactic lesionectomy, radiofrequency lesionectomy, volumetric resections and radiosurgery have variable safety and are not universally accepted but are effective in controlling intractable seizures with an advantage of resecting deep tissues involving functional and eloquent cortex, having a relatively low morbidity.

Complications of Epilepsy Surgery

Advanced techniques of presurgical evaluation, using the electrophysiology and imaging modalities and intraoperative evaluations and a microneurosurgical techniques sometimes with the stereotactic frame, has reduced the rate of complications following resective epilepsy surgery and permanent neurological morbidity of below 2.5 percent transient neurological morbidity of 3 percent, totaling about 5.5 percent, in most reputed centers. Mortality is nil to about 1 percent.

The complications expected are discussed with the relatives and patient preoperatively and are related to the type of procedure being done. Homonymous superior quadrantic hemianopia (due to optic tract or optic radiation being involved), language deficits such as nominal aphasia or dysphasia, manipulation contralateral hemiparesis caused by handling and spasm of sylvian artery, anterior choroidal artery supplying the cerebral peduncle, or perforating arteries supplying internal capsule causing lacunar infarcts may occur. Mostly, a reversible hemiplegia occurs due to temporary spasm but cases of permanent hemiplegia have also been reported.

Personality changes are seen with frontal lobe resections, Gerstmann syndrome seen with inferior parietal lobule resections and syndrome of mutism, disconnection syndrome of apraxia of nondominant lower limb contralaterally, with incontinence is seen with corpus callosum resections.

Classical hemispherectomy may lead to a delayed cerebral hemosiderosis. That may be prevented by the modified procedures or hemispherotomy.

Newer AEDs

Although the number of newer antiepileptic medications available for clinical use is growing in number, it is accepted that they have a limited impact on true intractable epilepsy because of their limited efficacy and frequent side effects. Less than 7 to 10 percent persons become seizures free and for this subgroup of intractable epilepsy it is not sufficient for improving the quality of life if they have a significant reduction of seizures. The newer antiepileptic drugs have modes of action which may be on sodium channels, calcium channels, potassium channels, GABA, GABA transaminase, NMDA³³ or novel receptors like SV2A, on neuronal membranes and synaptic regions, with sometimes better tolerability and efficacy as compared to standard AEDs, enabling one to choose the drug as add on or monotherapy, to get better effect. Special subgroups of patients with epilepsy may benefit from these appropriately chosen drugs, e.g. children with West or Lennox Gastaut syndrome, women of childbearing age with epilepsy and obese or underweight children.

Most drugs are effective for partial epilepsy and some for generalized epilepsy as well. Detailed discussion is better sought elsewhere being outside the scope of this chapter.^{34,35}

Unconventional Therapies

Psychological approaches to treatment of seizures include direct and indirect inhibition of cortical areas responsible for seizure generation and contingent relaxation techniques. Seizure precipitants are looked for specifically and avoided and desensitization procedures are useful. Acceptance and commitment therapy and other short course psychotherapies, negative slow cortical potentials, and parasympathetic stimulation of the limbic system are of use in few patients. Parasympathetic stimulation may be effected by vagus nerve stimulation or yoga and have shown to be of benefit in some patients.^{30,32} Left vagus nerve stimulation through an implanted, programmable stimulator device has been used for over 7 years especially in persons who cannot undergo surgery due to multiple foci, generalized epilepsy or other causes and has shown that 44.1 percent patients achieved more than 50 percent reduction of seizures at 3 years but only a few are seizure free.

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Movement Disorders in Children

Nandan Yardi

INTRODUCTION

Although Parkinson, Huntington, Sydenham and others have recognized the disorders of movement, including those affecting children for centuries, in the classical descriptions of the disease, the interest in movement disorders in children has been only recent. These conditions are usually transient lasting for days, weeks or months, unlike the neurologic conditions in adults that may last a lifetime. The conditions of movement disorders in children are often self-limiting, resolving completely, often without neurologic sequel. In otherwise normal infants, choreiform, choreoathetoid and dystonic movements may be apparent for several days or weeks with subsequent resolution and normal development. Examples are paroxysmal torticollis in infancy,¹ benign myoclonus of infancy (that must be differentiated from Infantile spasms) and Precht's choreiform movements² seen in the extended hands of some children, all of which resolve without neurocognitive or motor sequel. Stuttering, motor tics and vocal tics are very common in children and are not necessarily early manifestations of the Gille de la Tourette syndrome.

The childhood movement disorders are difficult to classify based on the type of movement because observation has been the mainstay of diagnosis. The problem is that many of the disorders have several manifestations such as bradykinesia with rigidity and tremor (Parkinson's disease); tremor, dystonia and rigidity (Wilson's disease); and dystonia, spasticity and bradykinesia (Juvenile dystonia-Parkinsonism). At any given time of clinical examination, one manifestation may be prominent and misleading to the clinician. Evaluation of movements using videotaping at the clinic or home has been of great help in evaluation by experts in movement disorders.

Topographical classification has been used consistently for Parkinsonism, chorea and tremor. However, focal, hemifocal, multifocal, segmental and generalized forms

that have been described for dystonia are not useful as dystonia often progresses from focal forms to segmental, hemi- and generalized forms over months or years. It is important to exclude focal lesions of the basal ganglia by magnetic resonance imaging scan with contrast enhancement, whenever these major clinical manifestations are presented focally.³

Out of respect to the conventional traditions of neurology, most clinicians classify movement disorders as those conditions with predominantly hypokinesias (Parkinsonian state) and those with hyperkinesias (choreas, tremors, dystonias, ballismus, choreoathetosis, and tics). Although this framework is useful, kinetic manifestations often overlap in a particular syndrome. The bedside manner of classification is to include the neurological basis for the presenting manifestations such as genetic, developmental, metabolic, traumatic, degenerative, infectious, oncology, intoxication and so on.

Neuropathologically, the pathologic process is imposed on an evolving and developing neural substrate, partially explaining the prominent rigidity and bradykinesia in Juvenile Huntington's chorea and the dystonia in levodopa-responsive juvenile idiopathic dystonia – Parkinsonism syndrome. Fluctuations may occur in the clinical manifestations such as temporary deterioration of dystonia or chorea due to intercurrent infections and a latent period before onset of dystonia in a child with hemiplegic cerebral palsy. Disorders of movement have been traditionally ascribed to the abnormalities of the central nervous system and of basal ganglia and the connecting structures in particular, with a strong evidence of structural and ultrastructural basal ganglia abnormalities in Parkinsonism, Huntington's chorea and many focal dyskinesias. Many other conditions presenting with movement abnormalities have no obvious neuropathological basis for the clinical manifestations and are often

considered biochemical in nature based on the response to a specific pharmacological treatment. The neurochemical basis of classification of movement disorders has been studied for decades particularly for Parkinson's disease (dopamine deficiency) and Huntington's chorea (gamma amino butyric acid deficiency). There is postulation and some evidence of multiple neurotransmitter and neuro-modulator deficits, making this classification nonviable, as single agent replacement therapy is usually only effective in relieving the specific abnormal movement and not associated movements or progressive neural degeneration. Recent studies are aimed at neuronal interactions and neural growth factors that are involved in nervous system development and functional maintenance. There is a defect in complex- I of the Oxidative phosphorylation pathway in brain, muscle and platelets of patients with Parkinsonism.⁴

A genetic basis for many movement disorders has been recognized for a few centuries. Many dominant conditions have variable clinical expression and improper penetrance, and such multiplex families or trios require investigation using molecular or specific markers. Mitochondrial DNA abnormalities may be demonstrated revealing maternal transmission. Early onset of movement disorders in children precludes reproduction and future transmission of the genes.

ATAXIAS

Congenital anomalies of the cerebellum, posterior fossa such as Chiari malformation, Dandy-Walker syndrome and its variants and encephaloceles have ataxia as the predominant presentation because of their destruction or replacement of the cerebellar structure.

Agenesis of the cerebellar vermis is associated with generalized hypotonia and decreased deep tendon jerks and the children affected usually have varying degrees of delayed milestones, mental retardation and truncal ataxia. The presentation is often seen in infancy.⁵

A familial variant of agenesis of the cerebellar vermis called Joubert disease is inherited as an autosomal recessive trait. These patients have ataxia, mental retardation, abnormal eye movements and respiratory problems especially during infancy with alternating periods of apnea and hyperpnea.

CT scan may not be useful to detect agenesis of cerebellar vermis and other congenital cerebellar disorders and MRI scans are needed to make the diagnosis.

Infections and cerebellar brain tumors are the most common causes of ataxia seen in children. The infectious causes include acute cerebellar abscess, acute cerebellar ataxia and acute labyrinthitis.

Cerebellar abscesses account for 10 to 15 percent of brain abscesses and are frequently associated with mastoiditis or chronic otitis media. A cerebellar abscess is

characterized by nystagmus, ipsilateral ataxia and dysmetria and vomiting with headache as predominant symptoms. Antibiotics of choice for cerebellar abscess are vancomycin with ceftazidime or third generation cephalosporin along with metronidazole to cover organisms from mastoid or middle ear. Surgical drainage is indicated for posterior fossa abscesses. Behavior or incoordination problems are sequel that occur in survivors.

Acute cerebellar ataxia occurs in children at 1 to 3 years following a viral illness by 2 to 3 weeks, commonly by varicella, coxsackie or echovirus, probably as a result of an autoimmune response by the cerebellum to the viral inflammation in its tissue. It is characterized by a sudden onset of truncal ataxia that may be so severe, that the child may be unable to stand, walk or sit, and horizontal nystagmus is seen in half the cases. There may be vomiting but no fever or meningeal signs, a point to differentiate from meningitis. Occasionally dysarthria may be obvious or a presenting feature preceding the ataxia by hours or days. CSF examination is usually normal initially but may show slight pleocytosis and mild rise of proteins after a few days. Most children recover completely within a few weeks to a few months but some may have residual behavioral problems, dysarthria, incoordination and ataxia.⁶ The diagnosis is made by exclusion of other acute causes of ataxia such as acute labyrinthitis that presents with otitis media, intense vertigo, vomiting, and abnormal labyrinthine function and diagnosed by cold water caloric testing.

Toxic causes of ataxia are uncommon and caused by anticonvulsants like phenytoin at levels above 30 µg/ml, or alcohol and thallium used as a household pesticide.

Brain tumors are frequently posterior fossa tumors such as cerebellar astrocytomas, medulloblastomas or ependymomas.⁷ Vomiting typically associated with headache, diplopia, nystagmus and ataxia are characteristic diagnostic criteria. The ataxia is often associated with posterior fossa tumors especially those of the cerebellar vermis that cause truncal ataxia that is heightened by sitting or standing while those of the anterior cerebellum results in a typical broad based gait. Ipsilateral extremity ataxia is diagnostic of cerebellar hemisphere tumor or pathology.

The treatment is primarily excision of the tumor, followed by radiation and chemotherapy for tumor residual. Childhood posterior fossa tumors have a good outcome with 5 years survivals of more than 70 to 80 percent if early diagnosis and complete excision are carried out.

The metabolic disorders characterized by ataxia are abetalipoproteinemia, arginosuccinic aciduria and Hartnup disease. Abetalipoproteinemia occurs in children who present as failure to thrive with ataxia, retinitis pigmentosa, muscle weakness, peripheral neuropathy, loss of joint and vibration sense, and mental retardation and show acanthocytes in a blood smear with undetectable serum vitamin E levels.

Degenerative diseases of the central nervous system are rare but important causes of ataxia as they have a poor prognosis clinically and genetically. They are ataxia telangiectasia, Friedreich's ataxia and its variants, olivopontocerebellar atrophies and rare causes of progressive cerebellar ataxia such as vitamin E deficiency related ataxia, Pelizaeus-Merzbacher disease, neuronal ceroid lipofuscinosis and GM2 gangliosidosis.

Ataxia telangiectasia⁸ is the most common of the inherited degenerative ataxias and begins at about 2 years of age progressing to loss of ambulation by adolescence. Difficulty in fixating the eyes on an object with overshooting of the target and refixating by use of lateral movement of the neck, called 'oculomotor apraxia' and horizontal nystagmus are frequently the presenting features. Telangiectasia over bulbar conjunctiva, bridge of the nose, ears and exposed surfaces of the skin over the extremities with loss of elasticity occur by 5 to 10 years of age. Abnormalities of immunological function with frequent sinopulmonary infections and up to 100-fold greater chance of developing lymphoreticular tumors as well as brain tumors are well known. Elevated alpha-fetoprotein, reduced secretory IgA, IgG2, IgG4, IgE and increased incidence of chromosomal breaks (especially Chr 14) are the laboratory abnormalities seen. Death is usually by infection or tumor dissemination.

Friedreich's ataxia is usually an autosomal recessively inherited disorder but autosomal dominant forms are also seen.^{9,10} Ataxia is slowly progressive, involving the lower extremities more than upper extremities, with positive Romberg's test, absent deep tendon jerks, extensor plantar responses, and loss of joint position and vibration sense due to involvement of posterior columns, characteristically seen beginning at about 8 to 10 years of age. Nystagmus, explosive dysarthric speech, significant distal muscle weakness with a preserved intellect, musculoskeletal abnormalities such as pes cavus, progressive kyphoscoliosis with abnormal visual, auditory brainstem and somatosensory evoked potentials help in the diagnosis.

Spinocerebellar ataxia, and its variants are similar to Friedreich's ataxia. Roussy-Lévy disease has similar features but in addition has wasting of the lower extremity muscles with a "stork-like" contour. The Ramsay Hunt syndrome has myoclonic epilepsy associated with it.

The olivo pontocerebellar atrophies^{11,12} are rarely seen in children with a dominant inheritance presenting as ataxia, cranial nerve palsies, abnormal sensory findings, nystagmus, dysarthria and seizures.

CHOREA

Sydenham's chorea is the most common acquired chorea of childhood and the only neurological manifestation of rheumatic fever.¹³ It has been known for three centuries and its association with rheumatic fever has been known

for two centuries, yet it is often misdiagnosed. It is probably caused by an autoimmune response of the central nervous system to the beta-hemolytic *Streptococcus*. A organism leading to vasculitis of the cortical arterioles, with round cell infiltration of the brain in the surrounding area, especially in the caudate nucleus, cerebral cortex and subthalamic nuclei, causing over activity of the dopaminergic system. Demonstration of beta-hemolytic streptococcal infection by culture and serology may be difficult because chorea appears several months after the infection.¹⁴ Anti-streptolysin-O titers tend to be transient and are elevated in only two-thirds of cases, other titers such as anti-DNase B and anti-NADase may be more persistently elevated. Careful cardiac auscultation, electrocardiography and echocardiography assist in diagnosis of carditis observed in one-third of patients with Sydenham's chorea. Children present with chorea, emotional lability (weeping, dysphoria and inappropriate laughter) and hypotonia. Subtle early behavioral changes (encephalopathy) and hypotonia may be severe enough to confine the child to the chair or bed. The encephalopathy may be marked by anxiety, inattentiveness and learning deterioration such that a dementing illness is suspected. The chorea is characteristically symmetric but may be unilateral with rapid jerky movements prominently seen in the face, trunk and distal extremities and are increased by stress, disappear in sleep and may fleet from one muscle group to another. Hypotonia may be disabling causing inability to feed dress or walk especially if chorea is also severe. Characteristic signs associated with Sydenham's chorea are "milkmaid's grip" caused by relaxing and tightening handshake, the "choreic hand" caused by flexion of the wrist and extension of the fingers, "darting tongue" as the tongue cannot be protruded for prolonged periods, and the "pronator sign" when the arms and palms turn outward when held above the head.

Sydenham's chorea lasts for a few months to two years and may recur within two years of remission. The treatment consists of avoidance of stress, diazepam, phenothiazines and followed by haloperidol if the former is not successful, besides penicillin prophylaxis till adulthood. Haloperidol overdose should be avoided by using a dose that does not completely suppress chorea. Valproate and steroids have been recently recommended for Sydenham's chorea. The chorea may fluctuate in severity for several months and recurrent episodes are observed in 10 percent of cases. The intellectual impairment and emotional lability persist for many years in some children, despite appropriate short-term and long-term antibiotic management, requiring appropriate educational placement and counseling.

Paroxysmal kinesogenic choreoathetosis is characterized by a sudden onset of choreoathetosis, unilateral or bilateral, or dystonic posturing of a leg or arm and associated facial grimacing and dysarthria usually lasting a few

seconds up to a minute. The condition has definite precipitating factors such as sudden movement, excitement or stress. It is seen at 2 to 14 years with several attacks daily or only an occasional attack a few months apart. There are no findings on neurological examination, EEG and neuropathology. A familial autosomal recessive inheritance is commonly noted. The drug of choice is phenytoin that can be withdrawn successfully by adulthood.¹⁵

Huntington's chorea is a rare progressive degenerative disorder of the CNS of unknown etiology and inherited as an autosomal dominant trait with the gene located on the long arm of chromosomal 4p 16.3. Although most commonly seen in mid adult life, it may begin at both extremes of life and in children as early as 5 years of age.^{16,17} About 10 percent of children present in childhood (Juvenile form) and 80 to 90 percent inherit this dominant condition from their father.¹⁸ Chromosomal imprinting involving parental gene methylation has been implicated in this genetic phenomenon. Rigidity and dystonia are more prominent in children than the chorea that involves the proximal muscles causing semi-purposeful acts in order to mask the involuntary movements. Behavioral and speech changes may precede intellectual deterioration by a number of years. General tonic clonic seizures (prominent in more than 50% of children) resistant to antiepileptic medication with cerebellar signs and oculomotor apraxia are seen frequently in children and they have a fast progression leading to death by adolescence needing proper counseling of the patient and the family. The mean bicaudate to bifrontal ratio is diagnostic on CT scan and is the neuro pathological correlate of severe atrophy of the caudate and putamen of the basal ganglia with variable neuronal loss in the frontal cortex, hippocampus and cerebellum. The cerebrospinal fluid analysis shows decreased GABA in about two-thirds of patients.¹⁹ The dopamine metabolite, homovanillic acid may be decreased in the juvenile, rigid form. Despite the genetic advances in this disorder, the cause for progressive neuronal loss is speculative ranging from an excess of excitotoxin to disturbance of growth factors for neuronal survival. There is no specific therapy for the disease and the pediatrician should provide appropriate counseling to the family of the patient. Because many juvenile onset Huntington's disease patients are genetic and rarely sporadic, a careful family history is necessary to diagnose early and to find out minimally affected family members.

The progressive intellectual and motor decline in children with Huntington's chorea is unresponsive to pharmacological treatment, seizures can be controlled by anticonvulsants and rigidity may be partially reduced by dopamine agonists. Neuroleptic agents can be used to control behavior and chorea.²⁰ Children tend to survive for a shorter time (5-10 years) than adults (10-15 years) so that they are unable to reproduce and genetically transmit the disease.

BALLISMUS

Ballismus is uncommon in children and considered by many to be a severe form of segmental or hemichorea and is usually seen in Sydenham's chorea, following encephalitis or closed head injury. The relation with vascular event involving the subthalamus is not evident in children as it is in adults. Treatment with dopamine receptor blocking agents is effective.

PARKINSONISM

Parkinsonism is characterized by bradykinesia, tremor, rigidity, and abnormal posture and is usually uncommon in children and adolescence. It is usually a minor component of a major neurological involvement due to encephalitis or head trauma, olivopontocerebellar degeneration or pallidopyramidal syndromes or a major manifestation as isolated idiopathic Parkinson's disease. The rigidity seen in continuous motor fiber activity syndromes (Issac's syndrome, neuromyotonia) need to be considered while diagnosing Parkinsonism in children. The puzzling feature of juvenile onset Parkinsonism is that the dystonia is out of proportion and prominent as compared to bradykinesia a condition recognized as 'Juvenile onset idiopathic dystonia Parkinsonism' (responding to dopamine in addition to levodopa.²¹ It is further defined as sporadic or hereditary (dominant or recessive) and with or without diurnal fluctuations (Segawa syndrome).²² Deterioration of symptoms in the evening is a pointer to the diagnosis of idiopathic juvenile dystonia Parkinsonism and many children diagnosed as dystonia that respond to dopamine belong to this category.²³ Hence, all patients with sporadic or familial dystonia, particularly with manifestations of Parkinsonism must be given a fair trial of levodopa or dopamine agonists.²⁴ In this way many children that are bedridden due to rigidity and abnormal movements can be restored to normal function including walking and running.

DYSTONIAS

Dystonia in children is a disorder of the basal ganglia and is characterized by contraction of opposing agonist and antagonist group of muscles of limb and axial musculature. Initially the dystonia is apparent with initiation of movement such as reaching for an object or walking. The forceful muscle contractions increase with anxiety, emotional situations and reduce in sleep and may be mistaken for a conversion phenomenon but later in the illness, there is obvious slow or rapid, forceful twisting movements of limbs and trunk including the head and neck characteristic of dystonia.

Retrocollis and anterocollis may be strong enough to produce fracture-dislocation of the atlantoaxial joints. Tremors may be present and enlarged affected muscles are prominently by inspection and palpation and may be the clue to the dystonic state in the absence of obvious dystonia.

In the late stages of dystonia, abnormal posturing may persist at rest deforming the body and limbs causing motor disability.

In children, as the dystonia evolves over the years, often beginning focally in the foot and becoming segmental or generalized, topographical classification is not appropriate. However, hemidystonia is a condition in which underlying structural lesions of the basal ganglia such as tumor, arteriovenous malformation or cerebrovascular accident must be ruled out by MRI scan studies.²⁵

Torsion dystonia (idiopathic dystonia musculorum deformans) is a prototype form of dystonia occurring in late first or early second decade of life.^{26,27} At rest, neurological findings may be absent and intermittent changes in gait and posturing may occur and may be confused with a psychogenic condition. The movements and posturing dissipate in sleep and are exacerbated by physical and emotional stress. Over a period of time, progression of forceful, twisting and sustained movements and posturing of the limb and trunk musculature, co-contraction of muscles producing bizarre contortions during walking (prancing) and backward walking or 'dromedary' gait on all fours may be seen. The forceful muscle contractions are painful and work hypertrophy of affected muscles are noted, producing gross deformities due to sustained muscle contractions of trunk and limbs prevent walking and sitting. Variability of progression is important to stress in counseling the parents and affected children. Variability in expression of phenotype may be linked to the uncertainty that exists whether most cases are inherited as dominant or sporadic mutations or rarely as X-linked or recessive types with improper penetrance.²⁸ No specific test exists for the diagnosis of torsion dystonia, as neuropathological studies of the basal ganglia have been unrevealing and many measures of neurotransmitters, receptors, specific enzymes and growth factors have shown no consistent defect. The diagnosis, therefore, depends on a careful family history and examination of the child and exclusion of other known causes of dystonia in children.

As the torsion dystonia evolves in a previously normal child, both physically and intellectually to a progressively deforming and debilitating condition, management can be difficult. Some patients, however, do achieve a plateau in their natural history after an initial progression especially after use of pharmacotherapeutic agents. As a first step, all patients with torsion dystonia must have a trial of levodopa, as it is the only way of distinguishing levodopa responsive dystonia - Parkinsonism. Anticholinergic agents are the mainstay of treatment as they are quite well tolerated as compared to adults. Trihexyphenidyl or other agents may be used frequently at increasingly tolerable doses. Alternatively, carbamazepine and dopamine receptor antagonists such as haloperidol or Pimozide may be useful or a combination of agents may be rarely useful. Intramuscular injections of botulinum toxin²⁹ are useful

to manage focal incapacitating aspects of dystonia such as writer's cramp, spasmodic dysphonia or torticollis. Treatment of torsion dystonia is one of the more difficult conditions to manage in pediatric neurology practice yet the role of stereotactic surgery is limited due to proper use of drugs to control it. Alternative therapies such as biofeedback, relaxation psychotherapy and acupressure – head bracing at sensitive “pressure points” have been successfully tried to control dystonia.

Other Causes of Dystonia

The other forms of dystonia are more common and require specific treatment as compared to the conventional gold standard of torsion dystonia used for comparison. Transient, intermittent, persistent or progressive dystonias may be seen in infancy. Abnormal twisting postures of arms, legs or tongue may appear in the first few months of life and resolve completely in several years called ‘Transient dystonia of infancy.’³⁰ Spasmus nutans in infancy is characterized by head tilt that is prominent and persistent and may be the only early manifestation till associated head nodding and nystagmus appear as a classic triad.

Torticollis is relatively common in infancy and may be due to short sternocleidomastoid with or without a tumor, bony and ligamentous abnormalities of the atlantoaxial joint, posterior fossa tumors and upper lobe pneumonia. Retrocollis may be seen in some conditions such as retropharyngeal abscess or severe cardiorespiratory distress.

A condition called paroxysmal infantile torticollis is seen in infants with intermittent torticollis lasting for a few minutes to hours or a few days and recurring every few months. It is important to exclude intermittent dislocation of the neck as a cause of paroxysmal torticollis by doing a routine neck and craniocervical X-ray examination.

Another common cause of transient dystonic state in children is an abnormal sensitivity to medications especially neuroleptics such as haloperidol, pimozide or fluphenazine and antiemetics or antihistaminics. Metoclopramide is well known for its production of oculogyric crises, trismus, neck rigidity, dystonia and abdominal board-like rigidity in a dyskinetic extrapyramidal reaction. A rapid response to oral or parenteral anticholinergic medication (diphenhydramine) is both diagnostic and therapeutic.³¹ Acute dystonic reactions to high doses of phenytoin and carbamazepine are uncommon and are related to high serum levels of the antiepileptic medication.

Paroxysmal dyskinesias may begin in childhood or adolescence with dystonia as the prominent manifestation with abnormal movements resolving in sleep, although occasionally paroxysmal dystonia may be seen during sleep. The observation that consciousness is maintained throughout the episode differentiates it from seizures.

Kinesogenic dystonia or chorea, already been mentioned above, responds well to phenytoin or carbamazepine. A non-kinesogenic form of choreoathetosis can

begin in childhood, and dystonic posturing occurs sometimes focally, in a previously normal or neurologically impaired child with cerebral palsy or mental retardation. There is no loss of consciousness, the episode lasting for minutes to hours with normal electroencephalograms and responding well to anticholinergic medication, showing no response to antiepileptic drugs.

A perplexing condition is that of dystonia in a child with hemiplegic cerebral palsy, often starting focally as new abnormal movements (dystonia and tremor) in the affected limb, and progressing to limitation in an already handicapped limb. These movements may reach a plateau and may be difficult to treat but standard management of dystonia should nevertheless be tried. Neuroradiological studies do not show demonstrable reason for the progression but evidence of the static deficit leading to cerebral palsy.

The most common treatable dystonic condition,³² often not considered, is probably the Sandifer's syndrome. There is gastroesophageal reflux (excluded by pH probe and radiological studies) and failure to thrive, intermittent or persistent opisthotonus, retrocollis and torticollis, and behavioral instability. The children are generally mentally retarded, with a history of repeated chest infections but occasionally regurgitation and vomiting may not be prominent, the condition further confused by the dystonic reaction to metoclopramide used. The condition is often confused with choreoathetoid cerebral palsy or a progressive neurodegenerative disorder but responds well to medical or surgical treatment of the gastroesophageal reflux with both social and physical improvement in development.

Occasionally, acquired dystonia may be seen as a sequel of any of a number of conditions including infections (meningitis, encephalitis, tubercular meningitis, acquired immunodeficiency syndrome), head trauma, hypoxic ischemic encephalopathy (near drowning, burn encephalopathy), cerebrovascular event (acute hemiplegia of childhood) tumors (gliomas, craniopharyngiomas) and hydrocephalus. The dystonia may occur as a delayed onset after the obvious neurological manifestations of the original brain insult.

Rare, genetic and metabolic disorders affecting the central nervous system may involve the basal ganglia and produce movement disorders in children and adolescents. Wilson's disease, a recessive disorder of copper metabolism must always be excluded by looking for the K-F ring (by a slit-lamp examination of the Descemet's membrane in the eyes) and by blood and urine studies.

Hallervorden Spatz disease,³³ a recessive, degenerative disorder affects basal ganglia producing dyskinetic movements like dystonia and rigidity with dysarthria and dementia with iron deposits in basal ganglia regions demonstrable on neuroimaging.

Some disorders of genetic or metabolic causes produce progressive dystonia, recurrent coma and seizures such as neuronal ceroid lipofuscinosis (electron microscopy of skin, sweat glands or rectal mucosa) hexosaminidase deficiency, mitochondrial cytopathies (Leber's optic atrophy, Leigh's disease, and Kearns-Sayre syndrome), aminoacidopathies (classical phenylketonuria), Rett's syndrome,³⁴ neuroacanthocytosis (blood film acanthocytes) and several organic acidemias (blood gases, blood pH, leukocyte enzymes) need to be recognized.

Tremors

Tremors are rhythmic, oscillatory, involuntary movements observed at rest or with movement. They are common in children and are a benign form of movement disorder, as Parkinsonism with resting tremor is uncommon in children, most being related to an activity such as maintaining a posture (static) or a motor task (kinetic). It is common to note an exaggerated tremor due to sympathomimetic drugs for asthma or to antiepileptic drugs (valproate or carbamazepine), occasionally incapacitating enough to change treatment.

A fine tremor denoting high anxiety or exaggerated physiologic tremor is much more commonly seen.

Benign essential tremor, which is classically intentional, is a common cause of tremor in children and may be a chance finding during a neurological examination for another reason. It is transmitted as autosomally dominant and a family history is often positive. Head nodding, vocal tremor, and severe body tremors while standing (orthostatic) are seen and need counseling of the parents and occasionally beta-adrenergic blocking agents such as propranolol or metoprolol and vocational guidance (avoidance of artistic, musical and architectural and other careers needing fine motor coordination). Other causes of tremors are unusual like wing beating tremor of Wilson's disease, tremors following closed head injuries, acute (Guillain-Barré syndrome), subacute or chronic (Charcot-Marie-Tooth syndrome and Roussy-Lévy syndrome with a possible contiguous gene defect between the two) and the tremor of infantile tremor syndrome.

The Gilles de la Tourette's syndrome is a lifelong condition having a prevalence of 1:2000 presenting between 2 and 21 years of age and inherited as autosomal dominant the gene having mapped to chromosome 18q 22.1. The syndrome is characterized by motor tics, vocal tics, obsessive compulsive behavior, and attention-deficit disorder with hyperactivity, not all of which may be present in a single patient, the symptoms waxing and waning and exacerbated by stress and anxiety. The severity of the disorder can be usually determined from the severity of symptoms during adolescence. Medication should be considered when the motor tics or vocalizations interfere significantly with the child's social and academic interactions. Although

the management is largely multidisciplinary and behavior and biofeedback programs are successful in some patients, Haloperidol 0.25 mg/day increased weekly by 0.25 mg till 2-6 mg/day, penfluridol, pimozide, clonidine (0.05 mg/day increased to 0.0125/day) may be useful. However, a close watch for the side effects of the medication is necessary. Stimulant medication such as methylphenidate is a common cause of Tourette-like symptoms and all children receiving it must be closely monitored.

A tropical disorder, of obscure variety, affecting infants from 6 to 18 months, characterized by coarse tremors, regression of motor and mental milestones and anemia, accounting for 0.2 to 1 percent admissions in developing countries is called the infantile tremor syndrome.³⁵ It is a diagnosis of exclusion when hologram, bone marrow, CSF examination, chest radiogram are found to be normal. The proposed etiological theories nutritional, degenerative or infective and treatment consists of blood transfusion for severe anemia, treatment of intercurrent infections on war footing, and iron, folate, vitamin B₁₂ supplementation and occasional use of phenobarbitone for severe tremors.

Myoclonus

Myoclonus is a brief, involuntary contraction of a muscle or group of muscles producing regular, often irregular movements at a joint such as fingers and toes, wrists elbows, hips and orofacial musculature, at rest or in response to a tactile, aural or visual stimulus.

Myoclonus is a common manifestation of preterm newborns and can be difficult to distinguish from fragmentary neonatal seizures except when it is clinically associated with opsoclonus. Perinatal injury and metabolic disturbances (hypoglycemia, hypoxia, hypocalcemia) should be considered, however, in most neonates the opsoclonus is transient with a normal neurological development.³⁶ Many children have sleep myoclonus while falling asleep (hypnagogic) or on awakening. Benign myoclonus of infancy³⁷ is difficult to differentiate from infantile myoclonic epilepsy (West's syndrome) because the clusters of myoclonic jerks are similar but in the former the serial electroencephalograms and neurological outcome are normal, the myoclonic clusters disappearing by 2 years. Myoclonic movements on awakening may be a prominent feature of Juvenile myoclonic epilepsy of Janz,³⁸ the myoclonic jerks preceding generalized seizures, usually with a positive family history in two-thirds and polyspike waves at 3 to 4 Hz on the electroencephalograms. Myoclonic dystonia is a distinct syndrome of an autosomal dominant disorder giving rise to a combination of 'lightning jerks' associated with dystonic postures and spasms, characteristically resolved by alcohol, and needs to be distinguished from hereditary essential myoclonus and benign hereditary chorea.³⁹

Symptomatic myoclonus may be associated with a previous hypoxic or hypoxic-ischemic event or be one of several neurological manifestations of a multisystem disorder

such as neuronal ceroid lipofuscinosis (neuraminidase deficiency), Lenora body inclusion disease, mitochondrial cytopathy, subacute sclerosing panencephalitis and multiple system atrophy (Ramsay-Hunt syndrome). Most of these disorders are characterized by progressive cognitive decline and behavioral change and require specific investigations. Mitochondrial encephalomyopathy⁴⁰ accounts for a substantial proportion of cases of progressive myoclonic ataxia. Muscle biopsy shows presence of ragged red fibers in most patients, a syndrome called myoclonic epilepsy with ragged red fibers (MERRF). A mutation of mtDNA at position 8344, detectable in leukocytes, is common in the syndrome with cortical reflex myoclonus, occasional tonic clonic seizures and ataxia. Other variable features include muscle weakness, deafness, optic atrophy, dementia, lipomas and peripheral neuropathy, maternal relatives having monosymptomatic varieties or the full MERRF phenotype.

The opsoclonus-myoclonus syndrome or myoclonic encephalopathy of infancy is rare. The onset is of a subacute severe myoclonic jerking of the head and trunk especially while sitting usually requiring support, with a rapid flurry of conjugate eye movements in different directions, known as opsoclonus. The disorder represents a more severe form of acute cerebellar ataxia of childhood usually following encephalitis. With a history of prior viral (varicella) exanthem and cerebrospinal fluid showing mononuclear pleocytosis and high protein levels. Most children recover completely over days, weeks or months but some children have persistent ataxia, with intermittent worsening during intercurrent infections and neurocognitive and behavioral impairment. A course of oral steroids or ACTH is justified in children with persistent findings. Rarely opsoclonus-myoclonus may be caused by neural crest tumors (neuroblastoma or ganglioneuroblastoma) and persistence of symptoms is an indication for a magnetic resonance imaging of the abdomen to rule out the tumor that can be surgically completely removed.⁴¹

Startle Syndromes

The Startle syndromes are heterogeneous with confusion between the normal startle response, other 'jumps' or 'starts' that may resemble startle or even stimulus sensitive myoclonic or epileptic events.

Hereditary hyperekplexia^{42,43} consists predominantly of an exaggerated startle response. Inheritance is autosomally dominant with variable expression. The disorder presents in infancy with increased tone, which may be enhanced by handling (the stiff baby syndrome). On first waking the children have momentary attacks of generalized muscle stiffness and loss of postural control following startle, and a broad-based gait. They exhibit an exaggerated motor response to many stimuli, including tapping the body or loud noise representing an exaggerated startle response (and may be associated with echolalia or coprolalia in syndromes such as Jumping Frenchman of Maine,

latah and myriachet). The disorder tends to progress over many years although it can fluctuate. The disease locus was linked to chromosomal 5 and recently shown to be the $\alpha 1$ subunit of the inhibitory glycine receptor.

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Neuromuscular Disorders in Children: A Clinical Approach for the Pediatricians

Nitin Maheshwari

A wide variety of neuromuscular conditions present in childhood. They all have their different way of presentation. However, some of them may share some features. These neuromuscular conditions may be genetically determined or non-hereditary, congenital or acquired, acute or chronic, and progressive or static. As specific therapy is available for some of these conditions, and because of genetic and prognostic implications, precise diagnosis is important. This review discusses an approach to diagnose neuromuscular conditions in clinic practice.

The term neuromuscular disorders refers to disorders of the “motor unit” and specifically exclude supra-segmental disorders like cerebral palsy. The motor unit consist of four components:

- A motor neuron in the brainstem and anterior horn cells of the spinal cord
- Its axon together with other axons, forms the peripheral nerve
- The neuromuscular junction
- All muscle fibers innervated by single motor neuron.

On the basis of this basic anatomy, neuromuscular disorders can be classified into various groups like primary muscle disorders, primary nerve disorders, disorders of neuromuscular junction and disorders of anterior horn cells (Table 1). The classification on the basis of genetics exists as well. Many clinically defined entities are genetically heterogeneous. However, as most of the genetic tests are not readily available in India, the anatomical classification remains the most useful one, in practice.

This review outlines a diagnostic approach for neuromuscular conditions in clinical practice. An approach to diagnose and investigate “floppy infant” is not included here. No attempt is also made to describe each neuromuscular condition. The review outlines presenting features, salient points in history taking, clinical examination, role of investigations and finally a diagnostic algorithm for

Table 1: Anatomical approach to neuromuscular conditions

Disorders primarily affecting muscles

Muscular Dystrophies

- X- linked (Duchenne, Becker, Emery-Dreifuss)
- Autosomal (Facioscapulohumeral, Limbgirdle)
- Congenital muscular dystrophies

Myopathies

- Congenital (central core, multicore, nemaline rod, myotubular)
- Metabolic (glycogenoses, lipid disorders, oxidative phosphorylation and mitochondrial)
- Inflammatory myopathies (Dermatomyositis, inclusion body myositis)

Myotonic syndrome

- Myotonic dystrophy, myotonia congenital, paramyotonia congenita

Disorders of neuromuscular junction

Myasthenic syndromes

- Congenital, transient neonatal and juvenile myasthenia, lambert eaton syndrome

Disorders primarily affecting nerves

Hereditary

- HMSN (CMT), HMSAN

Acquired

- Guillain-barre (AIDP), CIDP, toxic metabolic, endocrine (hypothyroidism)

Disorders of anterior horn cells

- Spinal muscular atrophy
- Poliomyelitis

pediatricians for clinic practice. Principles of management are also discussed in brief.

PRESENTING FEATURES

Neuromuscular conditions can present with wide variety of symptoms (Table 2). Most of the children present in early childhood with symptoms like frequent falling, toe

Table 2: Presenting features of neuromuscular conditions in children*Non-specific symptoms*

- Weakness
- Frequent falls
- Clumsiness

Symptoms due to lower limb involvement

- Abnormal gait, i.e. waddling gait
- Toe walking
- Difficulty in climbing stairs
- Difficulty in getting up from sitting or lying position
- Swelling of calf muscles

Symptoms due to upper limb and back involvement

- Difficulty in elevation of arm
- Difficulty in combing hairs, dressing or undressing
- Weakness of hand grip
- Change in handwriting
- Pain in hands following prolonged writing

Symptoms due to head face and neck involvement

- Double vision, drooping of eyelids
- Difficulty in swallowing chewing, sucking, whistling
- Change of voice
- Floppy neck

walking, clumsiness and difficulty in getting up from floor. Some of them present with inability to do normal jumping or hopping. A good proportion of them have reportedly normal motor milestones. However, in retrospect some of them may have definite delayed motor milestones. Primary muscle disorders have proximal distribution of muscle weakness and wasting and symptoms may include abnormal gait, difficulty in getting up from floor, difficulty in elevating arms or combing hair.

Primary nerve disorders present with distal distribution of muscle weakness and wasting and symptoms may include weak hand grip or pain in hands after prolonged writing. Excessive foot arch, abnormalities of sensations, limb pain may be the presenting feature of some. Generally speaking muscular disorders are more common than primary nerve disorders.

Metabolic myopathies are relatively uncommon but may present with multisystem involvement. Conditions affecting neuromuscular junction presents with fatigable weakness, like progressive drooping of eyelid as the day progresses. In recent years many congenital myasthenic syndromes have also been described. Diagnosing them could be a challenge. These disorders may present with ptosis, reduced eye ball movements (ophthalmoplegia) and difficulties in feeding, swallowing and chewing in first couple of years of life.

HISTORY

Apart from an understanding of the presenting complaints, a detailed history is also essential to reach to an appropriate diagnosis. The history should include antenatal history, birth history, family history and developmental history.

Polyhydramnios and reduced fetal movements are one of the earliest indicators of neuromuscular weakness in fetus. Arthrogryposis, undescended testicles, talipes and history of choking whilst feeding may also be suggestive of neuromuscular weakness in newborn period. A history of similar disorder in other male members of family suggests X linked recessive pattern of inheritance like in DMD. A child with suspected myotonic dystrophy may have a mildly affected mother. A good proportion of neuromuscular conditions are associated with developmental delay. Few children may have reportedly normal milestones. However, in retrospect some of them may have definite delayed motor milestone.

EXAMINATION

A proper exposure is essential for a comprehensive examination of the child. It is always helpful to observe the child in different postures and positions (sitting, standing and walking). Making a video recording of the gait and analysing it with the physiotherapists or other experts in team may be of help. Examination of the neuromuscular system should include assessment of the muscle bulk, tone, strength, deep tendon reflexes and sensory examination. Tongue should also be examined for presence of fasciculations. Table 3 outlines some salient features of examination which may help in distinguishing primary nerve and muscle disorders.

Proximal distribution of muscle weakness is seen in primary muscle disorders like myopathies and muscular dystrophies with an exception of myotonic dystrophy. Primary nerve disorders usually present with a distal distribution of muscle weakness with reduce or absent deep tendons reflexes. Fasciculations of muscle, which are best seen on the tongue, are a sign of denervation and seen in conditions like spino muscular atrophy (SMA). Sensory abnormalities indicate neuropathies. Fatigable weakness is characteristic of neuromuscular junction disorders like myasthenia. Myotonia is specific for condition like myotonic dystrophy. Examination of the parents may be helpful in certain situations. Mother should be examined for evidence of myotonia when suspecting myotonic dystrophy. Similarly, parents should be examined for presence of pes cavus when hereditary neuropathies are suspected.

INVESTIGATIONS

A careful clinical examination in conjunction with good history is usually sufficient to make a distinction between

Table 3: Examination findings which may help in distinguishing nerve and muscle disorders*Features indicating primary muscle disorder*

- Proximal distributions of weakness and muscle wasting
- Preservation of deep tendon reflexes (although, may be diminished)
- Calf muscle hypertrophy (Especially DMD)

Features indicating primary nerve disorder

- Distal distribution of weakness and muscle wasting
- Absent or diminished deep tendon reflexes
- Fasciculations: best seen over tongue
- Sensory abnormalities may be present
- Pes cavus

Features not helpful distinguishing between primary nerve and muscle disorders

- Muscle pain or myalgia: can be present in both
- Muscle contractures: can be present in both

Features indicating neuromuscular junction involvement

- Fatigable weakness

primary nerve and muscle disorder. A diagnostic algorithm is provided here to help clinicians in selecting investigations thereafter. In few cases, history and examination may not be enough to differentiate between primary nerve or muscle disorders. In these cases a combination of tests or repeating the same test again may be needed. Brief details of commonly required investigations are given here (Table 4).

- *Serum creatinine phosphokinase:* Severe lysosomal enzymes are released by damaged or degenerating muscle fibres and may be measured in serum. The most useful of these is the creatine phosphokinase (CPK), which is found in only three organs and may be separated into corresponding isozymes: MM for skeletal muscle, MB for cardiac muscle, and BB for brain. The serum CPK is by no means a universal screening test for neuromuscular disease because many diseases of the motor unit may not be associated with elevated enzymes. However, the CPK is characteristically elevated in certain conditions like duchenne muscular dystrophy (DMD).
- *Nerve conduction studies:* Motor and sensory nerve conduction can be measured electrophysiologically by using surface electrodes. In clinical practice, three parameters are routinely measured; amplitude, conduction velocity and latency. On the basis of those demyelinating conditions can be differentiated from conditions with primary axonal involvement. Neuropathies of various types can also be differentiated. The site of a traumatic nerve injury may also be localized.

Table 4: Investigations*Commonly required*

- Serum creatinine phosphor kinase (CPK)
- Nerve conduction studies
- Muscle biopsy
- Genetic Studies

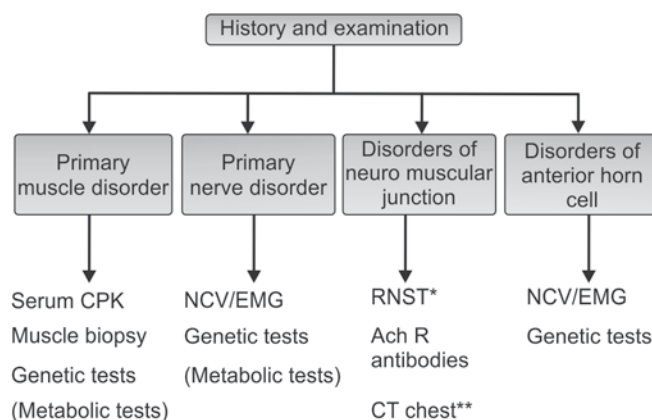
Uncommon required

- Electromyography (EMG)
- Nerve biopsy
- Metabolic investigations

- *Muscle biopsy:* The muscle biopsy is the most important and specific diagnostic study of muscle. Not only are neurogenic and myopathic processes distinguished, but also the type to myopathy and specific enzymatic deficiencies may be determined. The muscle biopsy usually can be done under local anesthesia if the child is big enough to cooperate. However, some young children may require general anesthesia for this. The vastus lateralis (quadriceps femoris) is the muscle that is most commonly sampled. The deltoid muscle should be avoided in most cases. Certain centres are also preferring to do needle biopsies in selected cases, which can be done on outpatient basis.

Histochemical studies of frozen section of the muscle are obligatory in all pediatric muscle biopsies, because many congenital and metabolic myopathies cannot be diagnosed from paraffin section using conventional histologic stains. Immunohistochemistry is useful supplement in some case such as for the demonstration of dystrophin in suspected muscular dystrophy. A portion of the biopsy should be fixed for potential electron microscopy, but ultra structure has additional diagnostic value only in selected cases. Muscle biopsy interpretation is complex and should be done by and experienced pathologist only.

- *Electromyography (EMG):* EMG is less useful in pediatric practice than in adult medicine, in part because of technical difficulties in recording young children and in part because the best results require patient cooperation which is usually not possible from small kids. In the present era, EMG is usually done only if the diagnostic dilemma persists, despite performing other investigations.
- *Genetic tests:* A spectacular development has taken place in field of genetic testing for neuromuscular conditions in last decades or so. Many genetically diverse neuromuscular conditions with similar clinical presentation have been identified. In recent years, genetic tests for common conditions like DMD, HMSN, and SMA have become available in India. Diagnosis of conditions like DMD can be confirmed by performing genetic tests directly, without going for muscle biopsy

Flow chart 1: Diagnostic approach to a child with suspected neuromuscular condition

*Repetitive nerve stimulation test

**Should be considered when suspecting autoimmune myasthenia

if clinical examination and history is consistent with the diagnosis.

A careful selection of investigations is important and at the same time certain diagnostic pitfalls must be avoided. Some practical points to remember include that a single CPK measurement does not necessarily rule out muscular dystrophies. A child, who clinically appears to have a muscular dystrophy but has normal CPK level, should be investigated for myopathies. Electromyography (EMG) is technically difficult to perform in children, and results of this should always be interpreted with caution keeping in mind the false positive and negatives. Nerve biopsy is rarely needed nowadays, as genetic tests to diagnose common neuromuscular conditions like DMD, HMSN, SMA are available in India (Flow chart 1).

PRINCIPLES OF THE MANAGEMENT

A multidisciplinary approach is required to provide appropriate care to children with neuromuscular conditions. Although majority of them do not have any specific drug treatment, some of them do have definitive treatment like pyridostigmine in myasthenia. Steroids are of proven value to increase the ambulatory period, heart and lung function in children with DMD. A pediatrician or neurologist

should help in coordinating the care/ inputs from different specialities.

- Physiotherapy—stretches aimed at prevention of contractures
- Occupational therapy—appliances, improvement of posture and function, facilitating activities of daily living
- Evaluation and treatment of associated cardiac dysfunction
- Respiratory support—assessment of requirement for invasive or noninvasive ventilation and or tracheostomy
- Orthopaedic intervention in setting of established or evolving joint contractures, prevention and correction of scoliosis
- Encouragement of overall development and stimulation of learning
- Prevention (influenza and pneumococcal vaccination) and prompt treatment of respiratory infections.

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CHAPTER 123

Acute Bacterial Meningitis: Issues and Controversies

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INTRODUCTION

Acute bacterial meningitis (ABM) is an important cause of mortality and morbidity in children in developing countries. In a multicentric survey in India, ABM constituted 1.5 percent of admissions in pediatric wards and the mean case fatality was 16 percent.¹ Even though the mortality due to this disease has decreased over the years with the availability of potent antibiotics, a significant number of patients are left with neurological sequel.²

EPIDEMIOLOGICAL ISSUES—DEVELOPED VERSUS DEVELOPING COUNTRIES

Any organism can potentially cause meningitis. Causative agents of ABM vary with age, immune system and immunization status of the patient. During the first 2 months of life, *Escherichia coli* K1 and other gram-negative enteric bacilli, *Streptococcus agalactiae* and *Listeria monocytogenes* are the usual offending organisms. In children between 2 months and 12 years, bacterial meningitis is primarily due to *H. influenzae* type b (Hib), *Streptococcus pneumoniae* (Sp) and *Neisseria meningitidis* (Nm). In children with severe malnutrition, compromised immunity or anatomical defects, infection can occur with other microbes like *Staphylococcus*, *Salmonella*, *Pseudomonas*, etc. Reports from developing countries indicate Hib and Sp account for most of the cases though a sizeable proportion of cases presumed to be bacterial in nature fail to demonstrate any pathogen.³

The widespread use of conjugate vaccine against *Haemophilus influenzae* type b in many developed countries has lead to marked decline in number of cases of meningitis. However, it remains a significant pathogen in resource poor countries. Hib is widely given to infants of the affluent population in India as well. There is no data to demonstrate the decline in incidence of meningitis in this group after change in immunization practices. In

countries with routine Hib vaccination, the median age of ABM has shown an increase with proportionately more cases occurring in adults.⁴ This trend is likely to continue after initiation of routine immunization with conjugate pneumococcal vaccine in many developed countries. Sp colonizes the upper respiratory tract of healthy individuals. However, disease often is caused by a recently acquired isolate. Of the 84 serotypes of Sp, serotypes 1, 3, 6, 7, 14, 19, and 23 are the ones most often associated with bacteremia and meningitis. Transmission is person-to-person, usually by direct contact, and secondary cases are rare.

Most cases of ABM are sporadic except meningococcal meningitis, which often occurs in epidemic form especially in sub-Saharan Africa and Indian subcontinent. Meningococcal meningitis occurs most frequently in young children with peak attack rates in 6 to 12 months infants. A second peak occurs in adolescence. Clusters of meningococcal disease among adolescents and young adults have been reported with increasing frequency in the last decade. Disease rates in adolescents are high because this age group has the highest rate of carriage of *Meningococcus*.⁵

CLINICAL FEATURES

Early symptoms of meningitis in young children are often vague and ill-defined. In general, younger the infant the more nonspecific are the symptoms. History suggestive of upper respiratory infection may be noted in nearly 75 percent of patients. The main symptoms, which are highly suggestive of a diagnosis of ABM in infants are fever (with or without vomiting), alteration of behavior (infant becomes lethargic or drowsy, irritable, feeds poorly), a high-pitched cry, seizures and a full or tense anterior fontanelle. Specific signs of meningeal irritation may not be seen in infants. In older children, classical signs and symptoms of meningitis like fever, headache, vomiting, photophobia, neck stiffness and the meningeal signs are likely

to be present. Neck stiffness is the most important of all meningeal signs and is seen in 50 to 90 percent of patients. Kernig sign and Brudzinski sign are other meningeal signs. The meningeal signs are due to reflex muscle spasm in reaction to pain on stretching of contents of spinal cord. These signs may be absent in comatose patients.

The second mode of presentation is acute and fulminant in which manifestations of sepsis and meningitis develop rapidly and are associated with severe brain edema and raised ICP. This type of presentation is seen most often with *N. meningitidis*. Petechial hemorrhages appearing on the skin which rapidly coalesce producing areas of purpura are considered hallmark of this disease, although they may be seen in meningitis due to other organisms also.

Seizures occur in about 30 to 40 percent cases of ABM. Alterations of mental status and reduced level of consciousness is common and may be due to increased intracranial pressure (ICP), cerebritis or hypotension. Papilledema is uncommon in uncomplicated acute meningitis and when present suggests a more chronic process such as presence of intracranial abscess, or subdural empyema. Focal neurologic signs may be due to vascular occlusion, subdural collection or cortical infarction. Overall 14 percent of children of bacterial meningitis have focal neurological signs.²

Complications

Complications of ABM can develop early in the course of illness or later after several days of therapy or may be noticed on follow-up.

Systemic Complications

Peripheral circulatory failure is a sudden life threatening complication of meningitis occurring most commonly with meningococcal infection but can accompany other type of infections. About 15 percent children with Sp meningitis have been reported to present with shock.⁶ Antibiotic therapy may initially aggravate hypotension, hence intensive monitoring is required in the initial period.⁷ Other manifestation of acute bacterial sepsis may be seen such as coagulopathy, acidosis and hypoglycemia.

Pneumonia, pericarditis and arthritis occur occasionally. Prolonged fever (>10 days) is seen in some cases due to intercurrent viral infection, secondary bacterial infection, thrombophlebitis or a drug reaction. Secondary fever that is seen after an initial afebrile period is usually due to nosocomial infection. Syndrome of inappropriate antidiuretic hormone secretion (SIADH) has been reported to occur in 28 percent of cases of ABM.⁸ It leads to cerebral edema and hyponatremic seizures.

Neurological Complications

Increased intracranial pressure (ICP) is present in almost all cases of ABM initially though only 1 to 3 percent of

cases have persistent hydrocephalus.⁹ Raised ICP as a complication of ABM should be anticipated and treated promptly. When ICP is very high, herniation of brain tissue may occur at the incisura or at foramen magnum and may lead to sudden respiratory arrest and death. Cerebral herniation following LP is an important contributor to overall mortality.¹⁰ LP should therefore, not be done in children with clinical evidence of raised ICP.

Seizures occur in about 30 to 40 percent of children with meningitis. Generalized seizures occurring within first four days are of no prognostic significance. Seizures that present after 4th days and those that are difficult to treat and those that appear late in the course of meningitis are associated with poor prognosis. Children with focal convulsions are more likely to have neurologic sequel of meningitis. Causes of late onset seizures include cerebritis, subdural effusion, vascular thrombosis and abscess formation.

Subdural effusions develop in 10 to 30 percent of patients with meningitis and are more common in *H. influenzae* meningitis. These effusions are mostly asymptomatic. Effusions usually resolve spontaneously and aspiration is required only in case of increased ICP or a depressed consciousness. Subdural empyema requires more aggressive treatment in form of aspiration.

Transient cranial nerve dysfunction and motor deficits may be seen during acute phase of illness. Hearing loss is the most common sequel of ABM. Nearly 10 to 25 percent of cases of survivors are left with permanent sensorineural loss.^{2,11} All patients of ABM should have audiologic evaluation after recovery.

Diagnostic Issues

The diagnosis of ABM is based on documenting inflammatory response of meninges (e.g. CSF cell count, protein, sugar) and on tests that demonstrate the specific causative bacterial agent in CSF (Gram's stain, culture, tests for bacterial antigen/RNA). Since the clinical features of ABM are nonspecific, especially in infants LP should be performed whenever there is suspicion of meningitis. Occasionally, LP may have to be postponed due to cardiorespiratory compromise, signs of increased ICP and infection at the LP site. In case LP is deferred, empirical antimeningitic treatment should be started after taking blood culture.

CSF Examination

CSF examination includes a naked eye examination, pressure, microscopy—total and differential leukocyte count, Gram stain, estimation of proteins and glucose and CSF culture. The CSF should be examined immediately after doing the LP since the cell count tends to fall over a period of time and may be falsely low after 30 to 60 min. The normal CSF of children contains less than 6 WBCs/mm³ and in 95 percent of cases there are no polymorphonuclear (PMN)

leukocytes.¹² Hence, presence of more than a single polymorphonuclear leukocyte in a child over 6 weeks of age is suggestive of ABM. However, CSF lymphocytosis may be a predominant feature in 10 to 13 percent of cases.¹³ CSF lymphocytosis is believed to represent an early phase of infection and repeat CSF examination in these cases will show a PMN predominance. Prior antibiotic therapy also results in lymphocytosis. Protein in CSF is raised (normal value 40 mg/dl after 2nd month of life) in all cases of ABM. In patients of ABM, CSF glucose and ratio of CSF to blood glucose (normally about 66 percent) are low.

Gram stain of the smear is one of the most simple, cheap and rapid diagnostic bedside tools useful for detection of etiological organism. In a series of pneumococcal meningitis Gram stain of CSF was positive in 90 percent cases. Centrifugation of CSF increases the positivity. CSF culture provides a confirmatory evidence of ABM and is essential for selecting appropriate antibiotic for the etiological organisms. The rate of bacterial isolation is affected by antibiotic use prior to lumbar puncture, further rate of isolation is increased if direct plating of CSF is done at bedside.

Interpreting a Traumatic Spinal Tap

In case LP is traumatic, it is recommended to do the cell count and then lyse RBCs with acetic acid and repeat cell count. The ratio of WBCs to RBC's (normal 1:500 to 1:750) can give some indication of the total cell count though it is rather cumbersome. Besides, the biochemical parameters and the Gram stain and culture are not affected by blood in CSF. About 1,000 RBCs/mm³ raise CSF proteins by 1 mg/dl.⁷ Cerebrospinal fluid from a traumatic LP should, therefore be interpreted on a combination of factors.

Value of Rapid Diagnostic Tests

Various rapid diagnostic tests including counter immunoelectrophoresis (CIE), latex particle agglutination (LPA), and enzyme-linked immunosorbent assay (ELISA) are used to detect bacterial antigen. Of these the results of CIE and LPA can be available within 1 to 2 hours but ELISA takes a longer time. LPA is more sensitive than CIE. The sensitivity of CIE can be improved by screening multiple body fluids. LPA kits are commercially available for detecting antigen of Hib, Sp, and Nm group B streptococcus and *E. coli*. A negative test for bacterial antigen cannot exclude bacterial meningitis since these tests are limited to a few specific pathogens. Due to high cost these tests should be reserved for patients who have received antibiotics and those in whom Gram's stain is negative.¹⁴

PCR of CSF has been employed to detect microbial RNA in patients with ABM. Primers are available for simultaneous detection of the common organisms. PCR-based detection of Nm antigen in CSF has been found to be useful in patients with meningococcal disease who have been pretreated with antibiotics as bacterial DNA remains in CSF 2 to 3 days after treatment.¹⁵ PCR has shown promise as

a prognostic test as well. A recent study using quantitative PCR on blood revealed that meningococcal bacterial DNA load correlates with disease severity and that the maximum load is highest in those who die.¹⁶ A broad range PCR for 16S ribosomal RNA has been used to confirm the presence of bacteria in CSF.¹⁷ Another promising development is a Gram stain specific-probe based real time PCR using 16 S ribosomal RNA which allows simultaneous detection and discrimination of clinically relevant gram-positive and gram-negative bacteria directly from blood samples.^{17a} However, at present PCR cannot be used routinely because of high cost and need for special laboratories.

Various nonspecific markers of inflammation such as C-reactive proteins, serum procalcitonin, CSF lactate, CSF CPK, TNF- α , interleukins have been investigated to differentiate bacterial meningitis from aseptic meningitis and as markers of severity of ABM with relation to outcome.¹⁸ Recently it has been shown that CSF concentration of both IL-6 and IL-8 are increased in the presence of meningeal inflammation, IL-8 could be an important tool to differentiate ABM from aseptic meningitis.^{18a}

Despite advancements in lab techniques routine culture of CSF, blood, and Gram stain of CSF remain the standard methods of establishing the etiological agent of ABM. LPA and PCR-based tests are useful in patients pretreated with antibiotics. The molecular method can also be helpful in identifying the genotype of Nm in outbreak situation.

Blood Culture

Blood Culture is positive in a 2/3rd cases of ABM and should be done in all cases. It is especially useful in cases in whom LP cannot be done or is traumatic.

Smear of petechial lesion (if present) after puncture with a lancet should be made and subjected to Gram stain to see for Nm.

Should LP be repeated in all Cases?

If LP was deferred on admission it should be reconsidered after the patient is stable and attempt made to demonstrate organism on Gram stain or by LPA. A repeat spinal tap is not indicated in most of the cases of ABM. It should be done in case of poor clinical response to therapy of 48 to 72 hours, persistent fever, unusual etiological organism or suspicion of resistance, e.g. Sp. Similarly, end of therapy LP is not routinely required if the patient is well and afebrile for preceding 5 days.¹⁹ Examination of the CSF at the end of treatment has not proven helpful in predicting relapses or recrudescence of meningitis.

Which Patients with Suspected Bacterial Meningitis should Undergo CT of the Head prior to Lumbar Puncture?

Complications associated with lumbar puncture are variable, ranging from mild alterations in comfort to

life-threatening brain herniation, which may occur in the patient with elevated intracranial pressure. After lumbar puncture, there is normally a mild, transient lowering of lumbar CSF pressure as a result of removal of CSF. In patients with raised intracranial pressure, there is a relative pressure gradient with downward displacement of the brain that can be increased by lumbar puncture, thereby precipitating brain herniation. In a study of 302 infants and children with bacterial meningitis, brain herniation developed in 6 percent of patients, occurring within 8 hour after lumbar puncture in all patients. Papilledema is an infrequently observed sign in infants and young children with ABM. In patients with clinical evidence of raised ICP, a CT scan should be done to exclude a mass lesion and empiric treatment of meningitis started. Clinical signs of raised ICP are a more reliable indicator to withhold a lumbar puncture since even a normal CT scan does not exclude the imminent risk of coning.

Should Imaging be done in All Cases?

Sonography should be done in all neonates and infants less than 2 months since the risk of complications are higher. Contrast enhanced CT is the preferred modality if subdural empyema or parenchymal damage is suspected. CT is not required in uncomplicated meningitis.²⁰ These investigations should be considered in patients with:

- Sign of raised ICP
- Focal neurologic deficits
- Persistent fever
- Recurrent/focal seizures
- Prolonged coma
- Increasing head circumference.

What Laboratory Testing may be Helpful in Distinguishing Acute Bacterial from Other Neuroinfections?

Several other diseases particularly aseptic meningitis, tuberculous meningitis, cerebral malaria, brain abscess and lead encephalopathy present with signs and symptoms similar to ABM. A careful examination of CSF, which shows pleocytosis with polymorphonuclear predominance with reduced CSF sugar is highly suggestive of ABM. Gram stain and culture confirm the diagnosis. Partial treatment of meningitis with oral and systemic antibiotics often poses a diagnostic problem since CSF is rapidly sterilized though cell count, and CSF biochemical abnormalities persist. A combination of test results, however, may permit an accurate prediction of the likelihood of bacterial versus viral meningitis. Low CSF glucose concentration, high CSF protein concentration, a CSF leukocyte count of >1000 leukocytes/mm³ are individual predictors of bacterial, rather than viral meningitis.

TREATMENT ISSUES

Treatment can be broadly categorized into:

- Antibiotic therapy
- Supportive care
- Adjuvant therapy.

Antibiotic Therapy

What should the Initial Empiric Therapy for a Suspected Case of Meningitis?

The initial antibiotic regimen should be such that covers all the likely pathogens anticipated according to the age of the child, combination should not be antagonistic and it should achieve bactericidal concentrations in the CSF. Later the treatment can be modified depending upon the result of Gram stain and CSF culture. Various antibiotics used in initial therapy and subsequent treatment are shown in Table 1.

A combination of vancomycin and ceftriaxone is recommended as initial empiric therapy in USA.²¹ This is based on the fact that HIB is no longer a common organism in USA and the likelihood of *Pneumococcus* being etiologic agent has increased. Besides there is high rate isolation of PRSP in USA. Reports of increase in frequency of PRSP are emerging throughout the world.²² In areas, which have included pneumococcal vaccination the epidemiology may change yet further. The scenario in India is altogether different. Hib continues to be a major organism and PRSP is not a significant problem. There is no justification of giving vancomycin as initial empiric therapy in this context. A recent study conducted on children aged 5 to 10 years resistance in Sp was low (3.3 percent) but 22.9 percent of *H. influenzae* isolates were ampicillin-resistant.²³ Hence, the initial antibiotic recommended in our country continues to be third generation cephalosporin (cefotaxime or ceftriaxone). For patients with cerebrospinal fluid shunts, broad spectrum antibiotics against gram-positive and gram-negative organisms should be given, such as a combination of vancomycin and ceftazidime. In a recent trial patients given slower Intravenous infusion of cefotaxime along with oral paracetamol had lower mortality during the first 72 hours as compared to recipients of conventional bolus doses.^{23a} Further trials of this simple approach are warranted.

Role of Newer Antimicrobials

Fourth-generation cephalosporins: A fourth-generation cephalosporin, cefepime, has been shown to be safe and therapeutically equivalent to cefotaxime in the treatment of bacterial meningitis in infants and children.²⁴ Cefepime also has greater *in vitro* activity than the third-generation

Table 1: Antibiotic therapy in cases of bacterial meningitis

Initial empiric therapy			
	Age	Drug of choice*	
	0–2 months	Ampicillin + Cefotaxime	
	2 months to 12 years	Ceftriaxone or Cefotaxime	
Subsequent antibiotic therapy			
Pathogen	Drug of choice	Alternative choice	Duration of therapy (days)
Pathogen unknown	Ceftriaxone or cefotaxime	Cefipime	14
<i>H. influenzae</i>	Ceftriaxone	Cefipime	10
Type b <i>S. pneumoniae</i>	or cefotaxime		
• Penicillin-sensitive	Crystalline penicillin	Chloramphenicol	14
• Penicillin-resistant	Ceftriaxone + Vancomycin	Newer quinolone/ Meropenem	14
<i>N. meningitidis</i>	Crystalline penicillin	Ceftriaxone/Chloramphenicol	7–10
Staphylococci	Nafcillin	Vancomycin	2–3 weeks
<i>Pseudomonas</i>	Ceftazidime + Amikacin	Meropenem	3 weeks
<i>Listeria monocytogenes</i>	Ampicillin/Penicillin	Trimethoprim+ Sulfamethoxazole	21 days
Group B Streptococcus	Ampicillin/	Cefotaxime	14–21 days
<i>E. coli</i>	Cefotaxime + gentamicin	Meropenem/Aztreonam/Fluoroqui- nolones	21 days #

* Dosage Schedule (All drugs to be given intravenously)

Duration in the neonate is 2 weeks beyond the first sterile CSF culture or 3 weeks, whichever is longer.

cephalosporins against *Enterobacter* species and *Pseudomonas aeruginosa* and has been used successfully in some patients with meningitis caused by these bacteria making it a useful agent in the treatment of patients with bacterial meningitis.

Meropenem: Meropenem, which has a broad range of *in vitro* activity, has been studied in both children and adults with bacterial meningitis. In these studies, meropenem has been shown to have clinical and microbiologic outcomes similar to those of cefotaxime or ceftriaxone and can be recommended as an alternative to these agents for treatment of bacterial meningitis.²⁵ Meropenem is especially useful in patients with meningitis caused by gram-negative bacilli that produce extended-spectrum β -lactamases or those that may hyperproduce β -lactamases (i.e. *Enterobacter* species, *Citrobacter* species, or *Serratia marcescens*). However, meropenem may not be a useful alternative agent for treatment of pneumococcal isolates that are highly-resistant to penicillin and cephalosporins.

Fluoroquinolones: The fluoroquinolones have been used successfully in some patients with meningitis due to gram-negative organisms. The newer fluoroquinolones (e.g. gatifloxacin, and moxifloxacin) have enhanced *in vitro* activity against *S. pneumoniae* and have been studied in experimental animal models of pneumococcal meningitis. Trovafloxacin was compared with ceftriaxone, with or without vancomycin, in a multicenter, randomized trial in children with bacterial meningitis. The overall efficacy in both treatment groups was comparable in terms of CSF sterilization and clinical success at the end of treatment.²⁶ Although trovafloxacin was since been withdrawn because of concerns of liver toxicity, this study suggests the potential usefulness of the new fluoroquinolones in therapy of ABM. Because there is insufficient evidence of their clinical efficacy till now and these agents have not been studied in newborns and children, these should only be considered in patients who are not responding to currently recommended therapy.^{27,28}

Subsequent therapy depends on the organism isolated and its antibiotic sensitivity. Cefotaxime or ceftriaxone is adequate if pneumococci are susceptible to cefotaxime. However, if *S. pneumoniae* isolates have higher MIC for cefotaxime and fall in the intermediate resistance group, there have been concerns regarding prompt sterilization of the CSF, and a high-dose of cefotaxime (300 mg/kg/d) with vancomycin 60 mg/kg/d may be preferred. In the rare event that pneumococcal isolate has high resistance to cefotaxime or ceftriaxone, vancomycin alone may not be adequate for prompt sterilization of the CSF and rifampin should be added to the regimen or else alternative regimens such as cefepime be given.

For multiple drug resistant staphylococci, vancomycin remains the drug of choice. Combination beta lactam-beta lactamase inhibitor antibiotics (e.g. tazobactam, sulbactam) should not be used to treat meningitis because data are insufficient regarding their penetration of the CNS.

Duration of Therapy

The duration of antimicrobial therapy is based on the causative agent and clinical response (Table 2).^{6,29} The duration of treatment is 7 to 10 days for meningitis due to HIB, 10 to 14 days for Sp. Short courses of treatment are effective for meningococcal meningitis. In a recent RCT, treatment with ceftriaxone given for 5 days was as efficacious as 10 days in meningitis caused by HIB, Sp and Nm.

Since the study included children who had sterile CSF at 48 hours of treatment with ceftriaxone the results cannot be generalized.^{29a}

Longer duration of treatment is required in meningitis due to bacteria such as nontyphoidal *Salmonella*, *E. coli* and *Pseudomonas*. Complications such as subdural empyema, prolonged fever, persistence of meningeal signs or development of nosocomial infections need longer treatment. In such cases, discontinuation of antimicrobial therapy is individualized.

Supportive Therapy

Monitoring

The first 3 to 4 days of treatment are critical because life-threatening complications of meningitis occur most frequently during this period. It is advisable to manage infants and children with meningitis in hospital that has staff with expertise in caring for infants and children who are critically-ill. Vital signs of patients should be monitored regularly during the first 24 to 28 hours of treatment. The patient should be kept nil orally to prevent aspiration. Neurological examination should be performed initially and daily throughout hospitalization. Blood urea, blood sugar, blood gases, serum electrolytes, blood and urine osmolality, urine output, body weight should be monitored closely.

Table 2: Recommended dosages of antimicrobial therapy in patients with bacterial meningitis (A-III)

		Total daily dose (dosing interval in hours)	
		Neonate (Age in days)	Infants and children
Antimicrobial agent	0-7	8-28	
Amikacin	15-20 mg/kg (12)	30 mg/kg (8)	20-30 mg/kg (8)
Ampicillin	150 mg/kg (8)	200 mg/kg (6-8)	300 mg/kg (6)
Cefepime	150 mg/kg (8)
Cefotaxime	100-150 mg/kg (8-12)	150-200 mg/kg (6-8)	225-300 mg/kg (6-8)
Ceftazidime	100-150 mg/kg (8-12)	150 mg/kg (8)	150 mg/kg (8)
Ceftriaxone	100 mg/kg (12-24)
Chloramphenicol	25 mg/kg (24)	50 mg/kg (12-24)	75-100 mg/kg (6)
Gentamicin	5 mg/kg (12)	7.5 mg/kg (8)	7.5 mg/kg (8)
Meropenem	120 mg/kg (8)
Nafcillin	75 mg/kg (8-12)	100-150 mg/kg (6-8)	200 mg/kg (6)
Oxacillin	75 mg/kg (8-12)	150-200 mg/kg (6-8)	200 mg/kg (6)
Penicillin G	0.15 mU/kg (8-12)	0.2 mU/kg (6-8)	0.3 mU/kg (4-6)
Rifampin*	...	10-20 mg/kg (12)	10-20 mg/kg (12-24)*
TMP-SMZ	10-20 mg/kg (6-12)
Vancomycin	20-30 mg/kg (8-12)	30-45 mg/kg (6-8)	60 mg/kg (6)

Note: TMP-SMZ, trimethoprim-sulfamethoxazole. Dosage based on trimethoprim component

*Maximum daily dose of 600 mg.

Should Fluids be Restricted Routinely in All Cases of ABM?

Maintenance of systemic blood pressure is critical to maintain cerebral blood flow. Concurrence of shock and cerebral edema is a therapeutic challenge. The treatment of shock with fluids and inotropes takes priority in such cases. It is common practice to restrict fluids to two-third maintenance to prevent SIADH. Children with meningitis have excess total and extracellular water an appropriate secretion of ADH and mild hypertension, which is required to overcome raised ICT and maintain cerebral blood flow and perfusion. Hence, fluid restriction may increase the likelihood of adverse outcome.³⁰ A recent meta-analysis concluded that there is some evidence to support the use of intravenous maintenance fluids in preference to restricted fluid intake in the first 48 hours in settings where patients present late.³¹ However, fluid therapy should be dictated by clinical condition and care should be taken to avoid over hydration. Hyponatremia is a frequent finding in patients with meningitis and can be due to SIADH or volume contraction. Therefore, the cause of hyponatremia should be assessed along with clinical signs of volume depletion and biochemical parameters, i.e. serum and urine osmolality. The child should receive fluids sufficient to maintain systolic blood pressure at around 80 mm Hg, urinary output of 500 ml/m²/d, and adequate tissue perfusion.

To maximize venous drainage and reduce intracranial pressure elevate the head end of the bed by 30°. Osmotic diuretics such as Mannitol (0.5-1 g/kg) and oral glycerol can be used to reduce ICP. Glycerol was found to prevent severe neurological sequel in one large randomized controlled trial.^(31a) Because of its safety, wide availability, low cost, and oral administration, it should be particularly useful in resource-limited settings. Hyperventilation to maintain the arterial pCO₂ between 27 and 30 mm of Hg may also be used to reduce ICP. Aggressive hyperventilation may be counterproductive as it causes reduction of already compromised CBF with resultant ischemic damage.

Seizures are common during the course of bacterial meningitis. Metabolic complications like hyponatremia, hypocalcemia and hypoglycemia must be excluded and specific therapy instituted if present. Immediate management of seizures includes intravenous diazepam (0.1-0.2 mg/kg/dose) or lorazepam (0.05 mg/kg/dose). This is followed by a loading dose of phenytoin (15 mg/kg) and the maintenance dose of 5 mg/ kg/ 24 h for further control of seizures. Phenytoin is preferred over phenobarbitone because it causes less CNS depression and allows assessment of sensorium. Anticonvulsants can be discontinued after a few days unless there is evidence of persistent seizure activity.

Adjunct Therapy

Adjunctive anti-inflammatory agents, which may be of benefit in treatment of bacterial meningitis include

corticosteroids and newer anti-inflammatory drugs which are still in experimental stage.³²

Use of corticosteroids-steroids have anti-inflammatory effects and decrease the release of various cytokines. They inhibit the transcriptions of mRNA for TNF- α and IL-1, and the production of prostaglandins and PAF, reduce vasogenic cerebral edema, and reduce the production of inducible nitric oxide synthetase. The maximum benefit of dexamethasone is obtained when it is given along with the first dose of antibiotics. A dose of 0.4 mg/kg given every 12 hours for a total duration of two days proved to be safe and as efficacious as the dose of 0.15 mg/ kg given every six hours for four days.³³ The benefit of dexamethasone use in these studies was only moderate and limited to decrease in frequency of audiologic sequel in meningitis due to HIB.^{34,35} Similarly, better outcome was reported with use of dexamethasone in pneumococcal meningitis in children.³⁶ A recent cochrane review; concluded that use of corticosteroids in children reduced the incidence of deafness in meningitis caused by all common bacteria.³⁷ The experience from developing countries is, however, different. A recent large double blind placebo-controlled trial from Malawi showed no benefit of dexamethasone as an adjuvant treatment in children with acute bacterial meningitis.³⁸ In resource, poor countries where the patients are often malnourished and brought late to the health facility after receiving oral medications, one should use steroids with caution. There is only one published trial that has evaluated the efficacy of adjunctive dexamethasone in neonates with bacterial meningitis.³⁹ This trial was small and underpowered but did not find significant difference in outcome in 2 groups. There is insufficient data to support use of dexamethasone in treatment of neonatal meningitis. Dexamethasone should not be used if aseptic or nonbacterial meningitis is suspected and if it is started before the diagnosis is established it should be discontinued immediately. Dexamethasone should not be used in partially-treated meningitis.

Newer Drugs

Anti-endotoxin antibodies have been produced by monoclonal antibody technology and appear to have beneficial role in ABM caused by gram-negative organisms. Monoclonal antibodies against TNF, IL-1B and against CD 18 cells may help in reducing inflammation as shown in experimental studies. Other drugs tried in experimental studies include nonsteroidal anti-inflammatory agent, and pentoxifylline.⁴⁰

Prognosis

The prognosis of a patient with pyogenic meningitis depends on many factors including age, causative microorganism, bacterial density, intensity of host's inflammatory response and time taken to sterilize the CSF. Case fatality is reported to be 3 to 6 percent in developed countries but

higher mortality (16 percent) is reported from developing countries.¹ Most deaths occur within first 48 to 72 hours. Early fatality is most often due to septic shock. Close monitoring for signs of septic shock and brain herniation should be done in first 2 to 3 days of hospitalization.

Neurodevelopmental sequel are seen in 10 to 20 percent of patients.^{2,9} Baraff et al in a meta-analysis of 19 reports estimated that 83.6 percent patients had no sequel.² The common sequel reported were deafness (10.5%), mental retardation (4.2%), epilepsy (4.2%) and motor deficits (3.5%). The sequel of bacterial meningitis may improve with time and even resolve completely. The potential for recovery is attributed to the plasticity of brain. Focal neurological signs at admission have been found to be reliable predictors of permanent sequel especially later epilepsy. Persistence of fever, neck rigidity and reluctance to leave the supine position beyond the first week was associated with risk of neurologic complication or sequel.⁴¹ Prognosis is the poorest among infants less than 6 months, in those with delayed sterilization of the CSF, seizures beyond 4th day of hospital stay, coma, (Glassgow coma scale <8), focal neurological signs on presentation, infection with Sp, and other organisms like Salmonella or Pseudomonas infection. All infants recovering from meningitis should be screened.

PREVENTION

Prevention of ABM is possible with:

- Prevention of secondary cases with antibiotic chemoprophylaxis of index case and close contacts
- Vaccination of susceptible population with specific vaccines.

Vaccination is not a substitute for chemoprophylaxis because secondary cases develop within 2 to 7 days of presentation of index case and vaccination is not effective at that stage.

Primary Prevention

Immunization with *H. influenzae* type b vaccines-HIB OC (3 doses I/M at 2, 4, 6 months and a booster at 15 months) or PRP-OMP (2 doses I/M at 2, 4 months and booster at 12 months) are routinely given in most developed countries with impressive decline in meningitis due to HIB.⁴² Vaccine is efficacious and its cost effectiveness should be evaluated in developing countries.

Impressive results with use of pneumococcal 7 valent conjugate vaccine, (PCV7) which contains common prevalent serotypes have been reported till 2008.⁴³ Subsequently, PCV 7 was incorporated in immunization schedule of USA. Now, Since 2009 13 valent pneumococcal vaccine is available, it has additional strains 1,5,7F,3,6A,19A. Three doses of PCV 13 are recommended to be given at 2, 4 and 6 months of age and a fourth dose at 12 to 15 months. PCV 10 has been launched in India in 2011. It has 1,5 and

7F in addition to the PCV 7 strains. Both PCV 13, PCV 10 can be used for prevention of pneumococcal disease. High-risk group > 5 years should get 23 valent polysaccharide pneumococcal vaccine.^{43a}

Quadrivalent meningococcal vaccine Meningococcus A, C, Y, or W135 is available and given in selected groups, e.g. pilgrims going for haj; adolescents in dormitories and soldiers. Mass vaccination is recommended in areas with high incidence, e.g. in sub-Saharan Africa and during epidemics. Immunization against meningococcal serogroup C was introduced in the UK in 1999 and a marked reduction in the incidence of meningococcal infection has been observed since then.⁴⁴ A trial of combined pneumococcal-meningococcal vaccine demonstrated reduced immunogenicity to meningococcal group C as well as to concomitantly administered Hib vaccines.⁴⁵ The advent of new conjugated vaccines that include a larger number of *S. pneumoniae* serotypes will add broader coverage against Sp. worldwide. Effective conjugate vaccines against non-group B meningococci are already available and promising group B meningococcal vaccine candidates are currently undergoing phase III clinical trials. Further improvements in vaccine development may provide a single effective and cheap vaccine for common pathogens of ABM and reduce the global burden of ABM in coming years.

Recommendations for Prevention of Secondary Cases among Close Contacts⁴²

H. Influenzae Type b Infection

All household contacts should be given rifampicin 20 mg/kg/day (max 600 mg/day) for four days if there is child <5 years at home.

Pneumococcal Meningitis

Chemoprophylaxis not normally indicated for close contacts.

Meningococcal Infection (Should be given one of the Following)

- Rifampicin 600 mg every 12 hours for two days for adults; for children the dose is 10 mg/kg (under 1 year, 5 mg/kg) every 12 hours for two days orally.
- Ceftriaxone 250 mg in adults (child <12 years, 125 mg) intramuscularly as a single dose.
- Ciprofloxacin 500 mg orally as a single dose in adults

Emergence of antimicrobial resistant bacteria are posing a constant challenge in treatment of acute bacterial meningitis. Besides there is a need for effective strategies to prevent neuromorbidity which is hampered by incomplete understanding of pathogenesis of neurological sequelae. Most meningitis causing bacteria cross the blood brain barrier involving specific interaction between the pathogen and host receptors. Blockade of these host

receptors can prevent the microbial invasion of CSF.⁴⁶ This host based novel approach may help in prevention and treatment of bacterial meningitis.

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Cerebral Palsy: Diagnosis, Risk Factors, Early Intervention and Management of the Spastic Child

Maurice G Sholas

INTRODUCTION

The objectives of this chapter target primary care pediatricians. They include:

- A review of the epidemiology of cerebral palsy
- A review of categorization and definitions relevant to cerebral palsy
- A review of the differential diagnosis of and concepts central to the early identification of cerebral palsy
- A review of treatment options for cerebral palsy and common comorbidities
- A review of spasticity management.

The pediatrician, a family practitioner, or a physician extender is often the first point of contact with medical care for children. These primary care providers are essential members of the team that will ultimately be assembled to care for a child with cerebral palsy. Primary providers may not be required to diagnose and execute treatment in isolation from specialists. However, it is essential that primary care providers be familiar with the factors that predispose a patient to be at risk for and the early warning signs of cerebral palsy. This will lead to early diagnosis of affected individuals, early entry into specialized services, and effective education of the patient's parents. Many professionals argue for the diagnosis of cerebral palsy being made within the first year of life (Morgan et al 1996).

The care options available to a patient with cerebral palsy are heavily influenced by access to interventions that are recognized as the standard of care. Data shows that children with cerebral palsy from poor families, in rural settings, with illiterate parents had higher mortality than their counterparts in other social settings (Khan et al 1998). It is quite possible that these data from the developing world are also applicable in developed nations as some patients, by virtue of their psychosocial milieu, have less access to the standard of care. In addition to psychosocial barriers, geographic barriers can also influence

access. Thus, each practitioner must find how to deliver the best care that utilizes the best evidence available while respecting the realities that limit each medical professional, family and community.

Epidemiology and Definitions

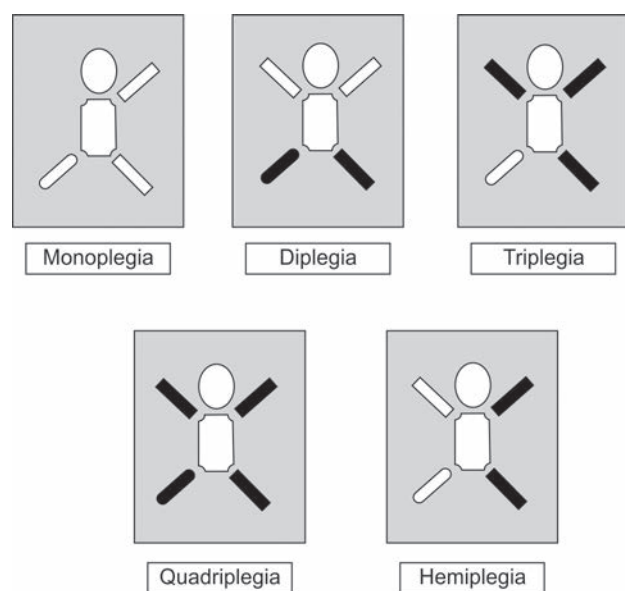
Cerebral palsy is a diagnosis, which is used for a constellation of findings that are the result of multiple etiologies. Children with this diagnosis have abnormal muscle tone, strength, and control. In addition, they have persistent primitive reflexes and abnormal postural reactions. These symptoms are due to a non-progressive lesion of the developing brain. Cerebral palsy is the most common physical disability of childhood (Kuban and Leviton 1994, Rosenbaum 2003). Nomenclature and standardization issues make it difficult to accurately assess worldwide prevalence. However, it is estimated to be 2 to 3 per 1000 and neither increasing or decreasing (Clark and Hankins 2003). Clark and Hankins compiled data for multiple countries in 2003 (Table 1). It is impressive that the rates in some developing nations are equivalent to those in developed nations. These data imply that cerebral palsy is a developmental event that in large part cannot be prevented (Clark and Hankins 2003).

Since diagnosis with cerebral palsy does not convey the primary type of tone abnormality or distribution, it is important to sub-classify the type of cerebral palsy and topographical distribution of the symptoms (Fig. 1). With respect to sub-type, the vast majority of cerebral palsy patients are spastic (Koman et al 2004), but there are others with a hypotonic variant, dystonic (athetoid) variant, or a mixed-clinical picture. For topography, the number and location of affected extremities is used. If one limb is affected, the patient has monoplegia. When primarily both lower extremities are affected the patient has diplegia. Triplegia implies that there are three extremities

Table 1: Cerebral palsy rates by country from 1985 to 1990

Country	Prevalence per 1000
Australia	1.6
Canada	2.6
Denmark	2.4 to 3.0
England	2.3
India	1.2
Ireland	2.2
Scotland	2.1
Slovenia	2.3
Sweden	2.4

Reference: Clark SL, Hankins GD. Temporal and demographic trends in cerebral palsy-Fact and fiction. *Am J Obstet Gynecol* 2003;188(3):628-33.

**Fig. 1:** Topographical distribution of cerebral palsy

affected. Quadriplegia denotes that all four extremities are involved. And, hemiplegia means that one side of the body, an arm and a leg, is involved and the other is intact. For example, a patient that has cerebral palsy with spasticity affecting their right arm and leg is called a spastic hemiplegic patient.

Diagnosis with cerebral palsy also does not imply functional severity or prognosis. Thus, there are scales for categorization that convey more information about the cerebral palsy patient. The gross motor function classification (GMFC) system was created (Palisano et al 1997) in the late 1990's. Eventually this system proved reliable over time and stable as the child grew and developed (Wood and Rosenbaum 2000). In this system (Table 2), children are classified from level I (mild) to level V (severe). The

functional domains are separated into goals for children before their second birthday, between 2 and 4 years old, between 4 and 6 years old, and between 6 and 12 years old. The tasks used for classification are heavily weighted toward physical ones, thus children with profound physical disability will be classified as more severe even if their cognitive function is within normal limits. Using this system, a 6-year-old patient with cerebral palsy that has spasticity affecting his lower extremities to the degree that he requires an assistive device to walk is labeled a spastic diplegic cerebral palsy patient with a GMFC III. Additional functional classification systems include the physician rating scale (gait analysis), gross motor performance index, pediatric evaluation of disability index, and the functional independence measure in children (Koman et al 2004).

Nearly, 70 percent of events that lead to cerebral palsy are *in utero* (Rosen and Dickenson 1992). The largest contributing risk factors to cerebral palsy are unexplained. Of those identified, some are prenatal, others are neonatal and those remaining are postnatal (Table 3). Prenatal risk factors include (Koman et al 2004, Holm 1982, Nelson and Grether 1999, Baawi et al 1998, Matthews and Wilson 1999): congenital malformation, maternal uterine infection, reproductive inefficiency, toxic/teratogenic agents, maternal retardation, maternal seizures, maternal hyperthyroidism, placental complications, multiple births, and abdominal trauma. Neonatal risk factors include (Koman et al 2004, Holm 1982, Nelson and Grether 1999, Badawi et al 1998, Matthews and Wilson 1999): prematurity, low birth-weight, abnormal presentation for delivery, intracranial hemorrhage, hyperbilirubinemia, infection, bradycardia, hypoxia, and seizures. Postnatal risk factors include (Koman et al 2004, Holm 1982, Nelson and Grether 1999, Badawi et al 1998, Matthews and Wilson 1999): trauma, encephalitis, intracranial hemorrhage, and coagulopathies. Overall, congenital infections account for 5 to 10 percent of cases (Paneth 1986). Undetected congenital brain anomalies are responsible for an additional 5 to 10 percent of cases (Paneth 1986). Genetic abnormalities are involved in 2 to 5 percent of cases (Paneth 1986). Cerebral palsy risk factors are often subdivided into those that affect term infants and those associated with prematurity. In term infants, perinatal asphyxia is present in only 25 to 30 percent of cases (Paneth 1986). Overall, infants that are at greatest risk are premies with intrauterine growth retardation delivered between 34 and 37 weeks (Blair and Stanley 1990).

Screening and Diagnosis

All children do not necessarily need to be screened for cerebral palsy. But, in patients that are at risk, a full differential diagnosis must be considered and the collection of medical data are important. Children most at risk are (Morgan et al 1996): less than 1,500 grams, required

Table 2: Gross motor function classification

	<i>Before 2nd Birthday</i>	<i>Between 2nd and 4th Birthday</i>	<i>Between 4th and 6th Birthday</i>	<i>Between 6th and 12th Birthday</i>
Level I	Move in/out of sitting both hands free Crawl on hands and knees Walk 18-24 months w/o assistive device	Sit hands free Move in/out of floor sitting and standing without help Walk w/o assistive device as preference	In/Out chair w/o hand support Transition to stand without using objects for support Walk in/out doors, climb stairs	Walk in/out doors Run and jump but speed and balance are reduced
Level II	Sit using hands for support Creep on stomach or crawl on hands and knees Pull to stand and cruise	Sit but difficult when both hands free Move in/out of sit w/o assist Crawl "w" reciprocal pattern Cruise or walk with assist device	Sit in chair with both hands free Move to stand from chair but will use object to "push off" Walk without assistive device Climb stairs holding rail No run/jump	Walk in/out doors Climb stairs holding rail Some challenge with uneven terrain Minimal run and jump ability
Level III	Sit with low back support Roll and creep forward on stomach	Floor sit via "w" sitting May need assist to assume sit Creep or crawl w/o reciprocal movement Walk short distances with device or assist	Sit regular chair with trunk or pelvis support Move in/out of sit using stable surface to push/pull Walk with assist device Transported for long distances	Walk indoors on level surface "w" assist device May climb stairs holding rail Propel chair manually or transport for distances or rough terrain
Level IV	Prone head control good Support required for floor sitting Roll to supine, may roll prone	Floor sit when placed but must use hands for support Adaptive equipment for sit and stand Roll creep or commando crawl	Sit with adaptive seating for trunk control Move in/out chair with assistance Walk with device but tough to turn or do uneven surfaces Transported in community Self-mobile "w" power chair	Maintain goals from 6 years old Use chair mobility for school and community Self mobility with power chair
Level V	Poor voluntary control of movement Unable to maintain antigravity head and trunk postures Assistance to roll needed	All areas of motor function limited No means of independent mobility Some self-mobile with power chair	All areas of motor function limited No means of independent mobility Power chair possible with extensive adaptations	All areas of motor function limited No means of independent mobility Power chair possible with extensive adaptations

Reference: Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. *Dev Med Child Neurol* 1997; 39: 214-23.

Table 3: Risk factors for cerebral palsy

<i>Prenatal risk factors</i>	<i>Neonatal risk factors</i>	<i>Postnatal factors</i>
<ul style="list-style-type: none"> • Congenital malformation • Maternal uterine infection • Reproductive inefficiency • Toxic/teratogenic agents • Maternal retardation • Maternal seizures • Maternal hyperthyroid • Placental complications • Multiple births • Abdominal trauma 	<ul style="list-style-type: none"> • Prematurity (< 32 weeks) • Low birth-weight (< 1500 grams) • Growth retardation • Abnormal presentation • Intracranial hemorrhage • Hyperbilirubipenia • Infection • Bradycardia with hypoxia • Seizures 	<ul style="list-style-type: none"> • Trauma • Infection (encephalitis) • Intracranial hemorrhage • Coagulopathies

assistive ventilation more than 48 hours, had five minute APGAR scores below 4, or infants with any neurological complication. Thus cerebral palsy must be considered in infants that present early in life with seizures, meningitis, hydrocephalus, intraventricular hemorrhage, or hypotonia (Morgan et al 1996).

A complete differential diagnosis for cerebral palsy is lengthy. Since it is an “umbrella term” encompassing a spectrum of findings, other more specific diagnoses must be ruled out. Badawi and colleagues were comprehensive in their description of the differential diagnosis in 1998. Genetic syndromes like hereditary spastic diplegia, trisomy 13 and trisomy 18 can lead to abnormal tone and mimic cerebral palsy. Similarly, metabolic disorders, such as mitochondrial pathology, and syndromes with vascular defects, such as Moyamoya disease, can cause insults to the immature brain that cause muscle tone abnormalities. Finally, neural tube defects, neuromuscular disorders and motor problems caused by tumors are also in the differential. If there are co-morbidities or findings consistent with an item on the differential diagnosis, that work-up should take precedence. None of the aforementioned entities are included in the spectrum of cerebral palsy.

The physical exam at the 4, 6, 9 and 12-month time points are critical to establishing or augmenting a clinical suspicion for cerebral palsy. Some investigators have devised a formal battery of test items to screen for abnormal motor patterns (Morgan and Aldag 1996). The early motor pattern profile uses a 3-point scale for rating each of 15 items (Table 4). Zero is given if the finding is absent, 1 if it is present intermittently, and 2 if it is severe. Any child at 6 months that scores greater than 7 is very likely to have cerebral palsy. The major drawback of this method is sensitivity, as many children with mild cerebral palsy do not score high enough to be screened in by the scale but later meet criteria for diagnosis. Allen and Alexander in 1997 found that no one test at any isolated point in time was as predictive as serial screening using 6 motor milestones:

- Roll prone to supine
- Roll supine to prone

- Sit with support
- Sit without support
- Crawl
- Cruise.

If there is a delay in any one of these milestones, the patient should be followed closely. A delay of more than three is very indicative that the patient may have cerebral palsy and needs a referral for a comprehensive developmental assessment. In addition to charting motor milestones, exam findings like a persistent dominant asymmetric tonic neck reflex (ATNR), trunk hypotonia with hypertonic extremities, asymmetric limb usage, and a paucity of typical movements are also predictive of major motor dysfunction (Lacey and Henderson Smart 1998, Aneja 2004). The need for missed or late motor milestones and persistence of primitive reflexes make it very difficult to come to cerebral palsy as a definitive diagnosis prior to 4 to 6 months of age (Davis 1997, Aneja 2004).

Imaging studies can be useful and predictive in the neonatal setting. Many use them as an adjunct to the physical findings and patient history. They have been used for term and premature infants. These findings may be the earliest clues that a child falls into a high-risk category to develop cerebral palsy (Palmer 2004). Cranial ultrasound and magnetic resonance imaging (MRI) are the most commonly used neuroimaging studies (Accardo et al 2004). The type of neurological lesion seen is suggestive of the future subcategory of cerebral palsy (Palmer 2004, Okumira, Hyakawa et al 1997, Okumira, Kato, et al 1997). Mild periventricular leukomalacia by ultrasound or MRI is associated with later development of spastic diplegia. Severe periventricular leukomalacia or global hypoxic ischemic encephalopathy is associated with spastic quadriplegia. Spastic hemiplegia is associated with prenatal strokes and intraventricular hemorrhage. Hypoxic ischemic encephalopathy affecting deep brain structures is associated with dystonia. Initial use of imaging studies were focused on the neonatal population in the intensive care unit, but many primary care physicians and specialists have begun using imaging studies to look for findings that corroborate clinical suspicion and/or historical data.

Table 4: Early motor pattern profile

Item	Description	Score
<i>Head Lag</i>	Pull to sitting from supine and assess alignment of head with trunk	0 – never present 1 – inconsistent or partial 2 – severe
<i>Slip through</i>	Support in vertical suspension with hands in axillae and assess need for lateral pressure to prevent child from slipping through	0 – never present 1 – inconsistent or partial 2 – severe
<i>Astasis</i>	Place in supported standing and assess weight bearing	0 – never present 1 – inconsistent or partial 2 – severe
<i>Hip abduction</i>	With legs flexed at the knees abduct hips and assess resistance	0 – never present 1 – inconsistent or partial 2 – severe
<i>Ankle dorsiflexion</i>	With leg extended dorsiflex foot at the ankle and assess resistance	0 – never present 1 – inconsistent or partial 2 – severe
<i>Reflexes at ankle</i>	Assess response at ankles	0 – never present 1 – inconsistently present or partial 2 – severe
<i>Asymmetric tonic neck reflex (ATNR)</i>	Rotate head to one side in supine and observe the position of the extremities	0 – never present 1 – inconsistent or partial 2 – severe
<i>Tonic labyrinthine reflex</i>	Place hands under shoulders in supine and lift slightly, then observe efforts to flex forward	0 – never present 1 – inconsistent or partial 2 – severe
<i>Equilibrium in sitting</i>	Sit in lap and shift from side to side and observe efforts to maintain neutral positioning.	0 – never present 1 – inconsistent or partial 2 – severe
<i>Protective extension</i>	Push to one side in sitting and observe efforts to stop falling with lateral propping	0 – never present 1 – inconsistent or partial 2 – severe
<i>Fisting</i>	Hands remain tightly clenched at rest	0 – never present 1 – inconsistent or partial 2 – severe
<i>Shoulder retraction</i>	Arms flexed and shoulders retracted posteriorly in sitting	0 – never present 1 – inconsistent or partial 2 – severe
<i>Tonic extension</i>	Backward thrusting in sitting or when lifted from supine	0 – never present 1 – inconsistent or partial 2 – severe
<i>Scissoring</i>	Legs adduct in a scissoring motion in vertical suspension or standing	0 – never present 1 – inconsistent or partial 2 – severe
<i>Equinus</i>	Up on toes in supported standing	0 – never present 1 – inconsistent or partial 2 – severe

Reference: Morgan AM, Aldag JC. Early identification of cerebral palsy using a profile of abnormal motor patterns. *Pediatrics* 1998;98(4):692-8.

Co-Morbidities and Symptomatology

A static lesion causes cerebral palsy, but the effects of this lesion are dynamic over the lifetime of the child. Multiple functions mediated by the central nervous system are disordered in association with cerebral palsy (Koman et al 2004, Matthews and Wilson 1999). Mental retardation is present in 30 to 40 percent of patients with cerebral palsy (Koman et al 2004, Liptak and Accardo 2004). If

patients that have mild learning disabilities are included, up to 75 percent of patients with cerebral palsy have disorders of higher cortical processing (Liptak and Accardo 2004). That percentage is high, but it is critical to note that diagnosis with cerebral palsy does not automatically imply mental retardation. Seizure disorders are present in 35 percent of these patients (Koman et al 2004, Liptak and Accardo 2004). Some older references placed this

number closer to 50 percent (Matthews and Wilson 1999). Both mental retardation and epilepsy have a higher incidence in profoundly impaired spastic quadriplegics than other types of CP. Hemiplegic children have less cognitive impairment, but a significant occurrence of behavioral problems like emotional disorders, conduct disorders, or situational hyperactivity (Liptak and Accardo 2004). With respect to complex motor task mediation, 25 percent of cerebral palsy patients cannot walk, while greater than 50 percent walk without assistance of the upper extremities (Koman et al 2004). Cognitive impairment, seizure activity and mobility impairment are present to varying degrees in cerebral palsy patients.

The musculoskeletal complications of cerebral palsy can be mild to severe. Scoliosis, hip dislocations, flexion contractures at the knees and hips, as well as equinovarus deformities of the feet must be considered (Staheli 2001). For patients that are non-ambulatory, routine screening of spine and pelvis is common practice. These patients seem to be more at risk than their more functional counterparts because abnormal tone contributes to neuromuscular scoliosis and weight bearing via standing is crucial to the normal development of the acetabulum and femoral neck. Upper extremity deformities like thumb-in-palm deformity, wrist flexion contracture and internal rotation at the shoulder also can convey morbidity in patients with cerebral palsy (Staheli 2001). In addition to causing pain and limiting care/comfort for the patients, musculoskeletal deformities can contribute to increased risk of pressure sores. Finally, patients that are non-ambulatory secondary to catastrophic disability are at significant risk for osteopenia (Henderson et al 2002, Tasdemir 2001). If the osteopenia is severe the patients have morbidity and possible mortality from pathological fractures. Treatment of disuse osteopenia is an area of active research, thus there are few evidence-based guidelines.

Gastrointestinal pathology and oro-motor dysfunction are associated with cerebral palsy. They are a large part of the reason these patient can be at risk for or relatively malnourished (Sleigh and Brockelhurst 2003, Rogers 2004, Matthews and Wilson 1999). One of the most common finding in clinical practice of cerebral palsy patients is constipation (Matthews and Wilson 1999). This is most likely related to some dysmotility or discoordination of the gut. Gastrointestinal reflux is also problematic in this population (Matthews and Wilson 1999). Both constipation and reflux may be independent or part of a larger oro-pharyngeal motor discoordination that impairs the ability of the patient to chew and swallow safely. Difficulty sucking, swallowing, chewing or controlling the tongue are associated with cerebral palsy as well as drooling (Matthews and Wilson 1999). Feeding or swallowing skills are powerfully prognostic of survival of children with CP (Rogers 2004). A large majority of cerebral palsy patients or their families report that feeding problems are present

(Rogers 2004), and this leads to the use of enteral feeding tubes in many (Rogers 2004, Sleigh and Brockhurst 2003). From drooling and dysphagia to constipation and reflux, gastrointestinal co-morbidities are common in this population. Ultimately, these findings contribute to the patient's nutritional status.

Pulmonary dysfunction is present in cerebral palsy patients (Matthews and Wilson 1999). These findings are secondary to reflux and aspiration of gastrointestinal contents. Plus there is an element of restrictive disease in cases of advanced scoliosis. Finally, infants born prematurely that ultimately develop cerebral palsy can have dysplastic lungs. Clinically, pulmonary findings can be mild to non-existent or quite serious. Severe cases lead to the need for tracheotomies and/or extreme caution when considering interventions that require surgical level anesthesia or conscious sedation.

Cerebral Palsy Treatment

Treating cerebral palsy is focused around treating the symptoms and sequel of the neurological insult. Considerable effort and resources have been used to find a "cure" to lesions of the central nervous system. None have been proven successful (Goldstein 2004). The quest to find cures parallels considerable efforts to find repairs for other processes that result in the death of terminally differentiated neural tissue. Some have postulated that since brain lesions in cerebral palsy have some relation to an ischemic insult, improving oxygen supply to the brain will improve neurological function and recovery. These inaccurate assertions are based on data from hyperbaric oxygen usage in acute traumatic brain injury (Rockswold et al 1992, Rockswold et al 2001). There is no evidence that delivering hyperbaric oxygen to patients with cerebral palsy will improve their neurological or functional status (Collet et al 2001, Hardy et al 2002). In fact, this intervention may cause harm, as it is associated with ear pain, myopia, convulsions, and pneumothorax (Essex 2003). The tank itself has also caused explosions and fires (Essex 2003). Other complementary or alternative treatments designed to improve the brain damage inherent in cerebral palsy include dietary supplements, herbal extracts, electrical brain stimulation, magnetic brain stimulation, acupuncture, craniosacral manipulation and spiritual energy channeling. "Reports of successful interventions [like these] are almost always anecdotal and lack the rigorous data that are collected in organized clinical trials." (Goldstein 2004).

Although the brain lesions themselves cannot be treated, physical interventions for patients with cerebral palsy are available through physical therapy, occupational therapy, speech/language therapy and various other therapeutic modalities. Early interventions to maintain range of motion and prevent progression of deformity are widely

practiced but do not have an irrefutable evidence basis (Turnbull 1993, Steultjens et al 2003). In spite of the data, therapeutic interventions serve an important role to assist with parent education, positioning, equipment acquisition, and functional optimization (Stempien and Gaebler-Spira 2000). Critics argue that patients who improve would do so with or without expensive, labor-intensive interventions. But, supporters counter that the benefits are plain and our experiments have not been designed well enough to capture these positive outcomes. Physical therapy (physiotherapy) focuses on mobility, range of motion, and positioning. Occupational therapy focuses on activities of daily living, self-care skills, sensory integration, and fine motor skills. Speech and language therapy seeks to improve the communication ability, cognitive capacity, and swallowing skills of patients. There is overlap of the disciplines through efforts to maintain normal positioning and reinforce functional skills for maximal independence. A new class of therapists is emerging. Functional therapists or therapy aids receive practical training in physical interventions without as heavy an emphasis on theoretical background. These professionals can be discipline-specific or a hybrid of physical therapy and occupational therapy without training in administration of modalities. The theoretical basis of many therapeutic interventions—including conductive education, neuro-developmental therapy (NDT) techniques, patterning, Adelphi Polish Suit Programs, and Vojta techniques – is varied, but no one philosophy has been shown to be superior to another (Stempien and Gaebler-Spira 2000, Goldsein 2004, Steultjens et al 2004, Turnbull 1993, Matthews and Wilson 1999, Koman et al 2004). In fact, many have very little objective evidence to support claims of efficacy (Stempien and Gaebler-Spira 2000, Goldsein 2004, Steultjens et al 2004, Turnbull 1993, Matthews and Wilson 1999, Koman et al 2004). Although evidence-based practice is difficult to establish for some physical interventions, there is solid evidence that muscle strengthening is efficacious for children with cerebral palsy (Koman et al 2004) as well as for the efficacy of functional (FES), not therapeutic (TES), electrical stimulation (Scheker et al 1999).

Therapists often fabricate splints and assist with durable medical equipment (Fig. 2) as part of their treatment program at the request of a physician. Splinting (orthotics) to increase the length of tendons limiting range of motion and to support weakened areas of the body (Koman et al 2004, Matthews and Wilson 1999, Stempien and Gaebler-Spira 2000) is a common approach in children with cerebral palsy that is non-invasive (Figs 3 and 4). Some splints are used passively as a conservative method of managing a flexible deformity. Others are used dynamically to improve function and mobility for identified tasks. Depending on the level of disability, complex seating systems, bathing chairs or communication devices are useful



Fig. 2: Young female with spastic quadriplegic cerebral plays, GMFC IV, in power wheelchair with her service dog (Photography credit: M Sholas, 2003) (For color version see plate 13)

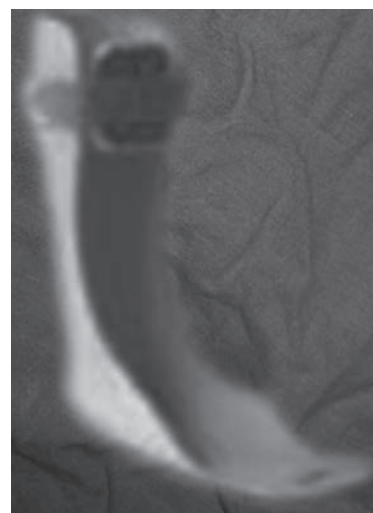


Fig. 3: Solid AFO (Ankle-Foot-Orthosis) (For color version see plate 13)

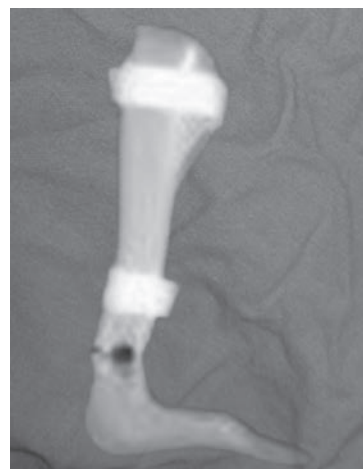



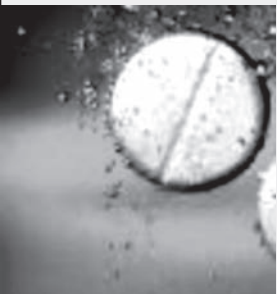
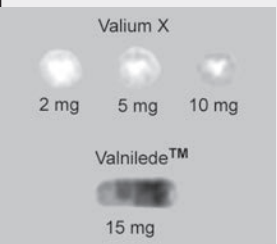


Fig. 4: Articulated AFO (Ankle-Foot-Orthosis) (For color version see plate 13)

for cerebral palsy patients (Stempien and Gaebler-Spira 2000, Matthews and Wilson 1999). Rehabilitation engineers are critical members of the team needed to treat functional limitations in these children. They work with the treating physician and therapists to fabricate and/or combine types of adaptive equipment. Cost and access to qualified professionals are common barriers to patients receiving appropriate equipment. In addition the environmental demands of some living environments can alter the effectiveness of splints, gait aids and seating systems used for patients with cerebral palsy.

Pharmacological and Surgical Agents of Spasticity Management

Pharmacological interventions that are the most evidence-based in children with cerebral palsy are those used to treat spasticity. Approaches to treat spasticity should have clear functional goals and involve the input of the patient/family and treating therapists. Spasticity can cause notable morbidity as it leads to contracture, exacerbates hip joint subluxation, increases caloric requirements, and contributes to pain/discomfort. Spasticity is commonly defined as velocity dependant tone. Table 5 lists large classes of

Table 5: Spasticity medications

	<i>Brand name</i>	<i>Generic name</i>	<i>Mechanism</i>	<i>Side effects facts</i>
	Lioresal® Dose 10-60 mg per day	Baclofen	CNS effect via GABA-B receptor	Nausea Sedation Lower seizure threshold 1st line
	Zanaflex® Dose not established in pediatric patients	Tizanidine	CNS effect via alpha 2 adrenergic receptor agonist	Nausea Sedation
	Valium® Dose 0.2-0.8 mg/kg/day	Diazepam	CNS effect via GABA-A receptor	Sedation Abuse potential Respiratory depression Easy to titrate small doses
	Dantrium® Dose 1-3 mg/kg	Dantrolene	Calcium channels in sarcoplasmic reticulum of muscle	Weakness in non-spastic muscle Interfere with voiding Elevated LFT's
	Catapress® Dose 5-30 mcg/kg/day	Clonidine	CNS effect via alpha 2 Adrenergic receptor	Hypotension Dry mouth Constipation PO and Transdermal preparations

pharmacologic interventions for spasticity. Oral medications, like baclofen, tizanidine and diazepam are excellent agents to treat global spasticity. Clonidine is also useful and it is delivered transdermally via a patch. Side effects for these agents include central nervous system depression and lowering of the seizure threshold. In spite of this, baclofen is commonly viewed as a first-line agent for spasticity management. Diazepam is useful in very young or small patients as it may be easily titrated to small doses. One final oral spasticity medication that is widely used is dantrolene. It does not affect the central nervous system. Instead, it works on the muscle fiber directly, but it can cause non-spastic muscles to be weak and impair bladder emptying. There are many types of spasticity medications.

Chemodenervation refers to regional spasticity management via interruption of the peripheral nerve and its communication with a spastic muscle (Koman et al 2004, Morton et al 2004, Pidcock 2004). Phenol (3-7% solution) and alcohol (45-100% solutions) nerve blocks cause a reduction in spasticity via chemically cutting the nerves that supply the spastic muscle. Given this mechanism, these agents are not used on mixed nerves or those that are primarily sensory. Good targets for phenol/alcohol nerve blocks are the obturator nerve and musculocutaneous nerve. Botulinum toxins are also a type of chemodenervation.

In, but they function via interruption of neural transmission by acetylcholine across the cleft from the nerve terminal to the muscle. Phenol/alcohol blocks require technical skill to perform, last for 4 to 8 months, and require general anesthesia to administer (Koman et al 2004). Botulinum toxins are costly, but they may be given to the unsedated patient in a clinic setting, and last 3 months (Pidcock 2004, Morton et al 2004).

The last major type of pharmacological treatment for spasticity involves using an intrathecal catheter to deliver baclofen directly to its site of action in the spinal cord. The intrathecal baclofen pump (ITB) is a technology that allows exquisite control of the administration of baclofen without systemic side effects (Albright 1996, Armstrong et al 1997, Coffey et al 1993). The doses used are 1/100th of the oral dose are adequate to control symptomatology. Aside from the significant cost of this technology, the pump implantation process and regular refills of the pump with medication, this intervention requires that the patient have regular access to a specialist trained in pump management. Plus, the patient must be near enough to emergency services that they could receive life-saving interventions if the pump or the catheter tubing malfunctions.

Surgical interventions are primarily neurosurgical or orthopedic surgery. In addition to implanting the ITB pump, selective dorsal rhizotomy (SDR) is an option to treat spasticity associated with cerebral palsy. SDR is a

permanent procedure that works to improve motor control by transecting a portion of the lumbar dorsal rootlets (Aiona and Sussman 2004, Koman et al 2004, Susman and Aiona 2004). This procedure is most often used on ambulatory spastic diplegic patients. It does not reverse or improve muscle weakness or treat dystonia so the patient population appropriate for treatment is specific (Koman 2004). Multiple tendon lengthening surgeries are performed to treat spasticity and its secondary consequences, contractures. Many of these surgical interventions are focused on preventing or ameliorating hip subluxation, excessive knee flexion, and equinovarus deformities of the foot. An important consideration when performing tendon lengthening is realizing that the treatment will weaken the treated muscle. Finally, scoliosis surgery is an important reality for many patients with cerebral palsy that have curves greater than 40 degrees and unresponsive to bracing (Koman et al 2004, Staheli 2001).

PSYCHOSOCIAL ASPECTS

In treating congenital physical disabilities, such as those associated with cerebral palsy, there are many issues unrelated to the disease process that strongly influence the outcome. The initial conversations with the parents are delicate and critical. Parents commonly have feelings of guilt, anxiety and anger (Wolraich 1986). These normal reactions must be acknowledged and managed to allow parent and child bonding. Anticipating the stress points of growth and development (Wolraich 1986)—diagnosis of the condition, start of schooling, reaching ultimate attainment, adolescence, and future placement—is important as any plan is constructed for treatment. Many parents hold out hope that the condition of their child will change, as there are children that are diagnosed early with cerebral palsy that subsequently “resolves” (Nelson and Ellenberg 1982). But, this subset appears to be composed of very mildly affected children. It is worthwhile to strongly encourage the parents to accept the permanence of diagnosis only when their beliefs compromise the ability of the child to receive treatment that is the standard of care. In the majority of children with cerebral palsy, aging into adulthood is an unexplored frontier. Improvements in care and technology have increased the numbers of adults with cerebral palsy. Many industrialized countries are planning and developing methods to cope with the changes that come with maturation. Sexuality, vocational opportunities, and independence are major challenges for the patient, the family and medical professionals (Matthews and Wilson 1999). For career planning, as reviewed by Matthews and Wilson, the following expectations are linked to these cognitive and physical deficits. Persons with an IQ less than 50, non-ambulatory and non-oral (feeders) are unemployable. Persons with an IQ between 50 and 79, those that ambulate with or without assistive

devices, and those with speech that is marginally intelligible can participate in sheltered employment. Those with and IQ greater than 80, have normal hand use, and intelligible speech can seek competitive employment. There are exceptions to these generalizations as technology can overcome physical limitations in the absence of mental impairment. The primary care doctor should assist the family in preparing for the future beyond childhood.

SUMMARY

- Cerebral palsy is a clinical syndrome rather than a specific disease entity.
- Diagnosis is based on persistent primitive reflexes, altered tone, and postural reactions.
- The etiology of cerebral palsy is multifactorial: including prenatal, neonatal and postnatal risk factors.
- Management of cerebral palsy is the management of the sequelae of the neurological insult like spasticity, scoliosis, cognitive impairment, and mobility impairment.
- Treatment options include physical interventions, pharmacological interventions and surgical ones.
- The psychosocial aspects of diagnosis and life with cerebral palsy impact the success the patient will have independent of the quality of medical management.

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Acute Flaccid Paralysis

Sarbani Raha, Varjesh Udani

This is defined by the World Health Organization (WHO) as the sudden onset of weakness and floppiness in any part of the body in a child less than 15 years of age or paralysis in a person of any age in whom polio is suspected.¹

Components of the definition:

Acute: Rapid progression of paralysis from onset to maximum paralysis.

Flaccid: Loss of muscle tone, “floppy”—as opposed to spastic or rigid.

Paralysis: Weakness, loss of voluntary movement.

The case definition is broad in order to maximize sensitivity. Objective of AFP surveillance is to detect areas where polio transmission is still occurring, decide strategies to stop transmission and reliably confirm absence of transmission. The strategies used include:

- All cases should be reported immediately, irrespective of diagnosis within 6 months of onset.
- Stool specimen must be collected within 14 days though they can be collected up to 60 days after onset of paralysis. Common conditions besides poliomyelitis and related illnesses, that may present as AFP include: Guillain-Barré syndrome, acute transverse myelitis, traumatic neuritis, postdiphtheric polyneuritis, viral/parainfectious cranial neuritis.

The WHO reportable AFP presentations include flaccid mono, para, hemi and quadriplegias, isolated cranial neuropathies like facial palsy, isolated bulbar palsy and peripheral nerve palsies. Many of the latter are not reported as often as the limb weakness presentations.

NATIONAL POLIO SURVEILLANCE PROJECT¹

National polio surveillance project (NPSP) is a collaborative project of the government of India and the WHO and is managed by WHO. NPSP assists union and state governments with building and maintaining surveillance

for acute flaccid paralysis (AFP) and poliovirus. NPSP also assists with planning and monitoring of polio immunization activities aimed at eliminating polio from India.

Prior to October 1997, surveillance for polio in India was conducted through routine passive reporting by physicians of clinically suspected polio cases. Because surveillance was not designed to search for all cases of acute flaccid paralysis (AFP), and because active surveillance for AFP was not conducted, the ability of the system to detect polio cases was limited. In October 1997, the World Health Organization (WHO) and the Ministry of Health and Family Welfare, Government of India (GOI) recruited 59 surveillance medical officers (SMOs) to be trained and posted throughout the country to establish active AFP surveillance for polio eradication.

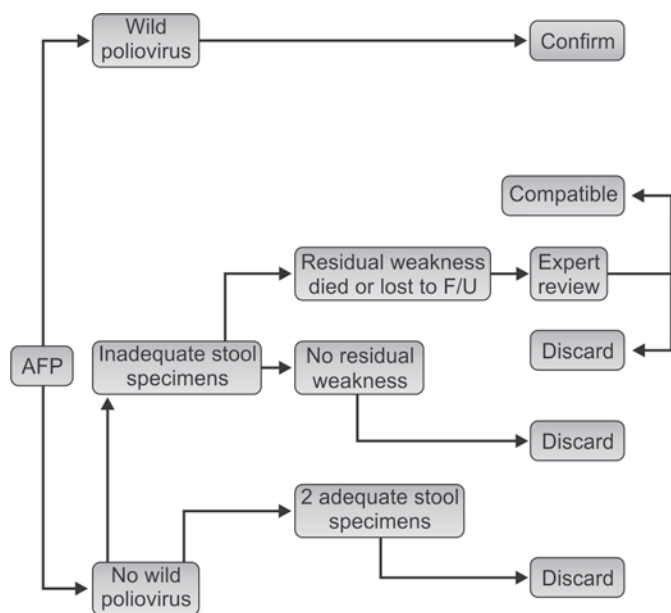
The four-pronged strategy has succeeded in eradicating polio from a large part of the world. This strategy involves maintaining high coverage of vaccination with at least three doses of live oral polio vaccine (OPV), providing supplemental rounds of vaccination, establishing an effective mechanism for the surveillance of AFP, and house-to-house OPV “mop-up” campaigns carried out at the final stage in a limited geographical region.

Polio situation: Globally only four countries are endemic for polio—India, Nigeria, Pakistan and Afghanistan. The P2 strain of poliovirus was eliminated in 1999.

From about 800 cases in 1998, confirmed polio cases have been reduced to 1 in 2011 (till 22 October) in India. In 2010, 42 wild poliovirus cases were confirmed; P1 strain-18 and P3 strain-24.

VIROLOGICAL CLASSIFICATION SCHEME

The Virological classification scheme (NPSP) scheme is used to classify polio cases on the basis of stool viral culture (Flow chart 1).

Flow chart 1: Classification of virological scheme

EFFECTIVENESS OF OPV

Between September 2002 and July 2005, type 1 wild poliovirus travelled from country to country, causing many outbreaks of polio. The number of cases ranged from 1 in Eritrea to 478 in Yemen. These cases had originated in Nigeria and India. In 13 of 21 countries, there were repeated outbreaks; in 8 of these 13 countries, transmission was later stopped. The countries that succeeded in halting the transmission had a median coverage with three doses of OPV of 83 percent, compared with 52 percent in the other 13 countries ($P = 0.001$). This experience suggests that the debate about ineffectiveness of the OPV is not valid and points towards failure to deliver the vaccine as the reason for continued virus transmission.²

ROLE OF INJECTABLE POLIO VACCINE (IPV)

Even with the eventual interruption of the transmission of wild poliovirus, outbreaks of paralytic polio will continue until the routine use of live vaccine is stopped. The public health benefits of OPV continue to outweigh the risks at the present time. This situation will reverse once transmission of wild virus is interrupted and it will be very difficult to eradicate polio using only OPV. The administration of the number of doses—sometimes as many as 10—required to confer the necessary immunity is a challenge. The possible solution may be that countries in which polio is endemic should organize three national immunization days with IPV with strategies like compulsory vaccination, which will give almost 100 percent protection to the children vaccinated. This may be followed by use of IPV in routine immunization programs to protect all successive birth cohorts. IPV in routine immunization would protect individual children while circulation of wild poliovirus

will be stopped with high coverage with OPV on national immunization days.²

VACCINE-DERIVED POLIOVIRUS (VDPV)

OPV contains a weakened version of poliovirus, activating an immune response in the body. A vaccinated person transmits the weakened virus to others, who also develop antibodies to polio, ultimately stopping transmission of poliovirus in a community. In very rare instances, the virus in the vaccine can mutate into a form that can paralyse—this is what is known as a vaccine-derived poliovirus or VDPV. If this virus regains the ability to circulate, it is called a circulating vaccine-derived poliovirus (cVDPV). As with naturally occurring poliovirus, the only protection against cVDPV is full vaccination. The important risk factors for cVDPV emergence include—low prevalence of immunity to poliovirus infection, low OPV coverage and poor sanitation—are likely to exist in populations where case ascertainment is incomplete.³

A fully-immunized population will be protected from all strains of poliovirus, whether wild or vaccine-derived.

Over the past 10 years, more than 10 billion doses of OPV have been administered to more than 2.5 billion children. As a result more than 3.5 million polio cases were prevented. During that time, 18 outbreaks of cVDPVs have occurred in 16 countries.

Reports of cVDPV outbreaks and references to other VDPV isolates have focused on the numbers of clinical cases involved in these episodes. Over some twenty years 114 virologically-confirmed cases of vaccine-derived polio have been reported worldwide. It is also possible that other vaccine-derived virus lineages have circulated for limited time periods, but failed to cause any clinical cases and were thus unrecognized. The risk of VDPV appearance and the incidence and spread of these infections will be important considerations for policies relating to the cessation of OPV, for future surveillance needs, and for planning for outbreak control in the future, including stockpiling vaccines.³

The small risk of VDPVs pales in significance to the tremendous public health benefits associated with OPV.

VACCINE-ASSOCIATED PARALYTIC POLIOMYELITIS (VAPP)

VAPP is defined as occurring in AFP cases if there is residual weakness 60 days after the onset of paralysis, if vaccine-related poliovirus was isolated from any stool sample, and if no wild poliovirus was isolated from any stool sample. A subset of recipient VAPP cases is defined as those VAPP cases with an interval of 4 to 40 days between the receipt of OPV and the onset of paralysis. One of the major risks of VAPP is host immunodeficiency especially hypogammaglobulinemia where virus excretion in stool can persist for a long time.

A report from India in 2002 estimates the following risk for VAPP cases: overall risk, 1 case per 4.1 to 4.6 million OPV doses administered; recipient risk, 1 case per 12.2 million; first-dose recipient risk, 1 case per 2.8 million; and subsequent-dose recipient risk, 1 case per 13.9 million.⁴ On this basis the estimated VAPP risk in India is evidently lower than that in other countries, notwithstanding the administration of multiple OPV doses to children in mass immunization campaigns. A reanalysis of the data however in 2003 by Mittal concluded that the risk of VAPP was 1 in 1.5 to 2 million doses,⁵ a rate which was higher than reported elsewhere in the world. Whatever the truth what is clear is that as wild polio infection declines AFP cases due to VDPV will persist as long as OPV continues. The ideal strategy would be to switch to IPV immunization over a few years after polio eradication.

In a study from Brazil⁶ where the last case of polio-myelitis was reported in 1989, a study of VAPP found that P2 and P3 virus were more commonly associated rather than P1. More than 95 percent were below 5 years of age and females were at higher risk. The majority of patients are vaccine recipients rather than contacts⁶ and constituted about 0.74 percent of all AFP reported. As in wild virus poliomyelitis a history of intramuscular injection was present in 30 percent of victims. Fever was prominent in 86 percent and >50 percent had monoplegia. In all, the illness was considered less severe than wild virus poliomyelitis. CSF showed pleocytosis in about 50 percent but interestingly an albumin-cytologic dissociation suggesting GBS was not uncommon.

GUILLAIN BARRÉ SYNDROME

Epidemiology

This has emerged as the major cause of AFP after the worldwide decline of poliomyelitis. The incidence <18 years is 0.34 to 1.34 cases per 100,000 per year⁷ which about half of that in adults. The average age is 4 to 8 years and is rare below the age of 2 years. Males appear more susceptible in all GBS variants. Unlike in Western countries, countries like China⁸ and Mexico⁹ seasonal peaks are seen with the acute motor axonal neuropathy (AMAN) variety of GBS. Acute inflammatory demyelinating neuropathy (AIDP) appears to lack this seasonal variation.

Mechanisms of Disease

The common demyelinating and axonal forms of the disease are both immune mediated involvement of both humoral and cell-mediated mechanisms. Triggers are mainly environmental pathogens like viruses—common ones noted include EB virus, CMV, hepatitis A and B, varicella, enteroviruses as well as *Mycoplasma pneumoniae*. *Campylobacter jejuni*, a gram-negative bacteria a leading cause of diarrhea appears particularly important as a trigger especially in the AMAN variant. Culture or serologic

evidence of preceding infection with this organism is seen in 17 to 66 percent of adult GBS.⁷ This association appears more common in Asian countries vis-à-vis western nations. In childhood developed countries like Germany report only 7.9 percent while developing countries like Mexico (44%) and India (28%) report higher figures probably linked to poor sanitation and close contact with animals.

Vaccinations like influenza, hepatitis B and less frequently the meningococcal vaccines confer an increased risk of GBS. The recent worldwide immunization with the H1N1 vaccine in 2009 resulted in an increased incidence of 0.8 cases per million doses.⁷

These triggers are believed to activate CD4⁺ helper-inducer T cells, which act against a variety of specific endogenous antigens, including myelin P-2, ganglioside GQ1b, GM1, and GT1a, etc. Resemblance of the triggering pathogens to antigens on peripheral nerves (i.e. molecular mimicry) leads to an overzealous autoimmune response mounted by T lymphocytes and macrophages.

Clinical Considerations

Typically, a progressive ascending symmetrical paralysis coming on over hours, days to a few weeks is the hallmark of GBS. Pain and refusal to walk are often presenting symptoms especially in preschool children (65%) and can often lead to misdiagnosis in as many as 68 percent in one study.¹⁰ Delay in treatment in preschoolers was up to a week in about a 1/4 of patients primarily because of misdiagnoses like arthralgias, myositis and other non-neurologic painful conditions.¹⁰ Autonomic manifestations are seen in up to a 1/3 with dizziness, hypertension, arrhythmia. Early areflexia especially the ankle jerk is usual though occasionally jerks may persist and rarely be exaggerated especially in the AMAN variant.

Evidence of radicular involvement is manifested by the straight leg raising sign (SLR) which is almost invariably positive. Bladder symptoms occur in about 10 percent but are usually transient. Cranial nerve involvement typically bifacial palsy occurs in half while bulbar palsy with dysphagia, drooling and dysphonia occurs less commonly. Ophthalmoplegia is exceptional except in the Miller-Fisher variant where ataxia and areflexia form the triad. The most dreaded complication is respiratory muscle weakness which can come on rapidly especially in the AMAN variant and leads to the occasional mortality.

AIDP and AMAN are the main types seen with segmental degeneration characterizing the former and axonal degeneration the latter. In western countries AIDP constitutes about 85 to 90 percent while in developing countries AMAN equals or exceeds AIDP, e.g. in China 70 percent are AMAN while in Mexico this pattern is seen in 49 percent vis-à-vis AIDP (32%).⁹ These differences are probably due to the high rates of preceding infections with *C. jejuni* in the developing world as elucidated earlier. *C. jejuni* typically leads to the AMAN variant which is often

associated with high anti-GM1A and anti-GD1A antibody titers.

Clinically the two syndromes could be remarkably similar though AMAN is probably more rapid in its evolution with higher grade of severity and more patients needing ventilation. The recent Mexican study did not find any major differences between the two variants. AMAN typically has little sensory manifestations while in AIDP dysesthesia is more common though objective sensory loss is mild or absent. The AMAN variant—acute motor and sensory axonal neuropathy is thought to be just a severe AMAN and some authorities have questioned the need to classify AMAN into its subtypes. Miller-Fisher syndrome typically has ophthalmoplegia, ataxia and areflexia and is seen in ~ 2 percent of all GBS.⁹ Generally, this is a milder disease with full rapid recovery. However, there are many patients with MFS/GBS overlap syndromes which can start as MFS and then develop into more generalized weakness. MFS and its variants are associated often with anti-GQ1B antibodies.

Diagnosis

It is imperative to reach a diagnosis as soon as possible. High CSF protein without a cellular response—so-called albumin-cytologic dissociation may take up to a week though changes are usually seen around 48 hours after onset. Sometimes there is a cellular response of up to 50 cells which can suggest a viral etiology GBS associated with HIV typically has a significant CSF pleocytosis. Nerve conduction studies peak in the second week though some specific changes may be seen in the first week like absence of late responses, etc. Hence, the problem with both CSF and NCV is that they may be normal in the first week of illness.

Recently spinal and sometimes cranial contrast MRI has gained popularity as changes are seen within 2 days in >90 percent of children.^{11,12} Typically the ventral roots of the cauda equine show enhancement though it is more common to have the more nonspecific both anterior and posterior root enhancement. Cranial nerves may also show enhancement fairly commonly—typically the abducens, oculomotor and facial nerves.

Antibodies to different ganglioside antigens have different sensitivities in different regions. It appears to be uncommon in western countries like Germany¹³ while is seen in up to 44 percent in Asian patients including India.¹⁴ This positivity is associated with previous diarrhea (presumably *C. jejuni* associated), AMAN variant and slower recovery times.^{14,15}

Though these antibody tests help in understanding GBS and its subtypes they really do not help in the diagnosis in the acute stage.

Treatment

Plasma exchange and IVIG have been shown to be equally effective in hastening recovery in all GBS including childhood GBS.¹⁶ However, the ease of administration of IVIG as well as less adverse effects makes this the first line treatment in childhood GBS. Studies have typically involved more severely affected patients and the dosage used has been high dose 2 gm/kg. Whether milder affected ambulant patients benefit from IVIG is not really studied. Also, in a resource-poor country like ours, we need to study whether lower doses of IVIG would suffice. It is not known whether IVIG given later than 2 weeks after onset of disease would hasten recovery as all studies have used early treatment. Corticosteroids have not been shown to hasten recovery and oral steroids may actually delay recovery.¹⁷

Prognosis

In general, the outcome in children is excellent. Mortality is unusual nowadays with modern intensive care. However in developing countries the mortality is still reported about 1 in 10.¹⁸

Though the AMAN variant reaches a more severe disability stage than AIDP and has a higher rate of respiratory failure needing ventilation, the final outcome at 12 months is excellent in both groups.¹⁸

AFP DUE TO OTHER VIRUSES

Nonpolio enteroviral (NPEV) are common isolates from AFP patients ranging from 20 to 72 percent of patients. It is difficult to be sure whether they represent background viral circulation or actually are causative of the AFP. In a study from the Americas¹⁹ 40 percent were clinically diagnosed as GBS and NPEV isolation was greater in older children. Fever, residual paralysis and atrophy were less likely than wild poliovirus positive cases and the paralysis was more often ascending (32 vs 18%) when compared to wild virus poliomyelitis. In a more recent study²⁰ from Pakistan, 60 percent of NPEV-associated AFP had fever at onset, about 2/3 had asymmetrical paralysis and the peak of the illness was rapid as in wild virus poliomyelitis. Twelve percent patients died and 39 percent had residual paralysis suggesting a much less benign course than the American study. Certain specific enteroviruses like EV 71 and coxsackie A7 have been clearly linked to AFP.

Japanese B virus, rabies and west Nile virus sometimes present as AFP.

ACUTE TRANSVERSE MYELITIS

This has an incidence of 1 to 8 per million per year and can occur alone or be a part of neuromyelitis optica,

multiple sclerosis or acute disseminated encephalomyelitis. The word “transverse” is often a misnomer as though the clinical findings suggest a single level often the MRI shows significant involvement. Mean age is ~ 8 years.²¹ Typical diagnostic clues include a history of preceding infection/ vaccination in about 2/3rd of the cases, back pain and fairly rapid progression of paraplegia/ quadriplegia (mean 3.9 days).²¹ It has been described after the many agents like measles, varicella, mumps, hepatitis, *Mycoplasma* and often has associated antibodies include anti GM1 ganglioside antibodies,²¹ antiphospholipid antibodies and others.

Sensory loss and persistent sphincteric involvement differentiates this from poliomyelitis like illnesses and GBS. Initial hypotonia and areflexia soon give way to spasticity and hyperreflexia. CSF may show increased protein with lymphocytic pleocytosis or can be normal. MRI makes the diagnosis with usually long segment cervicodorsal hyperintensity with occasional contrast enhancement. Concurrent brain MRI might show white matter lesions when the myelitis is part of an ADEM syndrome. Neuromyelitis optica comes with long-segment myelitis (>3 vertebral segments) and the optic neuritis may precede or follow the myelitis by up to 1 year. NMO-IgG antibodies help make his diagnosis which can be recurrent symptoms and would need ongoing immune-modulatory treatments. Multiple sclerosis presenting as myelitis is extremely rare and it does occur it usually is a partial lesion involving <3 segments.

Treatment is best with intravenous high dose methylprednisolone (30 mg/kg/day) for 3 to 5 days with oral steroids thereafter for 4 weeks. Outcome is fairly good in ~ 60 percent of cases though some children remain wheelchair bound. Motor symptoms improve earlier than bladder dysfunction.

Other disorders rarely presenting as AFP include snake-bite envenomation, myasthenic crisis, hypercalcemia/hypermagnesemia, hypokalemic/hyperkalemic periodic paralysis, organophosphorus poisoning and acute intermittent porphyria.

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Stroke in Children

KS Rana

INTRODUCTION

Childhood stroke is rarely considered as a significant medical problem in developing countries. Stroke in children is not rare and the burden of disability related to the neurological impairment from this disorder is significant. The incidence of childhood stroke is increasing and currently exceeds six per lakh children per year and adverse outcome including death in 10 to 40 percent children in the developed world.^{1,2} True impact of childhood stroke in developing countries is unknown and may be more because of prevailing risk factors like infections, anemia, dehydration, etc. Adults with stroke have benefited from the evidence based treatment trials but such trials have not been conducted in children with stroke. There are considerable differences in the vascular, coagulation and nervous system in children, compared to adults. Pathophysiology, risk factors and clinical features have age related differences. The diagnosis of stroke in children is often delayed due to the relative rarity of the disorder and lack of acquaintance with the diagnosis. The potential for recovery from the stroke in children may be different because of increased plasticity in the immature brain. Present chapter will cover children beyond neonatal period.

TYPES OF STROKE

Acute ischemic arterial stroke, acute venous stroke +/- hemorrhage, primary intracranial hemorrhage (intraparenchymal, intraventricular and subarachnoid)

RISK FACTORS

Common risk factors for ischemic stroke in children are arteriopathies (53%), cardiac disorders (31%), infections (24%), acute systemic disorders (22%) and prothrombotic states (13%). The prevalence of risk factors varied

with age/sex and geographical location. Arteriopathies are more common in children aged five to nine years (66%), acute systemic infections in less than five years of age (31%) and prothrombotic states in children more than 10 years of age.³ In Asia, arteriopathies, cardiac disorders and systemic infections contribute for majority of childhood stroke, whereas chronic head and neck disorders and prothrombotic states are the main risk factors for stroke in Europe and America. Posterior circulation stroke are more common in boys. Almost 50 percent children have multiple risk factors.³ Underlying causes for hemorrhagic stroke are arteriovenous malformations and coagulopathies. In developing countries more than one-third cases have no identifiable cause as compared to 10 percent in the developed world.³ Identifiable risk factors for childhood stroke are given in Table 1.⁴⁻⁷

CLINICAL PRESENTATION

The World Health Organization (WHO) definition of stroke is 'rapidly developing clinical signs of focal (or global) disturbances of cerebral function, with symptoms lasting more than 24 hours or longer, or leading to death, with no apparent cause other than of vascular origin'. Patients whose signs resolve within 24 hours have transient ischemic attacks (TIA), but many of children with TIA have recent cerebral infarction or hemorrhage on imaging.⁸

Clinical presentation depends upon the type of stroke. In arterial ischemic stroke (AIS) of anterior circulation, acute hemiparesis is seen in more than two-thirds. Altered sensorium, raised intracranial pressure and impending herniation symptoms are observed in large middle cerebral artery (MCA) territory infarction, vertebrobasilar circulation stroke, intracranial hemorrhage and venous sinus thrombosis (VST). Seizures and headache are common in VST. In posterior circulation stroke, other presenting symptoms are cranial nerves deficit with cross

Table 1: Risk factors for childhood stroke

<i>Cardiovascular</i>	
Congenital heart diseases	Complex congenital heart diseases, septal defects, aortic/mitral stenosis, coarctation of aorta, mitral valve prolapse, patent foramen ovale.
Acquired heart diseases	Rheumatic heart disease, prosthetic valve, infective endocarditis, cardiomyopathy, arrhythmias, cardiac surgery.
Systemic vascular diseases	Hypertension, dehydration, diabetes, atherosclerosis, hypernatremia.
<i>Vasculitis</i>	Infections (meningitis, systemic infections, varicella, acquired immunodeficiency syndrome, sinusitis, pharyngitis, otitis media), kawasaki disease, systemic lupus erythematosus, other rheumatic disorders.
<i>Vasculopathies</i>	Moyamoya, Ehler-Danlos syndrome, Fabry disease, neurofibromatosis
<i>Hematological disorders</i>	Hemoglobinopathies (sickle cell), polycythemia, anemia, thrombocytosis, thrombocytopenia, disseminated intravascular coagulation (DIC), leukemia, Vit K deficiency, acquired and congenital hemolytic anemia, Protein C and S deficiency, antithrombin-III deficiency, factor V G1691A mutation, prothrombin G20210A variant, elevated protein (A), dysfibrinogenemia, dysplasminogenemia, heparin cofactor-II deficiency, factor XII deficiency, lupus anticoagulant, anticardiolipin antibodies, Antiphospholipid antibodies, congenital coagulation defects, anticoagulants
<i>Metabolic disorders</i>	Homocystinuria, organic academia, mitochondrial cytopathies, ornithine transcarbamylase deficiency.
<i>Vasoplastic disorders</i>	Migraine, alternating hemiplegia, vasospasm.
<i>Vascular anomalies</i>	Arteriovenous malformation, hypoplastic/stenotic vessels, intracranial aneurysm, fibromascular dysplasia, cavernous angioma, hereditary-hemorrhagic telangiectasia, Sturge-Weber syndrome.
<i>Traumatic</i>	Child abuse, congenital bony anomalies of neck region, fat/air embolism, post traumatic arterial dissection, blunt cervical injury, trivial head injury, intraoral trauma, craniovertebral junction anomalies.
<i>Others</i>	Drugs like L asparaginase, oral contraceptives, cocaine/amphetamines, Down syndrome, arterial catheterization, post irradiation, bone marrow transplant, nephrotic syndrome, celiac disease, solid tumors, VP shunt, recent head surgery, and progeria.

hemiparesis, vertigo, ataxia, dysarthria and neck pain. Several classical syndromes (mesencephalic, pontine and medullary), based on the involvement of vessel or its branches affecting the brainstem have been described in posterior circulation stroke. Spinal cord stroke was rarely diagnosed until emergency MRI of the spinal cord became the norm. Patients in spinal cord stroke present with sudden onset of flaccid paraparesis or quadriplegia, loss of sensations and autonomic disturbances mainly bladder and bowel dysfunction. Silent infarction may be demonstrated on MRI in 'at risk' population.⁹

Differential Diagnosis of Acute Focal Neurological Deficit

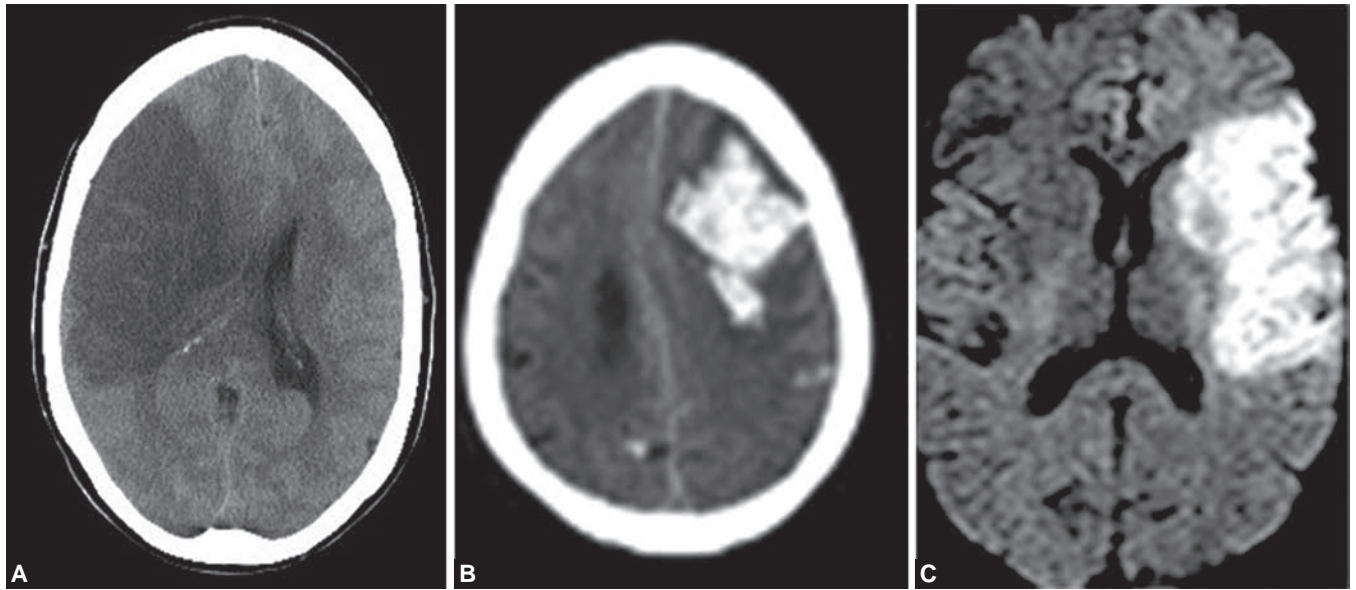
Stroke mimics include acute disseminated encephalomyelitis (ADEM), reversible posterior leukoencephalopathy (PRES), poststreptococcal inflammation, and metabolic stroke like mitochondrial encephalopathy, hemiplegic migraine, border zone ischemia, epilepsy, brain tumors, focal encephalitis like herpes simplex, alternating hemiplegia and some of neuro-degenerative conditions (Fabry disease). Around 15 to 20 percent of children presenting with acute neurological deficit have a nonvascular cause.¹⁰ There are often clinical features suggestive of these disorders and infarct on neuroimaging may also not be in the vascular territory. In ADEM, there is predominant white matter involvement. In hemiplegic migraine, electroencephalography (EEG) shows

unilateral slow background activity and epileptic discharges in epilepsy. In PRES, involvement is predominantly of posterior white matter and edema is vasogenic and not cytotoxic as seen in the stroke.

DIAGNOSTIC APPROACH

Aim of the diagnostic evaluation is to confirm the presence of stroke, identify its cause and eliminate other causes of acute neurological dysfunction. Detection of the cause of cerebrovascular disease is particularly important in children, because the recurrence risk is determined largely by the underlying cause. A child at risk for stroke faces the increased susceptibility and treatment of risk factors relatively for a long life than in adults.

First step in the evaluation is to do emergency neuroimaging to confirm the stroke and type of stroke (Figs 1A to C). It also detects the vascular distribution of stroke and excludes other causes of neurological deficit. Neuroimaging in childhood cerebral stroke has dramatically improved over the last decade. It should also include the neck for arterial dissection and other local causes. CT scanning has been the primary modality of brain imaging in acute stroke but has been surpassed by MRI techniques such as diffusion and perfusion sequences. Diffusion MRI can detect ischemic changes during hyperacute phase (first six hours after symptoms onset) when conventional MRI (T1 and T2 weighted) is normal.¹¹ CT remains the modality of



Figs 1A to C: (A) Contrast CT brain showing large hypodense lesion with mass effect no enhancement and (Right MCA infarct), (B) Noncontrast CT brain showing hyperdense lesion left frontal lobe (Fresh parenchymal hemorrhage); (C) MRI brain (Diffusion weighted image) in hyperacute stage of arterial ischemic infarct (Left MCA territory)

choice for detection of acute intracranial hemorrhage. Although MRI is more sensitive than CT in imaging acute stroke, CT is still performed as it is more widely available and affordable. One of the main disadvantage of CT is that ischemic stroke is often not obvious on CT with in first 24 hours. It can also miss venous sinus thrombosis and posterior circulation stroke. Magnetic resonance angiography (MRA) and venography (MRV) sequences use the inherent contrast of flowing blood and do not require the contrast. MRA and MRV sequences are used to delineate arterial and venous system and to detect any structural and flow abnormality. Conventional cerebral angiography is reserved for children with stroke with no obvious etiology provided by clinical assessment, investigations for various risk factors and in children with stroke with normal MRA.

Step two in the evaluation is to detect the underlying risk factor. There are numerous risk factors for stroke in children, but it is unnecessary to consider all of them in each child. While many children have multiple risk factors but it is not necessary to investigate the rare causes when the etiology is fairly obvious from the beginning as in case of heart disease and sickle cell disease. Diagnostic evaluation should be done in stages, with the next step influenced by the previous result. Noninvasive, low cost and high yield tests should be done first.

A complete blood count, peripheral smear, erythrocyte sedimentation rate (ESR), urine routine examination can provides clue to many conditions. Hemoglobin electrophoresis should be done on patients at risk of hemoglobinopathy. Coagulation profile (PT, PTT, and INR) is helpful in both

ischemic and hemorrhagic stroke. Clotting factors assay is done in intracranial hemorrhage when their deficiency is suspected. Blood sugar, lipid profile and serum proteins are also included in the initial workup.

Complete cardiac evaluation including X-ray chest, ambulatory cardiac monitoring, electrocardiography and echocardiography to be done in suspected cardiovascular etiology. Their yield is low if cardiac examination is normal. Lumbar puncture should be considered in any child with focal neurological deficit who has no mass effect and in whom the evaluation has not established any cause. Cerebrospinal fluid (CSF) examination is essential in stroke with unexplained fever or signs of central nervous system infection. Chronic infections like tuberculosis and syphilis can also manifest as stroke and should be evaluated when suspected. Head and neck examination should be done by expert for excluding local causes like otitis media and sinusitis. X-ray and MRI neck in suspected C-V junction and vertebral anomalies. Color carotid Doppler is done to look for flow abnormalities.

If the above evaluation does not establish a cause, include more uncommon risk factors such as metabolic and prothrombotic states.¹² Look for serum levels of protein C, S, antithrombin III, lipoprotein[a], fasting homocysteine, fibrinogen, plasminogen, factor VIIIc, factor XI, lupus anticoagulant, antiphospholipid antibodies, Factor V G1691A, prothrombin G20210A and methylene tetrahydrofolate reductase gene mutation (MTHFR C677T). For suspected metabolic causes of stroke in children, CSF and arterial lactate, blood ammonia, amino acids, fatty

acids and organic acid estimation are required in blood and urine. To prevent results of protein based assays from being affected by the acute thrombotic onset, blood samples should be taken at least three to six months after thrombotic episode. Homocystein and lipoprotein [a] levels should be obtained during fasting state. For all plasma based assays a clotting abnormality should be labeled as abnormal in at least two different samples at different times. Anticoagulants should be stopped at least seven to ten days before estimating plasma based assays.

ACUTE MANAGEMENT

General Care

Even in the present era majority of stroke children have irreversible focal brain damage by the time of their presentation to hospital, and therapeutic effort is usually concentrated on rehabilitation and the prevention of recurrence. Emergency management for raised intracranial pressure and impending herniation should be done under appropriate protocol. Priority is to maintain airway, cardiovascular status, hydration and blood pressure. Children with deteriorating consciousness should be ventilated. Management of seizures in acute setting should be according to appropriate protocol. Neuroprotective measures like preventing fever and maintaining body temperature just below 37°C.

Emergency Neuroimaging

CT brain remains the modality of choice in acute stroke but if emergency MRI is available, despite the need for general anesthesia in most cases, it has advantages over CT as, in addition to the essential exclusion of hemorrhage, ischemia can be documented within minutes, using diffusion-weighted imaging. MRI is also superior over CT in posterior circulation stroke and neck vessels. MRA and MRV sequences further help in establishing vascular pathology.

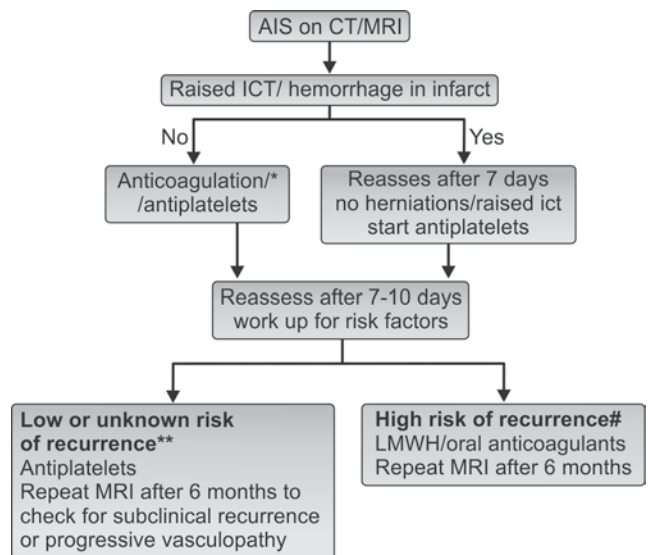
Specific Measures (Flow Chart 1A to C)

In hemorrhagic stroke, the main priorities are to prevent life threatening herniation, to reverse any thrombocytopenia or coagulopathy, to exclude STV, and treat any associated vasospasm as in subarachnoid hemorrhage, with volume expanders. Mass effect can be treated with hypertonic saline, mannitol or hyperventilation (PaCO₂ 35 to 45 mm Hg). Life-threatening herniation may benefit from craniotomy and hematoma drainage. Underlying coagulopathy is common in infants. Hemorrhagic disease of the newborn should be treated with vitamin K and DIC with fresh frozen plasma. Fresh platelet transfusion is required in thrombocytopenia and factor VIII in hemophilia.

Almost 50 percent children presenting with ischemic stroke or sinovenous thrombosis have a known underlying risk factor particularly sickle cell disease, anemia, cardiac disease, systemic illness and infection. Emergency management in them includes antibiotics in infections, exchange transfusion in sickle cell disease and anticoagulation heparin or low molecular weight heparin (1 to 1.5 mg/kg/12 hourly) in STV, extracranial vascular dissection, major prothrombotic states and underlying heart disease with high risk for recurrence of stroke. Contraindications for anticoagulation include: platelets less than 50,000/cu mm; recent intracranial hemorrhage; active systemic hemorrhage; major surgery in last 24 hours and uncontrolled severe hypertension. Aspirin in the dose of 3 to 5 mg/kg/day is indicated in remaining AIS.

Currently two to four percent children presenting with stroke receive thrombolysis with tissue plasminogen activator (tPA), but there have been no randomized controlled trials which address the use of tPA in the treatment of stroke in children.¹³ Although some children

Flow chart 1A: Management of arterial ischemic stroke



AIS, arterial ischemic stroke; CT, computerized tomography; MRI, magnetic resonance imaging; ICT, intracranial tension; LMWH, low molecular weight heparin.

* Anticoagulants for extracranial vascular dissection/cardioembolism/major prothrombotic states.

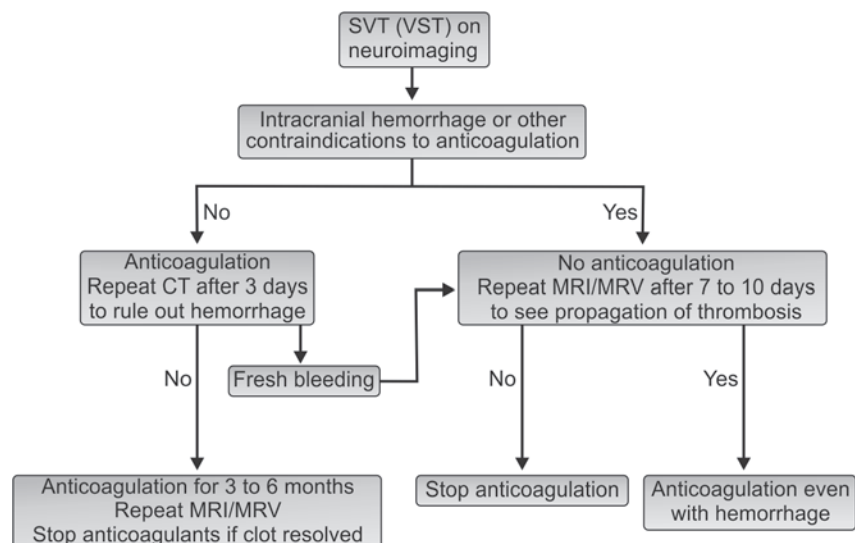
** Low or unknown risk of recurrence: Idiopathic stroke, cerebral arteriopathy, congenital heart disease like foramen ovale, mild prothrombotic states.

High risk of recurrence: Recurrent strokes or TIA while on aspirin, extra-cranial arterial dissection, severe arterial stenosis (>90%), high risk cardiac disease for recurrence, major prothrombotic states.

(a) After six months, anticoagulation and antiplatelets are stopped if recurrence risk is low/unknown.

(b) Exchange transfusion in case of sickle cell disease.

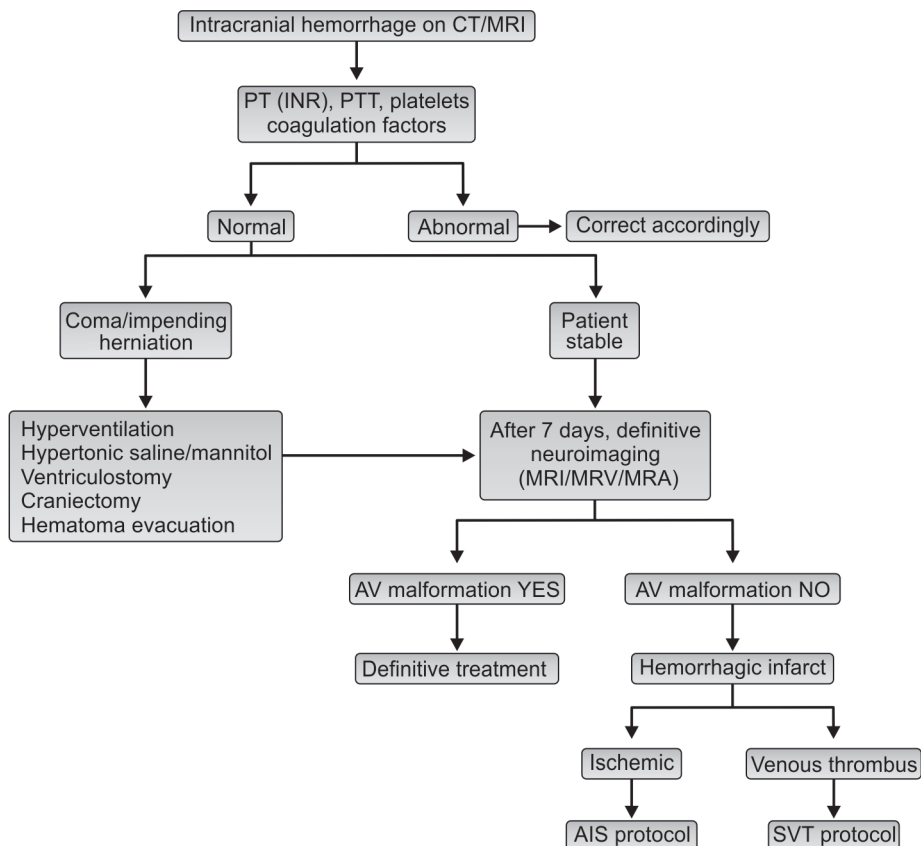
(c) Follow-up in stroke clinic every three to six months.

Flow chart 1B: Management of sinovenous thrombosis

SVT: sinovenous thrombosis; VST: venous sinus thrombosis; MRV: magnetic resonance venography; MRI: magnetic resonance imaging.

(a) Treat raised ICT, hydrocephalus and seizures as per standard protocols.

(b) In life-threatening situations surgical craniectomy may be considered.

Flow chart 1C: Management of hemorrhagic stroke

PT: prothrombin time; PTT: partial thromboplastin time; INR: international normalization ratio, AIS: arterial ischemic stroke; SVT: sinovenous thrombosis, MRA: magnetic resonance angiography; MRV: magnetic resonance venography; AV: arteriovenous.

can present to hospital within three hours, because rarity of stroke, low sensitivity of CT for acute infarction and the wide differential in this age group, the diagnosis of arterial occlusion is rarely made. In addition mortality in this age group is not very high and majority of such children can lead independent life as adult. It is therefore difficult to see a major role for thrombolysis in children at least in the present.

RECURRENCE AND PREVENTION

The overall risk of recurrence in arterial ischemic stroke is 10 to 25 percent.¹⁴ It may be as low as six percent in those with no risk factor or as high as 66 percent in moyamoya and 92 percent in children with sickle cell disease, who receive no treatment.¹⁵ Silent reinfarction is typical of sickle cell disease with an incidence of seven per hundred patients per year.¹⁶ Recurrence risk is six to 20 percent in cerebral venous thrombosis. Whilst there is no direct evidence that either antiplatelet agents or anticoagulants reduce the risk of recurrence in children with first AIS, both are commonly prescribed and advocated in published guidelines. Current clinical guidelines recommend antiplatelet doses of aspirin (3-5 mg/kg/day) in majority of children presenting with first AIS. Indications for long term anticoagulants (usually with warfarin 0.1 mg to 0.2 mg/kg/day) include patients with cardioembolic stroke, extracranial dissection, prothrombotic states like protein C, S deficiency and cerebral venous thrombosis. Dose of warfarin is adjusted according to INR and standard treatment of thrombosis is, maintaining INR 2.0 to 3.0. There may be a role of anticoagulation in children who develop stroke despite adequate antiplatelet therapy. Duration of the preventive treatment depends upon underlying risk factors. In children with low or unknown risk factors it is usually recommended for six months. Surgical revascularization is widely used as a treatment to prevent recurrence in moyamoya disease. Blood transfusion significantly reduces the risk of recurrent AIS in sickle cell diseases. The aim of regular transfusion is to maintain HbS percent below 25 percent and to maintain hemoglobin between 10 to 14 g/dl. Bone marrow transplant is an indication in sickle cell disease in many developed countries and it stabilizes imaging abnormalities in SCD. Closing foramen ovale to prevent stroke recurrence is controversial. Risk of stroke recurrence in foramen ovale depends upon the degree of right to left shunting and the risks and benefits of closure should be considered on an individual basis. Folate supplementation is advised to children with hyperhomocysteinemia and those who are homozygous for MTHFR C677T. Blood pressure should be monitored. Suggestion regarding diet, smoking and regular exercise is important. Children with risk of recurrence should be advised to maintain hydration, prompt treatment of fever and infections.

Rehabilitation

Rehabilitation needs multidisciplinary team to rehabilitate the child with stroke and to support the family. Aim is to restore and promote further development of optimal functional skills. It should be home and community based. Growth, development and occupations of the child (i.e. usual activities and participation) should be the central to practice.

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The Autistic Spectrum Disorders

RK Sabharwal

INTRODUCTION

Autism is an etiologically and clinically heterogeneous group of disorders, collectively referred to as the “autism spectrum disorders (ASDs)”. The concept of autism in children was first introduced by Leo Kanner in his seminal paper published in 1943. He described a pattern of behavior he called ‘early infantile autism’ characterized by severe impairment of social interaction and communication, and intense resistance to change. For decades after this publication, childhood autism was considered to be a rare condition.¹ Before and for years after Kanner’s first paper on his syndrome, autistic conditions were often diagnosed as childhood schizophrenia. A major change in the concept of childhood autism was evident in DSM-III. (American Psychiatric Association, 1980).² This introduced the term ‘pervasive developmental disorders’ (PDDs) as a general category, thus acknowledging the shift in the concept of autism from a psychiatric to a developmental disorder.

In 1944, Hans Asperger identified in four boys a pattern of behavior and abilities that he called “autistic psychopathy”. The pattern included *a lack of empathy*, little ability to form friendships, one-sided conversations, intense absorption in a special interest, and clumsy movements. Asperger called these children as *little professors* because of their ability to talk about their favorite subject in great details.³

Autism, also called infantile autism or autistic disorder, is a lifelong disorder that causes abnormal neurological development. It is one of five pervasive development disorders (PDDs) that also include Asperger’s syndrome (milder disorder with normal language), childhood disintegrative disorder, Rett disorder (severe disorder in female children), and pervasive development disorder-not otherwise specified (PDD-NOS). The severity of autism’s deficits is extremely variable. Therefore, the term autism spectrum disorders (ASDs), or “the autisms,” is appropriate because it denotes

a bell-shaped curve of impairment.⁴ While the autism spectrum disorders (ASDs) are also termed as pervasive developmental disorders (PDDs); the term “autism” or autistic disorder (AD) should be used for the classic pro-typical cases. Asperger’s syndrome refers to ASD children in whom speech is not delayed and whose IQ is at least 70.⁴ The acronym PDD-NOS (PDD not otherwise specified) applies to ASD children who do not fulfill criteria for Asperger’s syndrome or AD; these children form a heterogeneous group generally less severely affected than those who have AD. There are three key manifestations of autism:

1. Impaired sociability, empathy, and ability to read other people’s moods and intentions, with resulting inadequate or inappropriate social interactions
2. Rigidity and perseveration, including both stereotypes (purposeless repetitive movements and activities), the need for sameness, and resistance to change
3. Impaired language, communication, and imaginative play.

EPIDEMIOLOGY

Studies carried out in the late 1990s and the present century reported annual rises in incidence of autism in pre-school children, based on age of diagnosis, and increases in the age-specific prevalence rates in children. Prevalence rates of up to 60 per 10,000 for autism and even more for the whole autistic spectrum were reported. Reasons for this increase includes: changes in diagnostic criteria, development of the concept of the wide autistic spectrum, different methods used in studies, growing awareness and knowledge among parents and professional workers and the development of specialist services, as well as the possibility of a true increase in numbers. A recent surveillance study reported a 57 percent average increase in the number of autism diagnoses in specified regions of the United States from 2002 to 2006, and estimated the current prevalence to be one in 110 children.⁵ Although these

studies reflect a 10-fold increase from studies published a half-century ago that chiefly targeted AD alone, most of the newer studies also included individuals with Asperger's syndrome and PDD-NOS. Wide variations in the incidence of Rett's syndrome have been reported among various countries. Rates as high as 1 per 10,000 live female births have been reported.

ENVIRONMENTAL

In light of current evidence, it seems likely that the etiology of autism 'involves complex interactions between environmental factors and genetic mutations controlling either:

- the patterning of neuronal populations critical for the control of inhibition/excitation in the cortex, and/or
- the synaptic assembly of these excitatory and inhibitory neuronal networks and/or the neuronal networks involved in large-scale cortical neuromodulation (Fig. 1)".

An important concept in developmental neurobiology is that genes involved in the development of the CNS are extremely pleiotropic, i.e. several important genes involved in the early patterning and specification of neuronal subpopulations also act later in development to regulate the proper synaptic assembly of the same or other neuronal populations. Therefore, a mutation in one of the genes reviewed above will undoubtedly have many complex, non-redundant functions during development of the CNS that could lead to a divergent and complex neuropathology such as autism.⁷

Sex

Sex bias for PDD is significant. Autism and PDD-NOS may be 5 times more common in boys than in girls. Asperger's syndrome may be 10 times more common in boys than in girls. Only Rett's syndrome affects more girls than boys; in fact, Rett's syndrome is rarely diagnosed in boys. However,

new molecular testing for Rett's syndrome indicates that the incidence of the condition is greater in boys than previously reported. Finally, the male predominance noted above also suggests a genetic role in the inheritance of autism.

Race/Ethnicity

Identified ASD prevalence also varied by race/ethnicity, with some sites showing higher ASD prevalence estimates among non-Hispanic white children than among non-Hispanic black children and Hispanic children. Considerable variability has been reported across studies in the racial disparities of ASDs.

Prenatal, Perinatal and Neonatal Factors

The incidence of autistic disorder in survivors of neonatal intensive care appears to be elevated. It has been hypothesized that pregnancy, delivery, or neonatal complications may act through independent etiologic pathways to increase the risk of autism or may interact with a genetic disposition to increase the risk by interfering at critical times in the developmental process.⁸ High maternal age (≥ 35 years), multiparity (≥ 4), daily smoking in early pregnancy, were associated with increased risk for autism in the univariate analyses. Increased risks of autism were also found in pregnancies complicated by hypertensive diseases, bleeding, and a number of delivery and infant characteristics, including cesarean delivery, preterm birth (≤ 36 weeks), low birth-weight ($\leq 2,500$ g), small or large size for gestational age, low Apgar score (0–6) at 5 minutes, and congenital malformations.

Genetics

New technology, especially array chromosomal genomic hybridization, has both increased the identification of putative autism genes and raised to approximately 25

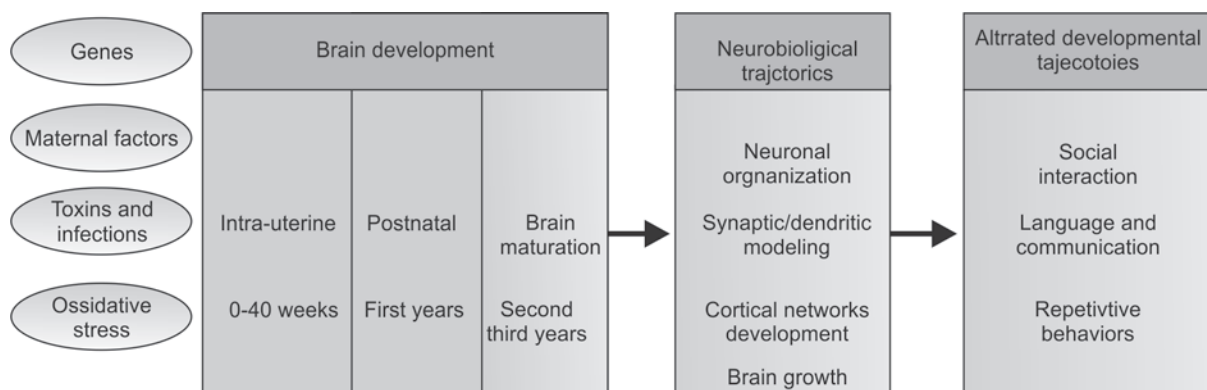


Fig. 1: Genetic and epigenetic factors involved in the pathogenesis of autism. Interactions between multiple genes and environmental factors, such as intrauterine infections, alcohol/ toxins exposure, and obstetrical sub optimality, can influence intrauterine and early postnatal brain development and disrupt crucial neurobiological pathways, from neuronal migration and cortical organization to synaptic and dendritic conformation, resulting in alterations of neurobehavioral trajectories that are involved in the pathogenesis of ASD.⁶

percent, the percentage of children for whom autism related genetic change can be identified.⁹ Using standard medical genetic evaluation techniques, a genetic cause can be identified in 20–25 percent of children on the autism spectrum. This number has increased with the use of array comparative genomic hybridization (aCGH) also called chromosomal microarrays (CMAs). Identified genetic causes of autism can be classified as the cytogenetically visible chromosomal abnormalities (5%), copy number variants (CNVs) (i.e. submicroscopic deletions). The most common autism related CNVs are the 15q11.2-11.3 duplications, similar to duplications revealed by FISH, and reciprocal 16p11.2 microdeletions and duplications (10–20%), and single-gene disorders (5%). Although at least 1 autism linked abnormality has been found on almost every chromosome, sites on a few chromosomes (X, 2, 3, 7, 15, 17, and 22) seem to be more promising than others.

Single Gene Disorders

Autism or autistic features have been reported in children with many other single gene disorders. Most are associated with severe mental retardation and significant dysmorphology, and the children are rarely referred with an initial question of autism. Autism in these cases is often referred to as “syndromic autism”.

- *Fragile X syndrome*: Approximately 1 to 3 percent of children with a diagnosis of autism diagnosis can be shown to have fragile X syndrome. At least half of children with fragile X syndrome exhibit some autistic behaviors, such as avoidance of eye contact, language delays, repetitive behaviors, sleep disturbances, tantrums, self injurious behaviors, hyperactivity, impulsiveness, inattention, and sound sensitivities.
- *Tuberous sclerosis complex*: About 25 to 50 percent of mentally retarded individuals with tuberous sclerosis complex (TSC) fulfill autism diagnostic criteria. Early onset infantile spasms and temporal lobe tubers on magnetic resonance imaging (MRI) examination increase the chance that children with TSC2 mutations will also develop autism, molecular genetic testing for the two causative genes, TSC1 and TSC2, is clinically available. Recurrence risks for families with a child with autism due to TSC may be significantly higher than for families with autism of unknown cause.
- Others:
 - Mitochondrial disorders
 - Adenylosuccinate lyase deficiency
 - Creatine deficiency syndromes
 - Smith-Lemli-Opitz syndrome
 - Angelman syndrome
 - Duchenne muscular dystrophy
 - Sotos syndrome
 - Neurofibromatosis 1, hypomelanosis of Ito, etc.

ETIOLOGY

Autism is not a disease, that is, it is not a condition with a well-defined single etiology. It is a behaviorally defined syndrome of neurological dysfunction. The evidence for a genetic contribution has come from twin and family studies. Concordance rates for monozygotic twins are significantly higher than for dizygotic twins, and heritability is more than 90 percent. Family studies have consistently shown that, although the actual recurrence risks are low (2-7%), the relative risk is 50 to 200 times higher than the population prevalence.¹⁰

In the vast majority of cases, autism has no evident cause. One can safely assume that etiology in such cases consists of a mixture of undetected acquired causes, non-syndromic genetic causes (new mutations, single cases of recessive inheritance, etc.) and perhaps in a majority polygenic inheritance or inheritance of a susceptibility gene to otherwise innocuous environmental factors.

An etiology may be found in 10 to 20 percent of children with autism (Table 1).

CLINICAL SYMPTOMATOLOGY

The behavioral features of autism involve affectation of abilities that can be remembered by the mnemonic SCALD (sociability, communication, affect, language and drive). Onset of autism is prior to 3 years of age and may be gradual with pre-existing evidence of difficulties in socialization and communication or may consist of an “autistic regression” in

Table 1: Some etiologies of autism

Unknown

Currently the most frequent situation

Genetic

- Known single gene defects, e.g. PKU, tuberous sclerosis
- Defined chromosome anomalies, e.g. fragile-X, Angelman, Down, Williams syndromes, etc.
- Syndromes with suspected genetic etiology, e.g. Cornelia de Lange, Joubert syndromes
- Polygenic inheritance (currently favored)
- Inheritance of enhanced susceptibility to some environmental factor
- Single Mendelian dominant, recessive, X-linked gene defects (rare?)

Non-genetic

- Intrauterine infection, e.g. rubella, CMV
- Brain malformation/ anomaly, e.g. hydrocephalus, some neuronal migration defects, Moebius syndrome
- Postnatal brain damage, e.g. bilateral herpes simplex, bilateral hippocampal sclerosis, severe ischemia/ anoxia
- Early malignant epileptic encephalopathy, e.g. infantile spasms, Lennox-Gastaut syndrome.

a child who had previous normal development, the latter occurring in 20 to 40 percent of this population.

The category of non-autistic PDD includes Asperger's disorder. This is a group of children with less severe impairment of socialization who has difficulty in interpreting and using social cues and has naïve/pedantic language use. Language is superficially normal but is still associated with problems of abstraction, interpretation, and pragmatics. By definition, all have normal or near normal intelligence. Whether this is a milder manifestation of autistic disorder or a separate entity is still not clarified.

Childhood disintegrative disorder, previously known as Heller's disintegrative psychosis, is behaviorally similar to autism with onset between age 2 and 10 years and a worse prognosis for significant improvement. These children comprise 5 percent of the autistic population and have a history of normal development until the onset of regression. This disorder is sometimes associated with severe epilepsies and progressive neurological disorders.

Rett's syndrome (RS) was first reported in 1966 by Andreas Rett, an Austrian pediatric neurologist. Rett's syndrome occurs almost exclusively in females and has a typically degenerative course. Before the discovery of Rett's syndrome, incidents were mistaken for many other neurologic disorders, especially in females. The specific mutation on the gene related to Rett's syndrome (methyl-CpG binding protein-2 [MECP2]) was identified late in 1999. At least 200 different mutations have been found to be associated with the disease, including missense and truncating mutations. The common BDNF polymorphism may modify disease severity in Rett's syndrome and the severity of the phenotype varies depending on the MECP2 mutation type and locations.

The disorder primarily affects females (though few males have been reported) with prevalence of 1:10,000-15,000 females. The most prominent clinical features include a developmental regression and arrest with microcephaly and motor changes. Abnormalities in respiration, seizures, growth failure, and gastrointestinal disturbances occur. Insidious loss of functional hand use followed by stereotyped hand wringing, and hand-to-mouth movements are pathognomic of the disorder.

A very important aspect of autism is the uneven ability across cognitive skills. The abilities of autistic children may vary from profound mental impairment to superior skills, but even the superior overall ability is associated with areas of lesser competence. In some autistic children the unevenness is so marked that truly exceptional talent may coexist with overall mental incompetence, the so-called savant syndrome. Exceptional ability for music, drawing, calculation, rote memory, visual-spatial abilities or other skills spawns untaught musical geniuses and artists, calendar calculators, and puzzle solvers.¹¹ The magnitude of impairment in autism is age-specific, with the most

profound disturbance in early preschool years and a gradual, though not total, improvement in function over time. While subtle features may be present in the first year of life, the diagnosis should occur between 2 and 3 years of age, but is often delayed.

The core defect in language involves social communication. All children have impairment in pragmatic features, including poor eye contact, voice modulation, problems understanding body meaning, poor use of gestures, and immediate or delayed echolalia.

Play in autism shows impairment in imagination and pretend play. It can have stereotypic features like absent copying, oral exploration or repetitive stereotypic play without vocalization. All children with autism have restricted activities and interests. These include repetitive actions as opening and closing doors and playing with light switches, water; motor stereotypes such as finger flicking, hopping, self spinning, clapping, rocking, etc. Obsessive routine like lining objects and preserving sameness, and a fascination in mechanical or cognitive themes (cars, dinosaurs, trains, numbers, letters, books, etc.) are usual. Most children have a significant resistance to change in routine.

Suspecting ASD in Infancy

It is clear that many parents are seriously concerned about the child's development in the first year of life, and almost 90 percent are very concerned by age 2 years. Common concerns include observations of social deviance or oddity, worries that the child may be deaf, and that the child's language fails to progress.

Clinical Picture

When autism becomes manifest in infancy, parents may complain that the baby is irritable, sleeps poorly, has to be walked by the hour because of screaming, resists being cuddled by arching his back, or that the baby is "too good", lying contentedly in the crib looking at his hands or at a mobile, does not insist on being picked up, and will go to anyone without evincing stranger anxiety.

Motor Skills

Gross motor development, such as sitting and crawling, is often quite normal, with the notable exception of children with overt brain pathology, notably of the girls who will later be diagnosed as having Rett's syndrome who fail to use their hands to grab a toy or feed themselves a cookie and who will be severely delayed or unable to walk.

Communication Skills

Most autistic infants have defective nonverbal communication skills (pragmatics), such as infrequent regarding of parents' face and reciprocal cooing, and lack of pointing or shaking the head "No".

Differentiating between Autism Spectrum Disorders and Other Developmental Disabilities

Children with ASD may have some warning signs similar to those in developmental disorders (DDs)/developmental language disorders (DLDs). However, some impairment may be more typical of those seen in children with ASD.¹² Most striking is the significantly more prominent and consistent impairment in social interaction skills, especially joint attention skills, in children with ASD:

- The ASD group is more impaired on other behaviors, such as imitation, facial expressions, eye contact, and sensory responses
- Young children with ASD are likely to be delayed in using words and their vocalizations are likely to lack consonants and to have unusual prosody
- They are likely not to respond to their name or to instructions even with contextual cues
- They are likely to be delayed in using objects conventionally in play and also are likely to display repetitive movements with their body or objects
- Furthermore, young children with ASD are very likely to be delayed in sharing attention with eye gaze, sharing affect, and drawing others attention to objects or events of interest
- They are very likely to lack the indicating gestures of pointing and showing and lack the coordination of gestures with eye gaze, facial expression, or vocalizations.

Mirror Neuron Systems

A new area of interest in autism research is the role of “mirror neurons” in the sensorimotor cortex, which are activated during the performance of motor acts and while watching others perform them. Discovered in primates, mirror neurons play a critical role in learning by imitation and in understanding similarities between oneself and others, and thus participating in the development of social cognition.¹³ The dysfunction of mirror neurons in imitation skills and empathy may play a significant role in the development of autism, but more research data to support this hypothesis are needed.

DIAGNOSIS AND WORK-UP OF AUTISTIC SPECTRUM DISORDERS

No single sign, symptom, clinical feature, associated handicap, or diagnosis suffices for a diagnosis of autism or invalidates it, and no individual presents all the impairments listed. At the present time no biological marker or simple laboratory test or procedure exists for the diagnosis of autism and related conditions except Rett's syndrome and syndromic ASD. Clinicians must, accordingly, rely on their clinical judgment, aided by guides to diagnosis such as DSM-IV and ICD-10 as well as by the results of various assessment instruments, rating scales or check lists. The latter instruments do

NOT substitute for the diagnosis by an experienced clinician. Recognizing the central importance of early detection and diagnosis, the American Academy of Pediatrics¹⁴ has recently recommended universal screening for ASD at both 18 and 24 months of age. Children identified as being at increased risk of ASD could then benefit from streamlining of subsequent referrals, and initiation of interventions targeted at areas of concern (e.g. development of communication skills). However, to achieve the primary goal of earlier diagnosis, screening for ASD must be followed by timely access to appropriate diagnostic assessment.

- Detailed history should be aimed at determining developmental milestones, developmental regression at any age, identifying any encephalopathic events, history of attention deficit disorder, seizure disorder, depression, mania, troublesome behaviors such as irritability, self-injury, sleep or eating disturbances, and pica for possible lead exposure
- Formal audiologic evaluation: All children with developmental delays, especially those with delays in social and language development, should undergo a formal audiologic hearing evaluation
- *Psychological/communication assessments*
 - Verbal and nonverbal skills must be assessed independently
 - Assessment of social-adaptive behaviors
 - Communication (not just speech) evaluation
 - Nature of social relatedness
 - Behavioral features
 - Play skills
 - Family/living conditions.
- *Medical evaluation:* Clinical examination
- *Metabolic Testing:*

The percentage of children with autism who prove to have an identifiable metabolic disorder is probably less than 5 percent. Metabolic testing or consultation is indicated by a history of lethargy, cyclic vomiting, early seizures, dysmorphic or coarse features, mental retardation or if mental retardation cannot be excluded, questionable newborn screening
- Genetic screening if dysmorphism, family history
- MRI/CT if indicated; EEG.

Tests of Unproven Value

There is inadequate evidence to support routine clinical testing of individuals with autism for hair analysis for trace elements, celiac antibodies, allergy testing (in particular food allergies for gluten, casein, *Candida* and other molds), immunological or neurochemical abnormalities, micronutrients such as vitamin levels, intestinal permeability studies, stool analysis, urinary peptides, mitochondrial disorders (including lactate and pyruvate), thyroid function tests, or erythrocyte glutathione peroxidase studies.¹⁵

Autistic Spectrum Disorders (ASDs) and Epilepsy

The association between autism and epilepsy is now well accepted. Numerous investigators have documented that there is an increased frequency of seizures in ASD. The range of seizure frequency has varied in the literature from a low of 7 percent to a high of 42 percent but the most recent studies suggest that about one-third of children on the autistic spectrum develop epilepsy. There appears to be a two peak distribution to seizures in ASD. One peak occurs in infancy prior to age 5 years and the other occurs in adolescence after age 10 years. Clinical epilepsy develops by adolescence in more than a third of children; its risk is tied to the severity of the underlying brain dysfunction.

Asperger's Syndrome

Autism without mental retardation or delayed language development. There are no specific studies on risk of epilepsy but extrapolation from the studies on risk factors for autism suggests that the likelihood for developing epilepsy is 5 to 10 percent in early childhood.

PDD-NOS

The risk of epilepsy is probably linked to the severity of the underlying brain dysfunction.

Child Disintegrative Disorder

Severe autism acquired between ages 2 and 10 years after entirely normal early development of language, sociability, and cognition. The risk of epilepsy may be as high as 70 percent.

Rett's Syndrome

Specific X-linked genetic deficit strongly associated with mutations of the *MeCP2* gene. It affects postnatal brain growth, resulting in severe mental retardation, motor deficits, and other features. The risk of epilepsy is more than 90 percent.

Management of ASD

Management of these children involves a multidisciplinary team comprising a pediatric neurologist, speech and language therapist, psychologist, occupational therapist, special educator and a social worker. The mainstay of intervention in autism is management of the environment—the physical environment, the people, and events. Individuals with autism are unable or slow to process information and are easily overwhelmed by the environment. They function best when the environment is highly structured and supervised, which means that the world is simplified, interactions are simple and limited, events and people are predictable, and known rules govern actions.

Table 2: Comorbid disorders in autism

<i>Medication—Responsive Problems</i>	<i>Autism—Associated Problems</i>
<ul style="list-style-type: none"> • Attention deficit hyperactivity disorder • Aggression/tantrums • Self-injurious behavior • Anxiety • Obsessive compulsive disorder • Affective disorders • Tic disorder • Sleep disturbance • Epilepsy 	<ul style="list-style-type: none"> • Eating disturbances • Accidental injury • Sleep disturbance • Tantrums • Stimulus hypersensitivity • Dyspraxia • Masturbation • Cognitive impairment • Learning disability

Pharmacological Intervention

There is no cure for autism. The role of medications in autism is to treat the co morbid disorders present (Table 2). The goal of pharmacological therapy is to make the child amenable for the most important therapy – “intensive education”.

Early Childhood Intervention Programs

A number of programs have reported substantial improvement in outcome in children participating in preschool programs that involve 15-40 hours of school-based intervention. Each of these programs focus on training 5 basic skills:

- Ability to attend people and to cooperate with teaching exercises
- Ability to imitate others both verbal imitation and motor imitation
- Ability to comprehend and use language
- Ability to play appropriately with toys
- Ability to socially interact with others.

The teaching should be done in highly structured teaching environment with a high staff to student ratio.

Prognosis

Approximately 50 percent of all autistics function in the retarded range throughout life. Initial cognitive scores are highly predictive. Children with seizures and other indications of organic brain dysfunction tend to be the most retarded, undeveloped, and ultimately impaired. The second group of 25 percent contains children whose motor development is relatively normal and who develop communicative language by 5 years. Children in this group become extremely shy, introverted, and passive in adolescence. They need continued supervision in living situations, but can often function in support employment. The third group of 25 percent has normal intelligence, are able to live and work independently. These persons, however, continue to show personality, social and cognitive impairment.

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Approach to a Patient with Delay in Language Development

Monica Juneja, Rahul Jain

INTRODUCTION

Delayed language development is one of the common problems with which children are referred to a pediatrician. Some children with language delays are also identified during screening in well baby clinics. Studies have shown that in pre-school children aged 2 to 4.5 years, the prevalence of language delay ranges from 2.27 percent to 19 percent.¹ Boys are affected much more commonly than girls.¹ Many children mainly those with developmental language disorders outgrow this condition, but in 40 to 60 percent of children with language delays, the problem persists if left untreated.²

Language typically has four components, any of which may be affected in children with language disorders:³

- *Semantics*: Meaning of words, phrases or sentences
- *Syntax*: Rules of grammar, which determine how words are combined to form meaningful sentences
- *Phonology*: The rules for combining sounds of language
- *Pragmatics*: The rules for the social use of language

Language can also be divided into receptive and expressive language. Receptive language refers to the child's ability to understand the nonverbal and verbal communication, while expressive language refers to the child's ability to formulate and express an idea. It is important to understand that speech, which only refers to the production of sound for the act of communication, is not synonymous with language e.g. sign language is also a type of language.³

Language delay can be a manifestation of many disorders, the common ones being hearing impairment, mental retardation, autism and developmental language disorder.³ Before going on to the details of these disorders it is important to know common language milestones (Table 1).⁴

Table 1: Important language milestones
(till 5 years of age)

<i>Receptive language</i>	<i>Expressive language</i>
<ul style="list-style-type: none"> • Recognizes own name 7 months • Response to 'No'-8 months • Understands some words or phrases-10 months • Follow simple one step command with gestures-1 year • Points 2-3 body parts-18 months • Follow simple one step command without gestures-2 years • Follows 2 step command-2 years • Obeys 2 prepositions-3 years • Listen to a short story and answer simple questions about it-4 years • Obeys 4 prepositions-4 years • Follows 3-4 step commands-5 years 	<ul style="list-style-type: none"> • Monosyllables-6 months • Combines syllables-8 months • First word with meaning-12 months • Vocabulary of 8-10 words-18 months • Vocabulary of around 50 words, two-word phrases -2 years • Uses pronouns-3 years • Three-word combinations-3 years • Knows his name and sex-3 years • Uses past tense-4 years • Four word sentences-4 years • Asks questions, converses, and tells stories-4 years • Five word sentences, uses future tense-5 years

CAUSES OF LANGUAGE DELAY

Hearing Impairment

Speech being a learned behavior, hearing impairment at an early stage of development severely affects its

development. Contrary to the popular belief, children with mild hearing loss (15-30 db HL) also have mild language delay miss voiceless consonants. Children with moderate hearing loss (31-50 db HL) cannot hear some speech sounds and hear others inaccurately, commonly missing unstressed words such as prepositions and relational words. Their language delay is associated with confusion related to word meanings and grammatical rules. They have commonly omissions of articles, conjunctions and prepositions. Language, on the other hand, will not develop in children with severe and profound hearing loss, without any intervention.⁵

Hearing loss can be conductive or sensorineural. Sensorineural hearing loss is typically more severe and affects higher frequencies. The common causes of sensorineural hearing loss in children are bilirubin induced neurological damage, bacterial meningitis, perinatal asphyxia, intrauterine infections, ototoxic drugs, and congenital syndromes.⁶

Global Developmental Delay/Mental Retardation

This is the most common cause of language delay, accounting for more than half of the cases. Commonly, there is delayed acquisition of milestones in all the domains of development; however, the language development is usually more severely affected (as compared to the motor development). The delay in language acquisition is global with poor comprehension, impaired gesture use and delay in expressive language, all being commensurate with the cognitive development. Presence of co-morbid hearing impairment may be responsible for disproportionate language delay in some of these patients.

Pervasive Developmental Disorders (PDD)

Impairment in communication is one of the core deficits in PDD. Failure to acquire language at the expected age is the most frequent presenting complaint for preschool autistic children. Approximately, 50 percent of children with autism never develop any speech and some children with PDD show language regression. Language delay however is not a feature of Asperger's disorder.^{7,8}

Children with autism manifest global deficits in language acquisition; however, these deficits are disproportionately more than their cognitive level. These children may poorly understand what is said to them, in fact, this is the only condition where expressive speech may sometimes be more than receptive speech. Children with autism are doubly handicapped as they not only have delayed speech but also have very poor nonverbal communication skills. Thus, they commonly have severe temper tantrums as they are unable to communicate their needs by any means. They may also have atypical gestures like immature pointing and 'handover hand pointing' (using their parents or any other adult's hand to point for objects).^{7,8}

Language acquisition is not only delayed in these children, it may also be deviant. Many verbal autistic children may exhibit immediate and/ or delayed repetition of words or phrases regardless of meaning (echolalia). Some of them also have pronominal reversal (the child refers to himself as 'you' or 'by name', rather than 'I' or 'me'), much beyond 2 to 3 years of age. Some children may speak in a sing-song or monotonous voice.^{7,8}

In addition, other pointers towards autism may be present. They have impairment in social interaction manifesting as poor eye contact, impaired interaction with peers, social aloofness and poor emotional response. These children also have repetitive behaviors in form of repetitive body movements like hand flapping, running in circles, etc. They may also have very unusual interests.^{7,8}

Communication Disorders

The Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) has included language and speech disorders under communication disorders and recognizes five diagnostic categories: (1) expressive, language disorder, (2) mixed receptive-expressive language disorder, (3) phonological disorders, (4) stuttering and communication disorders, (5) not otherwise specified.⁹ Out of these only expressive language disorders, mixed receptive-expressive language disorder and phonological disorders present with speech delay.^{9,10}

Language Disorders

These are behaviorally defined conditions in which there is a delay or abnormality in expressive or receptive language skills in the absence of global cognitive disability, PDDs, hearing loss, environmental deprivation, emotional disturbances, or identifiable neurological disorders.¹¹

Expressive Language Disorders

These children have age-appropriate language comprehension and nonverbal cognition, with delayed expressive language. They have limited vocabulary and have difficulty learning new words. They use short sentences with simplified grammatical structures. In general, these children acquire speech but at a much slower pace than their peers, the speech resembling that of a much younger child.^{9,10}

Fifty to eighty percent of these children outgrow their language difficulties during their preschool years and in these children there is very little risk of learning and behavioral problems later in life. However, when this disorder persists in to early school age years, the expressive language growth continues to lag behind, limiting communication in interpersonal and academic situations. They may also develop other problems like reading and spelling difficulties and Attention Deficit Disorders in early school years. Most of these children also acquire

normal language abilities by late adolescence, although subtle deficits may persist.⁹⁻¹⁴

Mixed Receptive-Expressive Language Disorder

There is impairment in both receptive and expressive languages which are substantially below the child's nonverbal cognitive abilities. Mostly the receptive and expressive languages are proportionately delayed. In addition to the features seen in expressive language disorder, these children have difficulty in understanding words and sentences. Thus, a 2-year-old child may understand names of familiar people or objects, but there may be limited understanding of simple one step commands. In mild cases, there may be difficulties only in particular type of words (e.g. spatial words like "behind", "next to" or "under") or statements (e.g., complex "if-then" sentences).^{9,10}

Mixed receptive-expressive language disorder is usually detected before age 4 years, however, milder cases may not be recognized till the child reaches elementary school. Some children eventually acquire language skills within the normal range but their overall prognosis is poorer than that of expressive language disorder. Two-third of school age children with persistent mixed receptive-expressive language disorders have psychiatric comorbidity, Attention Deficit Hyperactivity Disorder being the most common.⁹⁻¹⁴

Phonological Disorders

Phonological disorders are characterized by failure to use speech sounds that are expected for the age and dialect. This may involve omission (e.g. saying *nana* for *banana*), substitution (e.g. saying *tap* for *cup*) or distortion of certain sounds, lisping being the commonest phonological disorder. There may also be problems with organization of sounds in an individual word (e.g. saying *pakda* for *kapda*). In severe cases the speech may be delayed in onset and unintelligible. The phonological disorders include both disorders with no known cause and disorders arising from hearing impairment, structural abnormalities (e.g. cleft lip and palate) and neurological conditions (like cerebral palsy).^{9,10}

Speech Apraxia

This is a type of phonological disorder which results from impairment in planning and executing speech movements despite normal range of movement and muscle strength in oro-motor system. The apraxia may be limited to speech or be generalized, involving other activities. The child's effort to imitate a sound seems labored and ineffective and the speech is often confined to short utterances. The hallmark of speech apraxia is dysfluency, i.e. at times the child speaks a word clearly, but cannot repeat the same on command. These children also have feeding

problems, starting early in life and have excessive drooling. Boys are more commonly affected, and family history is often present.^{6,10}

Dysarthria

This is a phonological disorder associated with neurological conditions like cerebral palsy, neuromuscular disorders, etc. manifesting as slow, labored and slurred speech.^{6,10}

Elective Mutism

Elective mutism is a psychological disorder in which a child does not speak in school, public situations or with strangers, but will speak when he/ she is alone or with his/ her friends or parents. These children also manifest other features of poor adjustment like social withdrawal, excessive shyness and overdependence on parents.⁶

Psychosocial Deprivation

Psychosocial deprivation in form of inadequate exposure to language and child neglect, can adversely affect the speech development.⁶

APPROACH TO A CHILD WITH LANGUAGE DELAY

Most of the children with language delay present at 18 to 36 months of age. Screening and surveillance for language delay helps in picking up of these children at early age. A child should have a complete evaluation if he is having any of the following red flag signs:

- Not babbling by the age of 12 months
- No pointing by 12 months
- No words by 16 months
- Not understanding simple commands by 18 months
- No two-word meaningful phrases (without imitating or repeating) by 24 months
- Not making 2 to 3 word sentences by 3 years of age
- Any loss of speech.

In such a child, the first step is to take a detailed history of language development, including the comprehension level of the child and use of gestures. Any regression in language should be noted. This information can then be used to ascertain the language age of the child. A detailed developmental history in other domains is also obtained, to look for global deficits. The nonverbal cognitive abilities of the child help in differentiating language disorders and mental retardation (Table 2). The history of the child's response to being called and response to everyday noises including soft sounds should be obtained to evaluate his/her hearing.^{6,11,15,16}

If the child has poor language comprehension, impaired gesture use, language regression or differential responses to noises, the parents should also be interviewed in detail about the social interaction of the child including his play and other characteristic features of autism.

Table 2: Nonverbal cognitive abilities

- Object permanence (searches for hidden object)—12 months
- Cooperates with adult in simple household tasks—2 years
- Imitates vertical and circular strokes—2 years
- Enjoys simple make-believe play—3 years
- Copies circle—3 years
- Draw a man with 2 parts—3 years
- Matches primary colors—3 years
- Copies cross—4 years
- Draw a man with 3 parts—4 years
- Copies triangle—5 years
- Draw a man with 6 parts—5 years

An inquiry should be made for situational difficulties in speech, especially in children who are otherwise normal, to rule out elective mutism. Difficulties in feeding, excessive drooling and other neurological deficits are pointers towards phonological disorders.

Other pertinent histories are psychosocial history specially focusing on language stimulation at home and family history of speech delay.

Also, history should be taken for identifying etiology of mental retardation and hearing impairment including history of maternal illnesses during pregnancy, perinatal asphyxia or trauma, bilirubin induced neurological damage, prematurity, birth weight, past history of head trauma or infections of the nervous system, and use of ototoxic drugs.

It is important to remember that tongue-tie and bilingualism do not cause language delay.

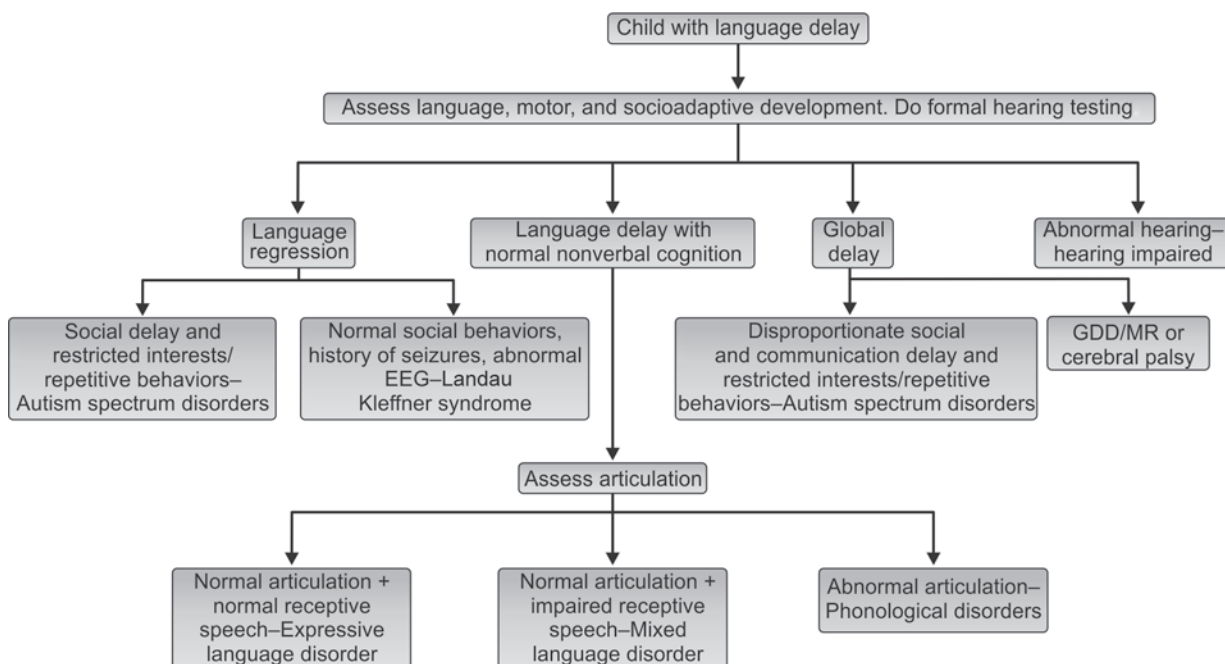
The physical examination should include a thorough examination of ear, nose and throat especially for any cleft lip or palate, and assessment for dysmorphism. A complete neurological assessment should be done including motor system examination, and hearing assessment. It is however important to remember that behavioral hearing evaluation is not reliable.

A physician should also spend some time observing the interaction of the child with his parents and observing his behavior. It gives a good clue of the child's language comprehension, use of gestures and cognitive ability.

Diagnostic Evaluation

All children with speech delay should have formal hearing evaluation. Hearing screen should be done using Otoacoustic Emissions (OAE) or screening BERA test. The advantage of screening BERA is that it evaluates hearing till brainstem level, while OAE evaluates till cochlear level only. Any child who fails on screen should have detailed evaluation by Full BERA or Audiometric Steady State Response. The gold standard for hearing evaluation is Pure Tone Audiometry, however, it can be done reliably only in an older and cooperative child.

All children have to be evaluated by a speech-language pathologist, who will do detailed speech and language assessment using formal test like Receptive-expressive Emergent Language Scale (REEL) or Linguistic Profile Test (LPT), besides hearing evaluation. He would also evaluate for specific phonological disorders.

Flow chart 1: Approach to a child with language delay

All children with language delay should preferably also have an assessment of their development/intelligence quotient, using standardized tools like Developmental Assessment Scale for Indian Infants (DASII), Binet Kulshrestha Test (BKT), Malin's Intelligence Scale for Indian Children (MISIC), etc. by a clinical psychologist. Special non-verbal tools like Raven's progressive matrices and Leiter-R scale can be used for assessing children with hearing impairment.

In a child with language regression or variation in the severity of language disorder, electroencephalography should be done to rule out subclinical epilepsy or syndromes like Landau-Kleffner syndrome. Other diagnostic evaluations like neuroimaging, chromosomal analysis, etc. should be based on findings on history or physical examination. A simplified algorithm for approaching a child with language delay is provided in Flow chart 1.

Early diagnosis and management are necessary to improve the outcomes in these children. A multidisciplinary team approach involving the pediatrician, speech therapist, audiologist and clinical psychologist is a must in the assessment and treatment of these children. The management plan is individualized with active involvement of parents in the treatment program. Early management of hearing impairment is of utmost importance.

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Attention Deficit Hyperactivity Disorders

Roma Kumar

These are children who never sit still. They are always into something or the other but they never prolong in a task. They don't pay attention to what others say. They never think before they act. In school, they are often up and out of their seats in a fraction of a second. They do not do well in school and often lag behind their peers. Such problems are of concern to parents and teachers. The children who exhibit these symptoms of inattention and impulsivity are diagnosed as attention deficit hyperactivity disorder (ADHD) children.

HISTORICAL BACKGROUND OF ATTENTION DEFICIT HYPERACTIVITY DISORDER

The deviance of behavior, which is at present termed 'Attention deficit hyperactivity disorder', has travelled a long road of conceptualization (Barkley, 1996). In the distant past, an English physician called George Still described a group of boys with a defect in moral control 'as inattentive, impulsive, and overactive' lawless and aggressive.

Earlier conceptualizations gave emphasis to the over activity or motor restlessness of these children. Hence the terms 'hyperkinesis' and 'hyperkinetic syndrome' were variously applied (Barkley, 1989). At present we use the term 'hyperactivity' to denote the excessive motor activity. Yet several other behavioral problems were recognized as being associated with hyperactivity, they are attention deficit and impulsivity. Gradually, attention deficits took central role and hyperactivity was downgraded in importance. This shift in conceptualization was reflected in DSM-III (1980) classification, which recognized attention deficit disorder with hyperactivity (ADHD) or without hyperactivity. In DSM-III-R (1987), the disorder was relabeled attention deficit hyperactivity disorder (ADHD). The category of attention deficit without hyperactivity was dropped. Children were diagnosed on the basis of displaying eight of fourteen behaviors, which

could be different mixes of inattention, hyperactivity and impulsivity. That is, ADHD was viewed as unidimensional, so that any mix of symptoms met the criteria. Along with the changing criteria, ideas about etiology also shifted and included brain damage, minimal brain damage and to a lesser extent, environmental influences.

CLASSIFICATION AND DIAGNOSIS OF ATTENTION DEFICIT HYPERACTIVITY DISORDERS

Due to the problem in defining the relationship among inattention, hyperactivity, and impulsivity as to whether view them as a part of a single dimension or co-occurring independent dimensions, DSM-IV-TR reconceptualized the disorder.

CLINICAL CHARACTERISTICS OF ATTENTION DEFICIT HYPERACTIVITY DISORDERS

Children with ADHD are often said to exhibit the characteristics, such as in attentiveness, distraction, lack of sustained attention, hyperactivity and impulsivity.

Inattentiveness

Inattention problems are noted in various ways among children with ADHD. The children with ADHD were tested on two other elements of attention: selective attention and sustained attention. 'Selective attention' refers to the ability to attend to relevant environmental stimuli or not to be distracted by irrelevant stimuli. The findings of Leung and Connolly (1996) indicate that the introduction of irrelevant stimuli does distract children with ADHD. For example, Milich and Lorch (1994) found that the boys with ADHD were more distracted from television watching by the presence of toys than the normal boys.

Similarly, 'sustained attention' refers to paying attention to a task over a period of time. The findings of Losier, McGrath and Klein (1996) reveal that the children

Diagnostic Criteria for ADHD

<i>DSM-IV-TR diagnostic criteria for attention deficit hyperactivity disorder</i>	<i>ICD-10 diagnostic criteria for hyperkinetic disorder</i>
<p>A. Either (1) or (2)</p> <p>(1) Six (or more) of the following symptoms of inattention have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:</p> <ul style="list-style-type: none"> • Inattention <ul style="list-style-type: none"> – Often fails to give close attention to details or makes careless mistakes in school work, work, or other activities. – Often has difficulty sustaining attention in tasks or play activities. – Often does not seem to listen when spoken to directly – Often does not follow through on instructions and fails to finish school-work, chores, or duties in the workplace (not due to oppositional behavior or failure to understand instructions). – Often has difficulty organizing tasks and activities. – Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as school work or homework). – Often loses things necessary for tasks or activities (e.g. toys, school assignments, pencils, books or tools). – It is often easily distracted by extraneous stimuli. – It is often forgetful in daily activities. <p>(2) Six or more of the following symptoms of hyperactivity—impulsivity have persisted for at least six months to a degree that is maladaptive and inconsistent with developmental level:</p> <ul style="list-style-type: none"> • Hyperactivity <ul style="list-style-type: none"> – Often fidgets with hands or feet or squirms in seat. – Often leaves seat in classroom or in other situations in which remaining seat is expected. – Often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, may be limited to subjective feelings of restlessness). – Often has difficulty playing or engaging in leisure activities quietly. – It is often “on the go” or often acts as if “driven by motor”. 	<p><i>Note:</i> The research diagnosis of hyperkinetic disorder requires the definite presence of abnormal levels of abnormal levels inattention, hyperactivity, and restlessness that are pervasive across situations and persistent over time and that are not caused by other disorders such as autism or affective disorders.</p> <ul style="list-style-type: none"> • G1. Inattention: At least six of the following symptoms of attention have persisted for at least six months, to a degree that is maladaptive and inconsistent with the developmental level of the child: <ul style="list-style-type: none"> – Often fails to give close attention to details, or makes careless errors in school work, work or other activities. – Often fails to sustain attention in tasks or play activities. – Often appears not to listen to what is being said to him or her. – Often fails to follow through on instructions or to finish school work, chores, or duties in the workplace (not because of oppositional behavior or failure to understand instructions). – It is often impaired in organizing tasks and activities. – It often avoids or strongly dislikes tasks, such as homework, that require sustained mental effort. – It often loses things necessary for certain tasks and activities, such as school assignments, pencils, books, toys or tools. – It is often easily distracted by external stimuli; – It is often forgetful in the course of daily activities. • G2. Hyperactivity: At least three of the following symptoms of hyperactivity have persisted for at least six months, to a degree that is maladaptive and inconsistent with the developmental level of the child: <ul style="list-style-type: none"> – Often fidgets with hands or feet or squirms on seat. – Leaves seat in classroom or in other situations in which remaining seated is expected. – Often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, only feelings of restlessness may be present). – Is often unduly noisy in playing or has difficulty in engaging quietly in leisure activities. – Exhibits a persistent pattern of excessive motor activity that is not substantially modified by social context or demands. • G3. Impulsivity: At least one of the following symptoms of impulsivity has persisted for at least six months, to a degree that is maladaptive and inconsistent with the developmental level of the child:

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DSM-IV-TR diagnostic criteria for attention deficit hyperactivity disorder	ICD-10 diagnostic criteria for hyperkinetic disorder
<ul style="list-style-type: none"> – It often talks excessively • Impulsivity <ul style="list-style-type: none"> – Often blurts out answers before questions have been completed – Often has difficulty awaiting turn – Often interrupts or intrudes on others (e.g., butts into conversations or games) <p>B. Some hyperactive-impulsive or inattentive symptoms that caused impairment were present before age seven years.</p> <p>C. Some impairment from the symptoms is present in two or more settings (e.g. at school [or work] and at home).</p> <p>D. There must be clear evidence of clinically significant impairment in social, academic, or occupational functioning.</p> <p>E. The symptoms do not occur exclusively during the course of a pervasive developmental disorder(PDD), schizophrenia, or other psychotic disorder and are not better accounted for by another mental disorder (e.g. mood disorder, anxiety disorder, dissociative disorders, or a personality disorder).</p>	<ul style="list-style-type: none"> – Often blurts out answers before questions have been completed. – Often fails to wait in lines or await turns in games or group situations. – Often interrupts or intrudes on others (e.g. butts into others conversations or games). – Often talks excessively without appropriate response to social constraints. • G4. Onset of the disorder is no later than the age of seven years. • G5. Pervasiveness: The criteria should be met for more than a single situation, e.g. the combination of inattention and hyperactivity should be present both at home and at school, or at both school and another setting where children are observed, such as a clinic. (Evidence for cross-situationality will ordinarily require information from more than one source; parental reports about classroom behavior, for instance, are unlikely to be sufficient). • G6. The symptoms in G1 and G3 cause clinically significant distress or impairment in social, academic, or occupational functioning. • G7. The disorder does not meet the criteria for pervasive developmental disorders, manic episode, depressive episode, or anxiety disorders.
<p>Code based on type:</p> <ul style="list-style-type: none"> • 314.01 Attention-Deficit Hyperactivity Disorder, Combined Type: If both criteria A1 and A2 are met for the past 6 months. • 314.00 Attention-Deficit Hyperactivity Disorder, Predominantly Inattentive Type: If criterion A1 is met but criterion A2 is not met for the past 6 months. • 314.01 Attention-Deficit Hyperactivity Disorder, Predominantly Hyperactive-Impulsive Type: If criterion A2 is met but criterion A1 is not met for the past 6 months. 	<p>Comments</p> <ul style="list-style-type: none"> – Many authorities also recognize conditions that are sub-threshold for hyperkinetic disorder. Children who meet criteria in other ways but do not show abnormalities of hyperactivity/impulsiveness, may be recognized as showing attention deficit; conversely, children who fall short of criteria for attention problems but meet criteria in other respects may be recognized as showing activity disorder. In the same way, children who meet criteria for only one situation (e.g. only the home or only the classroom) may be regarded as showing a home-specific or classroom-specific disorder. These conditions are not yet included in the main classification because of insufficient empirical predictive validation, and because many children with sub-threshold disorders show other syndromes (such as oppositional defiant disorder [ODD]) and should be classified in the appropriate category. – Disturbance of activity and attention. – The general criteria for hyperkinetic disorder must be met, but not those for conduct disorders. – Hyperkinetic conduct disorder. – The general criteria for both hyperkinetic disorder and conduct disorders must be met.

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Contd...

DSM-IV-TR diagnostic criteria for attention deficit hyperactivity disorder	ICD-10 diagnostic criteria for hyperkinetic disorder
Coding note: For individuals (especially adolescents and adults) who currently have symptoms that no longer meet full criteria, "In Partial Remission" should be specified.	<ul style="list-style-type: none"> – Other hyperkinetic disorder – Hyperkinetic disorder, unspecified. – This residual category is not recommended and should be used only when there is a lack of differentiation between disturbance of activity and attention and hyperkinetic conduct disorder but the overall criteria for hyperkinetic disorders are fulfilled.

with attention deficit hyperactivity disorder (ADHD) are deficient in sustained attention. When the length of the given task increases, a deficit in sustained attention would lead to a worsening of performance.

Hyperactivity

Children with ADHD are described as always on the run, restless, fidgety and unable to sit still. They squirm, wiggle, tap their fingers and elbow (Greenhill, 1991). Very often, they have minor mishaps, such as spilling drinks, knocking over objects as well as more serious accidents that result in bodily harm. They are excessively energetic, haphazard, disorganized and lacking in goals. They also appear to have difficulty in regulating their actions according to the wishes of others or to the demands of the particular situation. The devices, such as actometers and pedometers are helpful in measuring movement can be used to demonstrating the excessive movement of children with ADHD.

Impulsivity

Impulsivity refers to the deficiency in inhibiting behavior, which appears as 'acting without thinking'. The children with ADHD may jump in and try to solve a problem before figuring out the first step, heedlessly engage in dangerous behaviors, and take shortcuts while performing a task. Games that require patience or restraint are not well negotiated and they may also interrupt others or blurt out socially inappropriate or hurtful verbalizations. In short, they are unable to hold back, inhibit and control behavior and their behaviors often lead others to judge them as careless, irresponsible, immature, lazy or rude. The findings of Oosterlaan, Logan and Sergeant (1998) reveal that inhibition of motor responses is an important characteristic of children with ADHD. Although, the children diagnosed as ADHD are heterogeneous with regard to symptoms, the most frequently seen type is combination of inattention, hyperactivity and impulsiveness.

TYPES OF ATTENTION DEFICIT HYPERACTIVITY DISORDER

Attention deficit hyperactivity disorder (ADHD) has various forms, in which the three elements hyperactivity, impulsivity and attention deficit play a part.

- *Attention deficit hyperactivity disorder (ADHD), combination form hyperactivity-impulsivity-attention deficit:* Most children with ADHD fall under the combination form category and suffer from the three characteristics together. Children with ADHD combination form have a chaotic behavior style. They are extremely active, impulsive and have difficulty with concentrating. Their restlessness is uncontrolled. Transferring information into actions does not run correctly. Absorbing and processing signals and subsequently taking a decision is still apparent with these children in general. These children have learning difficulties and fear of failure, and as the requirements become higher, the problems increase. The criteria for the diagnosis ADHD combination form are, according to the DSM-IV, having at least six symptoms of attention deficit and at least six symptoms of hyperactivity-impulsivity.
- *Attention deficit hyperactivity disorder (ADHD), attention deficit:* With ADHD attention deficit, also called attention deficit disorder (ADD), the child does not come across as being active and chaotic. This disorder is generally only visible with tasks that require concentration. The concentration of the child with ADHD deviates from the concentration disorder of a child with limited intellectual powers. The child with ADHD, the concentration problems are there from the beginning of a task and are an issue continuously. The child will therefore, come across as being active. With a child with limited intellectual powers the concentration runs out, as it were, and the child is subsequently more likely to be tired than active. For diagnosis ADHD attention deficit, there have to be at least six symptoms of attention deficit and fewer than six of hyperactivity-impulsivity.
- *Attention deficit hyperactivity disorder (ADHD), hyperactivity-impulsivity:* In the case of the form ADHD hyperactivity-impulsivity the child is able to concentrate on tasks. It is however, extremely active and chaotic. In structured situations, where concentration is necessary, the child is often calm and the hyperactivity and impulsivity are less obvious. This often applies to the school situation. In that case teachers do not recognize the child's behavior that the parents talk about. It applies to the diagnosis ADHD hyperactivity-impulsivity that at least

six symptoms of hyperactivity-impulsivity are present and fewer than six symptoms of attention deficit.

ETIOLOGICAL THEORIES

Many theories have been developed to account for ADHD (Tannock, 1998), some of which are summarized below. These theories fall into three main categories. First, there are those that focus largely on the role of biological factors in the etiology of ADHD. Second, there are intrapsychic theories, which attempt to explain the syndrome of inattention, over-activity and impulsivity through reference to a central underlying deficit. Third, there are those that deal with the role of psychosocial factors in the development of the condition.

BIOLOGICAL THEORIES

Genetic Hypothesis

Genetic hypothesis suggest that ADHD symptomatology or a pre-disposition to hyperactivity is inherited by children who develop the condition. In support of this hypothesis, twin, adoption and family studies shows that rates of ADHD are higher in the biological relatives of children with ADHD than those without the disorder (Barkley, 2003; Thapar and Scourfield, 2002). Twin studies show that the heritability coefficient for ADHD is at least.⁸ (which is higher than that for intelligence, typically estimated at.⁵ to.);⁷ 20 percent of the variance in the ADHD symptomatology. Molecular genetic studies have found an association between ADHD and the dopamine transporter gene and dopamine receptor gene. The search for these genes was informed by evidence for dysregulation of the dopamine system in the prefrontal region of the brain, associated with executive function, in children with ADHD.

Neurotransmitter Dysregulation Hypothesis

The neurotransmitter dysregulation hypothesis attributes the symptoms of ADHD to abnormalities in neurotransmitter functioning in centers which sub serve behavioral activation and executive functioning. There is growing evidence to show that a dysregulation of the dopamine and noradrenaline systems in the prefrontal cortex and basal ganglia occur in ADHD (Barkley, 2003; Schachar and Tannock, 2002).

Hypoarousal Hypothesis

The hypoarousal hypothesis explains hyperactivity and inattention as a failure to be sufficiently aroused by signal stimuli to attend to them and regulate activity levels. Psychophysiological studies indicate that ADHD children show reduced psychophysiological responsiveness [as assessed by electroencephalography (EEG) and heart rate) to novel stimuli with signal value (Barkley, 2003)].

INTRAPSYCHIC THEORIES

Many intrapsychic theories have been developed to explain the patterns of symptomatology in ADHD. These are:

Inattention Hypothesis

The inattention hypothesis argues that problems with sustaining attention on a single task and screening out other distracting stimuli is the core difficulty that under-pins the other symptoms of impulsivity and overactivity in ADHD (e.g. Douglas, 1983). That is, youngsters with ADHD at the outset of a task requiring attention will perform at a level equivalent to normal children but, over time. They will show more errors, which are directly attributable to the inability to sustain attention. This problem with sustaining attention leads them to change the focus of the attention frequently and this is manifested at a behavioral level as excessive impulsivity and overactivity.

Hyperactivity Hypothesis

The hyperactivity hypothesis argues that a problem with inhibiting motor activity is the core deficit that under pins the ADHD syndrome and can account for inattention and impulsivity (e.g. Quay, 1997; Schachar, 1997). A large body of evidence shows that hyperactivity is a unique symptom to children with ADHD compared to children with other psychological problems, and that hyperactivity is a construct correlates with many academic indices of attention problems (Barkley, 2003).

Impulsivity Hypothesis

This hypothesis argues that a core problem in inhibiting cognitive and behavioral responses to specific stimuli leads to poor performance on tasks apparently requiring good attentional abilities and also to tasks requiring planning and careful regulation of behavior. Thus, the central problems in ADHD, according to this hypothesis, are with cognitive and behavioral impulsivity (Nigg, 2001).

According to this theory, with academic task apparently requiring high levels of sustained attention, children with ADHD have problems using systematic cognitive problem-solving strategies because they are cognitively impulsive. Also, in both academic and social situations, children with ADHD engage in careless work practices in school and in socially inappropriate behavior with peers, parents and teachers because they are behaviorally impulsive (Barkley, 2003).

Executive Function Hypothesis (Flow Chart 1)

Russell Barkley (2003) argues that the symptoms of ADHD (impulsivity, over-activity and inattention) reflect a central deficit in the core executive function of behavioral inhibition that is neurodevelopmental (rather than social) in origin. Children with deficits in behavioral inhibition cannot

delay immediate gratification, so reap better rewards later. This core deficit in behavioral inhibition is associated with, and reinforced by secondary deficits in four other executive functions:

- Nonverbal working memory
- Verbal working memory (or internalization of speech)
- Self-regulation of affect, arousal and motivation
- Verbal and behavioral creativity and fluency (or internalization of play). With poor verbal and nonverbal working memory, ADHD children cannot hold a picture of events of the mind, or obey a set of self-directed instructions and so delay gratification or sustain planned sequences of goal-directed behavior. With poor self-regulation of affect, motivation and arousal, ADHD children have difficulty in preventing strong emotional experiences and motives from interfering with planned goal-directed behavior.

With poor internalization of play, ADHD children have difficulty developing, rehearsing and implementing creative plans to achieve novel goals. The four secondary executive function deficits, according to Barkley, reflects failures to internalize and private functions that, in early development, were external features of child's interactions with caregivers. In normal development, the emergence of these four executive functions reflects a shift in the source of control of behavior from external events to mental representations of events, from control by others to control by the self and from immediate to delayed gratification. This complex and elaborate executive function hypothesis has to some degree supplanted earlier simpler psychological theories and is partially supported by a growing body of empirical evidence (Barkley, 2003).

SYSTEM THEORY

System theories have focused largely on the role of the family system or the wider social context in the etiology and maintenance of ADHD. With respect to family problems, high stress and low support; parent psychological

problems such as depression, aggression or alcohol abuse; exposure to marital discord; over-intrusive parenting and coercive parent-child interactions in childhood and adolescence have all been found to have associations with ADHD (Lange et al. 2005). With respect to the wider social system, the following factors have been found to be associated with ADHD: low socioeconomic status, institutional upbringing and peer relationship problems (Barkley, 2003).

ATTENTION DEFICIT HYPERACTIVITY DISORDER AND CO-OCCURRING DISORDERS

Attention deficit hyperactivity disorder (ADHD) is a highly co-morbid disorder and is often accompanied by another disorder. Approximately 66 percent of elementary school-aged children referred to clinics with ADHD have, at a minimum, one additional diagnosable disorder (Cantwell, 1994). One of the most often occurring co-morbid problems is delayed toilet-training, both encopresis, soiling and enuresis bedwetting. Attention deficit hyperactivity disorder (ADHD) children often show learning disorders which are connected with a disrupted maturation of the central nervous system: dyslexia (reading and writing disorder), mathematics disorder and dysgraphia (writing disorder). These learning disorders occur, just like other maturation disorder, predominantly with boys.

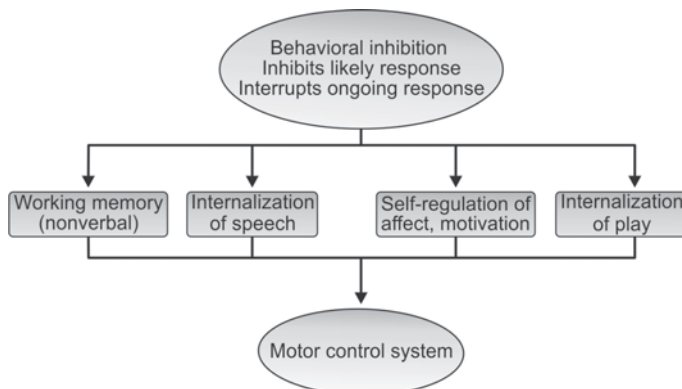
Children with ADHD frequently have difficulties in social interaction. They are frequently reported as non-compliant, oppositional, annoying and argumentative, in short, the behavior diagnosed as oppositional defiant disorder (ODD). Further, ODD may lead to conduct disorder (CD), which involves aggression, deceit and violations of rules. Children with ADHD, with co-occurrence of ODD and CD problems, show greater levels of aggression, lying, cheating and stealing (Jensen, Martin and Cantwell, 1997). Barkley (1998a) also reported that about 25 percent children with ADHD also have anxiety disorders. Along with the disruptions of ADHD, they experience the fears, worries and other internalizing problems of anxiety. The co-occurrence of ADHD and depression was also reported by Biederman et al (1996).

ASSESSMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER

Attention deficit hyperactivity disorder (ADHD) is conceptualized as a bio psychosocial disorder and hence assessment of ADHD must be broad based and include various procedures that are capable of evaluating the primary and secondary manifestations of disorder, family functioning and biologically functioning. Moreover, ADHD is situationally specific in nature at times; evaluation should include different settings, such as home and school. The widely used assessment tools for ADHD are interviews, rating scales, direct observation and other procedures.

Flow chart 1: Barkely model of ADHD symptomology

Adopted from: Barkley, RA. ADHD: A handbook by diagnosis and treatment. New York: Guilford Press, 1998



Interviews

In most case of ADHD, parents are the chief source of information. Hence, standard, structured or semi-structured interviews can be used. Information with regard to the child's as well as the family's history, the school, the child's behavioral problems and strengths should be obtained through interviews. Details about the situations identified as troublesome should also be obtained through interviews. Teacher interviews are of much value and the focus of teacher interview should be on learning and academic problems as well as on peer interactions. In addition, information can be obtained about parent-school interaction and co-operation as well as school services.

Rating Scales

Parent and teacher rating scales and checklists are other popular tools assessing ADHD and they provide much information with relatively little time and effort. Rating scales are useful not only to identify ADHD but also its co-occurrence with other disorders. Both broadband and narrow band rating scales are available. The broadband scales are helpful in determining whether the behavior is deviant from the norm and different from behaviors displayed by other diagnostic groups. The narrowband scales are useful in assessing specific aspects of ADHD, such as school behavior. For several of the instruments, both parent and teacher versions are available. There are also self-report versions, which are particularly useful for adolescents.

The Conners parent and teacher scales (Conners et al. 1998a) are widely employed for initial screening. They are easy to use and there is good evidence for their validity (Edolbrock and Rancurello, 1985). Moreover, both scales have been revised recently.

TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER

Various treatments have been applied to ADHD. Pharmacological medication and behavioral interventions are the best choice.

- *Pharmacological treatment:* Many pharmacological agents like stimulant, antidepressant and anticonvulsant drugs have been used for ADHD. The most commonly used medications are given below:
 - Most common medication for ADHD
- *Stimulants:* Medications of first choice
 - Ritalin (Methylphenidate)
 - Dexedrine (Dextroamphetamine)
 - Cylert (Pemoline)
 - Adderall (combined Amphetamine and Dextroamphetamine)
- Antidepressants: First alternative choice
 - Tricyclics (e.g. Desipramine, Imipramine)

- Other antidepressants
- Less –Used medication
 - Anticonvulsants
 - Antihypertensives
 - Antipsychotics.

An estimated 75 percent of stimulant medicated children show increased attention and reduced impulsivity and activity level, both in the laboratory and in the structured, natural environments that elicit ADHD behaviors (Whalen and Henker, 1998). Stimulant medications can also reduce co-occurring aggressive, noncompliant, oppositional behaviors (Hinshaw et al. 1989).

- *Behavioral interventions:* Since the pharmacological treatments have short-term success and cause intolerable side effects, behavioral interventions are often recommended to treat ADHD. Behavioral interventions are applied to a wide range of problems.
- *Psychotherapy* works to help people with ADHD to like and accept themselves despite their disorder. It does not address the symptoms or underlying causes of the disorder. In psychotherapy, patients talk with the therapist about upsetting thoughts and feelings, explore self-defeating patterns of behavior, and learn alternative ways to handle their emotions. As they talk, the therapist tries to help them understand how they can change or better cope with their disorder.
- *Behavioral therapy (BT)* helps people develop more effective ways to work on immediate issues. Rather than helping the child understand his or her feelings and actions, it helps directly in changing their thinking and coping and thus may lead to changes in behavior. The support might be practical assistance, like help in organizing tasks or schoolwork or dealing with emotionally charged events. Or the support might be in self-monitoring one's own behavior and giving self-praise or rewards for acting in a desired way such as controlling anger or thinking before acting.
- *Social skills training* can also help children learn new behaviors. In social skills training, the therapist discusses and models appropriate behaviors important in developing and maintaining social relationships, like waiting for a turn, sharing toys, asking for help, or responding to teasing, then gives children a chance to practice. For example, a child might learn to "read" other people's facial expression and tone of voice in order to respond appropriately. Social skills training help the child to develop better ways to play and work with other children.
- *Parenting skills* training, offered by therapists or in special classes, gives parents tools and techniques for managing their child's behavior. One such technique is the use of token or point systems for immediately rewarding good behavior or work. Another is the use of "time-out" or isolation to a chair or bedroom when the child becomes too unruly or out of control.

During time-outs, the child is removed from the agitating situation and sits alone quietly for a short time to calm down. Parents may also be taught to give the child "quality time" each day, in which they share a pleasurable or relaxing activity. During this time together, the parent looks for opportunities to notice and point out what the child does well, and praise his or her strengths and abilities.

This system of rewards and penalties can be an effective way to modify a child's behavior. The parents (or teacher) identify a few desirable behaviors that they want to encourage in the child – such as asking for a toy instead of grabbing it, or completing a simple task. The child is told exactly what is expected in order to earn the reward. The child receives the reward when he performs the desired behavior and a mild penalty when he doesn't. A reward can be small, perhaps a token that can be exchanged for special privileges, but it should be something the child wants and is eager to earn. The penalty might be removal of a token or a brief time-out. Make an effort to find your child being good. The goal, over time, is to help children learn to control their own behavior and to choose the more desired behavior. The technique works well with all children, although children with ADHD may need more frequent rewards.

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Idiopathic Mental Backwardness

Chhaya Sambharya Prasad

INTRODUCTION

Idiopathic mental backwardness refers to individuals with low intelligence who show no evidence of gross chromosomal defects or single-gene anomalies. It may also represent the lower end of intelligence quotient (IQ) distribution. Backwardness is defined as one which makes less progress than normal. Mental backwardness means a person with the intellectual capacity that developed at a below average rate during the early developmental years. Several syndromes (such as Downs, Fragile, Rett syndrome, and other well known conditions) can be easily suspected because of their association to specific dysmorphisms, behavioral peculiarities, and multiple congenital abnormalities. However, a consistent percentage of children with genetic mental retardation do not present a recognizable phenotype which is striking of a well-recognizable syndrome. Determining a specific etiologic diagnosis is central to understand the nature of the problem, providing answers to questions regarding prognosis, recurrence risks, directing specific therapies, and achieving meaningful inclusion of individuals with disability into society.

Mental backwardness represents one of the most frequently diagnosed disabling condition in our society, and a lifelong disability characterized by impairment of cognitive and adaptive skills. The etiology is very heterogeneous and, unfortunately, in more than one-half of cases the cause is still unexplained. Anything that damages and interferes with the growth and maturation of the brain can lead to mental backwardness. This might happen before, during or after the birth of the child (including complications of pregnancy/birth, toxics, malnutrition, trauma, infections, under stimulation). Moreover, genetically determined etiology (comprising chromosomal aberrations, single-gene disorders, and

other genetic conditions) account by itself only for 17 to 41 percent of cases, depending of the different techniques of analysis.

MAGNITUDE OF THE PROBLEM

Mental ability is always more likely to be underestimated than overestimated, especially in case of persons from lower socioeconomic groups. India is a vast country with variable social, cultural, geographical and economic background. Communicable diseases and congenital diseases are still a major problem adding to the number of disabled persons. Evaluation of mental backwardness is a big challenge with different social background, economic factors, extended family systems, low literacy rates, and virtually different habits/ADL. Mental backwardness is a disability characterized by significant limitations both in intellectual functioning and in adaptive behavior and may present as deficits in conceptual, social, and practical adaptive skills. This disability originates before the age of 18 years. It is a variable, heterogeneous manifestation of central nervous system dysfunctions, occurring in 1 to 3 percent of general population.

An estimated 10 percent of the world's population experiences some form of disability or impairment (WHO Action Plan 2006-2011). Global prevalence: 4 to 10 percent (Yeo 2001) 4 percent in developing countries and 7 percent in industrialized countries (Metts 2000) India and South Asia prevalence: 1.5-21.3 percent in WHO South East Asia member countries (<http://www.searo.who.int/>). 8 to 2.2 percent for India (Census 2001, NSSO 2002). Different prevalence rates for disability are available in India. According to the Census 2001, there are 2.19/thousand people with disabilities in India who constitute 2.13 percent of the total population (Census 2001). Out of the 21,906,769 people with disabilities,

12,605,635 are males and 9,301,134 females and this includes persons with visual, hearing, speech, locomotor and mental disabilities (Census 2001).

DIAGNOSIS

According to the latest edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV), three criteria must be met for a diagnosis of mental retardation: an IQ below 70, significant limitations in two or more areas of adaptive behavior (as measured by an adaptive behavior rating scale, i.e. communication, self-help skills, interpersonal skills, and evidence that the limitations became apparent before the age of 18).

It is formally diagnosed by professional assessment of intelligence and adaptive behavior. The following ranges, based on standard scores of intelligence tests, reflect the categories of the American Association of Mental Retardation, the Diagnostic and Statistical Manual of Mental Disorders-IV-TR, and the International Classification of Diseases.

Class	IQ
Profound mental retardation	Below 20
Severe mental retardation	20–34
Moderate mental retardation	35–49
Mild mental retardation	50–69
Borderline intellectual functioning	70–84

The diagnosis is not based only on IQ scores, but the adaptive functioning is also taken into consideration. Adaptive behavior, or adaptive functioning, refers to the skills needed to live independently (or at the minimally acceptable level for age). To assess adaptive behavior, professionals compare the functional abilities of a child to those of other children of similar age. There are many adaptive behavior scales, and accurate assessment of the quality of someone's adaptive behavior requires clinical judgment as well. Certain skills are important to adaptive behavior, such as:

- Activities of daily living, such as getting dressed, using the bathroom, and feeding oneself
- Communication skills, such as understanding what is said and being able to respond/reciprocate, verbally or nonverbally
- Social skills with peers, parents, siblings and other family members.

A three-generation pedigree helps to find out mental retardation in the family, and a detailed pre-, peri- and postnatal history should help to establish a definitive cause. A dysmorphic child may be at risk from the stress of birth, and later delay may be erroneously attributed to birth injury. A careful developmental history, with emphasis on milestones, formal assessments and behavior, is also a must. Medical records should be sought or requested

to validate any diagnosis of malformations. An accurate EEG study and/or brain MRI are sometimes sufficient to suspect several well-known and relatively common disorders (such as Rett syndrome, Angelman syndrome, neurocutaneous syndromes, etc.). The degree of MR is an important indicator: the so called "chromosomal" phenotype, which is well known to accompany larger aberrations, is frequently characterized by moderate-severe MR associated with one or more of major signs, including congenital malformations. The behavioral phenotype is also distinctive for several well-known syndromic conditions, such as Williams syndrome, Angelman syndrome, Prader-Willi syndrome. Abnormalities in head size, growth parameters, and neurologic signs should also be carefully investigated.

As compared to idiopathic mental backwardness, mental retardation may occur due to a number of causes such as listed below:

- *Genetic and chromosomal abnormalities:* One of the first genetic causes of mental retardation is Down syndrome. The extra chromosome interferes with the functioning of the brain, mostly leading to interference in intellectual functioning. Other causes such as Fragile X syndrome, Hunter syndrome, Hurler syndrome, Rett's syndrome, tuberous sclerosis, defective chromosomes, chromosome deletions/translocations also interfere with intellectual performance and lead to cognitive impairments.
- *Metabolic disorders such as phenylketonuria:* Endocrinological disturbances, e.g. cretinism, cranial malformations, hydrocephalous, microcephaly, all result in intellectual deficiencies of varying degrees.
- *Nutritional deficiencies:* Nutritional deficiencies are one of the biggest culprits of many a medical condition. A nutritional deficiency during pregnancy can be more disadvantageous to the unborn child than it can be to the mother. A lack of nutrients like vitamin A, iron, iodine, zinc, etc. has been known to cause problems pertaining to mental health for a large population across the world. With a mounting consumption of fast food/junk food, nutritional deficiencies are on the rise like never before. Apart from the above-mentioned, famine/conditions causing malnutrition is also one of the largest causes of this mental condition.
- *Environmental conditions and exposure to toxins:* One of the most important factors leading to mental retardation is those of environmental conditions, as well as exposure to toxins. Environment can impact by virtue of poverty and cultural deprivation. This idea also refers to the lack of mental stimulus, thus stunting mental growth. Exposure to toxins is an equal culprit leading to it too. One of the more common forms of these toxins would happen to be cigarettes. Expectant mothers who smoke are also a threat.

- Other conditions leading to mental retardation also are, traumatic conditions faced during pregnancy, problems at or after birth, metabolic disorders, infections, as also a multitude of unexplained reasons.

PROBABLE ETIOLOGY FOR THE IDIOPATHIC MENTAL BACKWARDNESS

- *Microdeletion/microduplication syndromes:* In the last few years, several emerging clinical entities have been described, due to the advent of newest genetic techniques, such as array comparative genomic hybridization. The detection of cryptic microdeletion/microduplication abnormalities has allowed genotype-phenotype correlations, delineating recognizable syndromic conditions. The presumed channel at the basis of remaining "pure idiopathic" forms of mental retardation, highlight possible environmental and epigenetic mechanisms as causes of altered cognition. With the advent of novel genetic techniques, several new cryptic chromosomal aberrations have been discovered in last few years and a consistent number of MR cases, previously considered "idiopathic" forms, are now classified as syndromic conditions with clinical recognizable phenotypes.
- *Parents with intellectual disability:* Studies of children raised in homes where both parents were retarded revealed that between 39 to 61 percent of children tested were retarded. In studies such as Halperin 1945, and Penrose 1963, nonretarded children tended to have borderline intelligence with IQ's varying between 70 and 90 in nearly 16 to 40 percent of cases whereas between 4 to 26 percent of children were of average intelligence. For purposes of general estimate these studies indicated that where both parents were retarded, nearly one-half had borderline intelligence and about 1/6th would be normal. Average IQ's of 65 and 74 have been noted among children of such parents (Reed and Reed 1965). The distribution of IQ's in these children, though not lending itself to any judgement as to the role of psychological factors because of the confounding effects of heredity does indicate that intelligence cannot be solely a function of the environment.
- *Home environment:* Yeates et al (1983) conducted a study to investigate maternal IQ and home environment as determinants of early childhood intellectual competence. Children at risk for socio-cultural mental retardation were studied longitudinally from birth to 4 years of age. Maternal IQ's were assessed before the child's birth and children's IQ and home environment were assessed at regular intervals during first 4 years of life multiple regression analysis was used to separate the contributions of maternal IQ and home environment to the child's IQ at 24, 36 and 48 months of age. The overall pattern suggested a monotonic increase in the predictability of the child's IQ within the context of a shift in the relative importance of maternal IQ and home environment as predictors.
- *Family size:* Another very important confounding factor has been the family size. One of the earliest and most consistently reported findings related to the effects of family size has been a decline in the IQ with an increase in the number of children. The majority of studies conducted in several nations have shown a negative correlation between family size and IQ with some indication, however, that this correlation may be less pronounced in higher socioeconomic status groups. Attempts to account for this decline in IQ with an increase in family size have generated a variety of hypothesis. All kinds of resources like financial, dietary, spatial, emotional are shared by more members in large families. In the lower socioeconomic classes, adverse physical conditions may be aggravated when many members of the family have to share a meagre subsistence. The increased size of the family also means that each child receives less attention from his/her parents and learns about life and the outer world more from the siblings who may be just a little older than the child himself. In a large family a child's development may also be affected because of the fact that so many of the role models are children themselves who use speech poorly. The decline in the IQ with increasing size of family in lower socioeconomic group mostly suggests that children from larger families would on an average be less successful academically. It would appear that compared to their IQ level, their academic achievement is much inferior. Many studies suggest that children from smaller families show higher achievement, motivation and superior performance in academics than those from larger families. Parents with higher educational and occupational aspirations for their children are likely to plan their family to match their resources. They are also likely to set goals for their children and impose standards of excellence beyond those imposed by parents who have fewer ambitions for their children. The primary effect of family size may be seen in respect of the physical development of children from large families which seems more problematic than that of children from smaller families. The probability of intra uterine problems rises with increasing number of child births. Passamanick et al 1956 reported a 10-fold increase in mental backwardness as one moves from the first to the sixth child born to the mother. In general, prematurity and its associated problems and maldevelopment also become more frequent with increasing number of child births.

- *Effect in siblings and relatives:* Idiopathic mental retardation has been documented in siblings and relatives in few studies. A genetic study of children in Birmingham Coventry has shown a recurrence risk of idiopathic mental retardation in siblings lying between 1 in 4 and 1 in 5. There was also a prevalence of mental retardation in other relatives that was greater than the population prevalence, and was less for second degree relatives than for first degree, and less still for third degree relatives. Recurrence in siblings was greater if more than one first degree relative was affected. There was no suggestion of a contribution by X-linked genes, once the fragile X syndrome had been excluded. The presence of perinatal and other environmental factors in the index children did not alter the recurrence risk for sibs except for very low birth weight. The results of many studies with pairs of siblings are similar and show that the higher the proportion of genes shared by two relatives, the higher the average correlation between their IQs. There was a low recurrence rate of mental retardation in Asian families, suggesting that they had a different distribution of intelligence from non-Asian families. Hereditary factors in the etiology of idiopathic autism are well established but particular genetic mechanisms have not been identified.

The study by Sarah Bunde et al in 1989 suggested that 60 to 70 percent of the total variation of intelligence in a population is the result of genetic factors and less than 10 percent the result of environmental factors outside the family. The genetic component is largely polygenic, that is, composed of many genes individually of little effect. Bouchard and McGue considered that there was no evidence of a contribution by X-linked genes, because like sex pairings did not differ from unlike sex pairings. However, an X-linked gene for spatial ability has been postulated. The relative contributions of genetic and sociocultural factors to the normal range of intelligence have been discussed by many authors.

- *Social impact:* Siblings of cases of ADHD have been documented to exhibit similar symptoms and lower academic performance due to behavioral and social adaptation difficulty. The family of a child with hyperactivity, attention deficits, and cognitive impairment must cope up with frequent and exceptionally high demands of parenting. The family is confronted with serious medical and environmental issues that rarely seemed to be solved.

COMORBID CONDITIONS

Conditions where mental backwardness has been documented, especially in children are listed below:

- *Mood and anxiety disorders:* Some of the common mental illnesses come under this category. Mood disorders (otherwise called affective disorders) include

conditions that are caused by persistent and extreme mood swings, like excessive happiness or sadness. Examples include depression, bipolar disorder, seasonal affective disorder (SAD), dysthymia, etc. Anxiety disorders are conditions characterized by excessive and abnormal fear and anxiety. The symptoms of these conditions can be so mild that others might not even suspect that the patient has any mental disorder. But, in some cases, the symptoms can affect the day-to-day activities, cognitive functioning and lead to a total disability. While some people develop such disorders after going through traumatic events, or can also be genetic or congenital or can be idiopathic too.

- *Specific learning disability:* It is a heterogeneous group of disorders manifest by significant difficulties in the acquisition and the use of listening, speaking, reading, writing, reasoning, or mathematical abilities. These disorders are intrinsic to the individual, presumed to be due to central nervous system dysfunction, and may occur across the life span. Children with a specific learning disability usually have a borderline to dull average intelligence. Problems in self-regulatory behaviors, social perception, and social interaction may coexist.
- *Mental retardation:* Educational and occupational histories are valuable in this regard. The patient should be asked at what age they achieved their highest educational grade, to ascertain whether they progressed normally through school.
- *Psychotic disorders:* This group includes certain types of mental illnesses that severely affect the brain and thinking process. These children/adolescents have difficulty thinking rationally and their judgments are impaired. Living their daily life becomes very, very difficult. The most prevalent symptoms of these mental disorders are delusions and hallucinations. Those affected with these disorders develop false beliefs (delusions) and perceptions (hallucinations—false sensations, like hearing or smelling something that is not there). Some other symptoms are strange behavior (may be dangerous to themselves or others), lack of personal hygiene, decreased interest in doing things, strange speech patterns that are not understandable, mood swings, relationship difficulties and slow or strange movements.
- *Psychiatric illness:* Organic illness can mimic many symptoms of psychiatric disease, especially the psychoses; some psychiatric illness may prevent adequate evaluation of a patient's intellectual functioning.
- Although loss of recent memory (learning capacity) is not a necessary accompaniment of organic mental illness, it is not seen in functional states. If adequate testing can be done, the finding of a definite recent memory deficit strongly militates against a diagnosis

of functional disease. The two major exceptions are depressive pseudodementia and malingering.

- Regressive reflexes are indicative of organic disease.
- Urinary incontinence is rarely seen in adults with functional disease.
- *Confusional states*: Deficits in maintaining attention may markedly reduce intellectual functioning. Many metabolic dementias (such as hepatic encephalopathy, delirium tremens, and cognitive deficits produced by many drugs) are manifested principally by the inability to attend to important stimuli. Lesions affecting the brain stem or thalamic reticular formation, if insufficient to produce stupor or coma, result in an attentional deficit. In general, these are referred to as confusional states or “encephalopathy”.
- *Organic psychoses*: Diseases affecting the limbic system or related structures may produce a wide variety of psychiatric findings. Persons with temporal lobe epilepsy commonly have low intellectual performance with behavioral disturbances, temporal lobe lesions or damage to the medial hypothalamus may trigger aggressive behavior; memory loss and low intelligence potentially accompanied by changes in appetite for food and sex. Damage to the left frontal lobe often produces depression, while the right frontal lobe can trigger mania.

MANAGEMENT

The primary goal of treatment is to develop the child's potential to the fullest. Special education and training may begin as early as infancy. This includes social skills to help the person function as normally as possible. It is important for a specialist to evaluate the person for other affective disorders and treat those disorders. Behavioral approaches are important for people with mental retardation.

Outlook (Prognosis)

The outcome depends on:

- Opportunities provided to the child with respect to his home environment, family support, community support
- Comorbid conditions and associated psychiatric disorders
- Personal motivation
- Therapeutic interventions in the form of speech therapy, physio-occupational therapy, special education

guidance, etc. Many persons can lead productive lives and function on their own; many others may require a structured environment to be most successful.

CONCLUSION

Pediatricians should be alerted by the presence of MR of unexplained origin associated with altered auxological parameters, multiple congenital defects, neurological and psychiatric signs, and/or minor dysmorphisms. The implementation of the so called “next generation sequencing” technologies (that allow the analysis of whole-genomes, transcriptomes and interactomes) could lead to detect single base mutations and structural variations, further broadening the possibility of diagnosis in “idiopathic” cases of MR. Understanding the pathological pathways underlying unexplained forms of MR represent a future challenge to increase both prevention and possible therapies. Because of the high incidence of CNS impairment and low overall interpersonal coping abilities, children/adolescents with mental backwardness have a greater than average risk for developing associated psychiatric disorders. Persons suffering from such a condition require constant care, intervention and custom-made system of education. Resources and services for mental and behavioral disorders are disproportionately low compared to burden caused by these disorders the world over. In most developing countries, care programs for the individuals with mental and behavioral problems still have a low priority. Provision of care is limited to a small number of institutions usually overcrowded and under staffed. Over past several decades, the model of mental health care is changing and community care approach is setting in. The mental health programs have played important role in this shifting paradigm. Early intervention and early stimulation programs are playing a vital role in the various Child Development Centres being set up across the country.

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Section 7

Gastroenterology

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Constipation and Encopresis in Infants and Children

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INTRODUCTION

Constipation is a symptom of underlying disorder and is more common in males as compared to female children. It is a very common problem in pediatric age group. 10 to 25 percent of all patients attending pediatric gastroenterology clinics are constituted by various fecal elimination disorders. About 1.3 to 5 percent of children suffering from chronic constipation have problem of encopresis. Chronic constipation is a real challenge to the parents, children as well as for the pediatricians to understand and to treat it effectively. The presence of encopresis adds to the parental anxiety and has a great impact on the overall development and social acceptance of the child. Chronic constipation has great impact on the education, personality, psychological well being and growth of the child. Children are usually isolated, cranky, irritable and lack concentration. The quality of life suffers a lot. So there is need of meticulous and well planned approach to manage a child with constipation.^{1,2}

PREVALENCE

Constipation is a very common problem encountered in pediatric gastroenterology clinics, constituting 10 to 25 percent visits whereas it is 3 percent in pediatric outpatient clinics. The problem is alarming and distressing frequently dealt by various disciplines like primary care physician, emergency general pediatrician, pediatric surgeons and pediatric gastroenterologists.

Prevalence varies with the age, usually peaks around 2 to 4 years when toilet training is often defective. The prevalence during first year is 2.9 percent, during 2nd year is 10.1 percent and in school age is 17.5-34 percent. In adult population it is 10 percent.³⁻⁵

DEFINITIONS

Constipation

Constipation is defined subjectively as a feeling of unsatisfactory evacuation. The other accompaniments could be passage of too small stool, too hard stool, too difficult to expel, too frequent and incomplete evacuation. But the objective and well accepted definition of constipation is passage of stools twice or less per week.

Based upon the symptomatology certain criteria have been used in literature to define constipation. According to the guidelines of the North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGAN), the constipation is defined as a delay or difficulty in the act of defecation present for 2 or more weeks and sufficient to cause significant distress to the patient. Loening-Baucke criteria also called as Iowa criteria given in Table 1 to define constipation have been used widely in various studies. According to this constipation is labeled when two out of the following symptoms are present in last three months: (1) less than 3 bowel movements per week, (2) encopresis more than once per week, (3) large amounts of stool every 7 to 30 days (large enough to clog the toilet) and (4) palpable abdominal or rectal mass on physical examination.³⁻⁵ Recently an attempt has been made to define the functional gastrointestinal disorders in children called Rome II criteria as in Table 2. But these criteria are too cumbersome and are difficult to follow in general practice and are not of much help. Paris Consensus on Childhood Constipation Terminology (PACCT) group has offered working definition of chronic constipation in children. The chronic constipation is defined based upon the defecation characteristics during last 8 weeks 7 given in Table 3.

Table 1: The Loening- Baucke criteria of pediatric constipation

At least two of the following criteria:

- Defecation frequency less than 3 times a week
- Two or more encopresis episodes per week
- *Periodic passage of very large amounts of stool once every 7-30 days
- A palpable abdominal or rectal mass at physical examination

*The criteria of a large amount of stool is satisfied if it is estimated to be twice the standard amount of stool, shown in a clay model, or if stools are so large to clog the toilet

Table 2: Childhood functional defecation disorders: Rome: II criteria*Infant dyschezia*

At least 10 minutes of straining and crying before successful passage of soft stools in an otherwise healthy infant

Functional constipation

In infants and preschool children at least 2 weeks of:

- Scybalous, pebble like, hard stools for a majority of stools; or
- Firm stools two or less times/week; and
- No evidence of structural, endocrine, or metabolic disease

Functional fecal retention

From infancy to 16 years old, a history of at least 12 weeks of:

- Passage of huge diameter stools at intervals <2 times/week
- Retentive posturing, avoiding defecation by contracting pelvic floor and gluteal muscles

Functional non-retentive fecal soiling

In children older than 4 years a history of once a week or more for the preceding 12 weeks of:

- Defecation into places and at times inappropriate to the social context
- In the absence of structural or inflammatory disease and
- In the absence of signs of fecal retention

Table 3: The PACCT definition of chronic constipation

When 2 or more of the following characteristics during last 8 weeks

- Frequency of bowel movements less than three per week
- More than one episode of fecal incontinence per week
- Large stools in the rectum or palpable on abdominal examination
- Passing of stools so large that they obstruct the toilet
- Retentive posturing and withholding behavior
- Painful defecation

Table 4: Classification of constipation

- I. Depending upon the age of onset
 - a. Congenital constipation (Since birth)
 - b. Functional constipation
- II. Depending upon the duration
 - a. Acute or simple constipation (2 weeks-8 weeks)
 - b. Chronic constipation (>8 weeks)
 - Mild
 - No megarectum/megacolon or impaction
 - No encopresis
 - Severe (complicated)
 - Associated with megarectum and megacolon or impaction
 - Associated with encopresis

Encopresis

Encopresis is the involuntary passage of formed, semi-formed or liquid stool in the child's underwear. Largely this is considered to be functional when there is no organic or anatomic cause or medication responsible for it after the age of 4 years. This is equivalent to enuresis in children. In presence of chronic constipation it is called overflow incontinence. This is present in around 5 percent of children with constipation. Before the age of 3 to 4 years, it is very difficult to recognize because, diapers are used and moreover, voluntary control on the act of defecation may not be achieved. This emphasizes the fact that encopresis could be functional or overflow incontinence.^{1,2,8}

Fecal Soiling

Fecal soiling is any amount of stool deposited in the underwear, independent of whether functional or organic or anatomic lesion is present.

Fecal Incontinence

Fecal incontinence is fecal soiling in the presence of an organic or anatomic defects such as anal malformation, anal surgery, anal trauma, meningomyelocele and other neurological and muscle diseases affecting the anorectal area and perineum. There is no retaining capacity due to lack of reflexes involved in retention of stool and act of defecation. But some authors have used these terms interchangeably in the literature.¹

CLASSIFICATION

This is not clear from the literature. For better understanding of the problem, the suggested classification is given in Table 4. There is no ambiguity to understand the congenital and acquired constipation. Congenital constipation is usually since birth and is associated with Hirschsprung's disease (HD) and congenital anorectal anomalies. Acquired constipation occurs any time after birth, but there are no neurological and anatomical abnormalities of anorectal region. Acute constipation is defined when it is of shorter duration possibly less than 8 weeks. On the other hand when the duration of constipation is more than 8 weeks and is labeled chronic constipation. This may or may not be associated with megarectum and megacolon or impaction and encopresis. Chronic constipation is mild when there is no encopresis or megarectum and megacolon or impaction whereas when it is complicated by presence of

encopresis, megarectum and megacolon or impaction is termed as severe chronic constipation.^{9,10}

PATHOPHYSIOLOGY OF CONSTIPATION

Normal Bowel Habits

The normal frequency of stools varies from 3 times per day to 3 times per week. But this may be as high as 4-10 times during breast-feeding period in infancy. Toddlers may pass stools 3 to 5 times per day but as the age advances, the transit time increases and normal adulthood frequency of 1 to 2 times per day is achieved after 4 years of age.

Bowel Training

Normal bowel training should be started at the age of one year when infant starts walking. Regular timing and passage of at least one stool per day are essential for the normal function of the bowel. For this use of appropriate potty or toilet where a child can sit in squatting position is required. Mother should ensure child sits comfortably on the lavatory seat without fear.

Mother should use one word for defecation training and if baby repeats this is a good sign. Child should be made to sit for 5 to 10 minutes. Normally children start attending toilet independently by the age of 2-3 years. Problems in the bowel training can arise because of dietary changes, low fiber diet, formula feeds, anal fissure, inter-current illnesses, travel, moving to new home, family dysfunction, birth of sibling, erroneous parents expectation, family problems, failed toilet training, unresolved stress in school, changing of school, privacy, drugs and various neurological disorders. Most of the times these precipitating factors are responsible for onset of constipation with some functional overlay.¹²⁻¹⁵

Physiology of Defecation

Infants have involuntary passage of stools and there is no control on defecation. They may cry or make some movements while passing stools. Mostly they pass stool while feeding due to exaggerated gastrocolic reflex. After the age of one year the voluntary control starts developing and by the age of 1½ to 2 years they have the control and tell about the act of defecation. This is achieved earlier in girls as compared to boys. By the age of one year the mother starts training the child to follow one word to pass stool. The good and early control depends upon the training by mother and the positive response by the child.

Normally the mass movements occur 3 to 4 times a day but only 1 to 2 times mature for defecation. The sigmoid colon acts as store house, once stool passes into the rectum then urge to defecate is generated. There are two types of nervous systems involved, the autonomic and the sensory. The autonomic is stimulated by contact of the stool to the mucosa of rectum and afferent impulses

move to central nervous system to stimulate efferent so that internal sphincter relaxes. The internal anal sphincter is formed by thickening of the terminal inner layer of smooth muscles of rectum. Below this, there is anal canal and external anal sphincter. The striated muscles form the pelvic floor and external anal sphincter. These are innervated by pudendal nerve and 4th sacral nerve. The puborectalis muscle is the part of levator ani and at the level of internal sphincter it makes a sling around the lower part of rectum and gets inserted into symphysis pubis. This is very important muscle to form the anorectal angle to maintain the continence. Normally this angle is right angle (85-110°) and during the act of defecation the angle becomes straight or obtuse in squatting position to ensure smooth passage of the stool during defecation. Once the fecal matter descends from sigmoid colon to rectum, mere distension of rectum initiates the urge for defecation. There is relaxation of internal sphincter but contraction of external sphincter. The external sphincter can be contracted or relaxed voluntarily. If there is no conducive atmosphere the contraction leads to postponement of urge hence, more accumulation of fecal matter. If individual wishes to pass stool and sits in squatting position, the anorectal angle gets straightened, the puborectalis muscle and external sphincter relax to fire the stool in the toilet. The rectosphincteric reflex is generated by rectal distension only. The pelvic floor also descends by 1 to 3.5 cm to facilitate the passage of stools. At the same time the abdominal muscles contract and the glottis is closed to generate the intra-abdominal pressure to push the stool in a smooth fashion. The abnormality at any of the levels of act of defecation results to dysfunctional fecal elimination disorders. The constipation is the most important problem to develop.^{9,11}

PATHOGENESIS OF CONSTIPATION

Constipation during childhood is confluence of variations in physiological tendencies like development transitions, environment factors and parental response. Most of the times constipation is a problem in toddlers and this may become passive if tackled in time. There is always a precipitating cause.

Infancy

During infancy the constipation is mostly pathological due to Hirschsprung's disease, anorectal problems, mental retardation or anatomical abnormalities of anorectal area. This may also be due to formula feeding and lack of cereal supplementation after 6 months of life. Infants largely on animal or formula milk feeds and on low fiber diet are prone to develop constipation. Lack of breast feeding predisposes the infants to develop constipation due to top milk feeds. Sometimes janam gutti and opiate

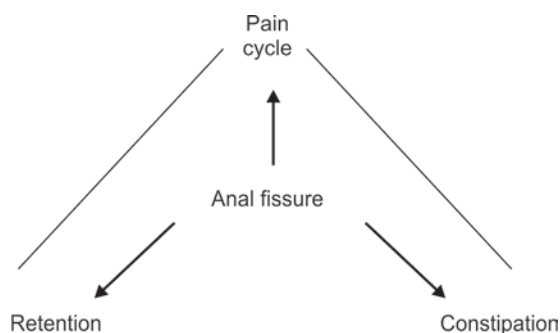


Fig. 1: Pain a common factor in constipation in toddlers

like drugs given by parents may be responsible for constipation in infants.^{16,17}

Toddlers/Preschool Children

In toddlers the most important factor is the painful act of defecation due to anal fissure. The head of the stools is always hard and can injure the anal canal leading to fissure formation. The anal fissure is very painful. Child tries to defer next act of defecation, and goes on withholding the stool as there is fear of pain to the next act of defecation. The anal injury occurs due to passage of hard stool and later on this gives rise to retention and pain cycle given in Figure 1. This goes on and results into chronic constipation. Children start adopting different postures to evacuate. This leads further injury to anal canal. As they start going to school other confounding factors come in operation. The most important confounding factor is the low fiber diet in form of junk foods, soft drink beverages and bakery products available in ready made form in the market. The children have more liking for these foods and they dislike fiber rich home made diet. Parents have no time to feed their children with home made stuff. Moreover the media is highlighting junk foods in a big way to exploit the children. Prolonged fecal impaction leads to chronic rectal distension and loss of rectal sensation so there is further stool impaction resulting in megacolon and megarectum to accommodate large volume of stool. The retention of large volume of stool is responsible for pain abdomen and encopresis or soiling in the underwear subsequently. The other most important factor is lack of toilet training after the age of 1 year. If it remains unsupervised due to the lack of interest by mother, it results in constipation.

School Children

The lack of privacy and positive reinforcement leads to problem of chronic constipation. Psychologically children are withdrawn and develop other functional problems also.^{2,3} This is more common in female children who do not find appropriate hygienic toilets and bath rooms in the school. Various other causes of acute and chronic

Table 5: Etiology of acute constipation in infants and children

<i>Infants:</i>	<i>Toddlers and older children</i>
Lack of breast milk	Change of diet
Formula feeds	Change of place
Cow milk based diet	Traveling
Change of diet	Anal fissure
Low fiber diet	Boil
Anal fissure	Abscess
Inflammation in perianal area	Infected hemorrhoids
Boil	Dermatitis
Dermatitis	Low fiber diet
Drugs: Opiates, <i>Janam gutti</i> , etc.	Drugs

constipation in children are given in Tables 5 and 6 respectively.¹⁸⁻²⁰

Associations of Chronic Constipation

Children suffering from recurrent abdominal pain (RAP), 50 percent may be constipated and 20 percent of them may show psychiatric problems. Chronic constipation may be associated with irritable bowel syndrome (IBS).

With the impaction of stools other associations are enuresis, UTI, palpable mass, soiling/encopresis/overflow incontinence, finger evacuation, solitary rectal ulcer, rectal prolapse, irritability, scissoring of legs, passage of stool while standing (unphysiological way to pass stools). Usually there is loss of appetite and poor weight gain.^{4,5,21}

CLINICAL PRESENTATION

The main complaint of the parents is the longer interval between bowel movements in the child. The clinical picture associated with chronic constipation includes pain abdomen, vomiting, abdominal distension, excessive flatulence, fecal soiling, prolapse and blood streaked stools. The infants and toddlers become more irritable and cranky. They are in the habit of withholding the stools and pass stool at irregular intervals. The stools may be hard and come out in form of hard large caliber casts, balls, or ribbon or pencil like. The amount may be small but at times large. They have to strain a lot to pass stools. Infants squeeze their buttocks and flex the legs and cry a lot while passing stools. The toddlers develop scissoring (cross their legs) squeeze their buttocks and strain a lot. They can not sit because of fear of pain and pass stool in standing posture behind the curtain or door or sofa in an isolated place. They are afraid of pain and do not allow to touch the abdomen and perineum.

Constant withholding of stools, leads to impaction of fecal matter and is responsible for development of encopresis. This is also called soiling in the under wears. The frequency of soiling may vary depending upon the severity

Table 6: Etiology of chronic constipation with or without megarectum, megacolon or encopresis

<i>Congenital</i>	<i>Acquired constipation</i>
<ul style="list-style-type: none"> • Anorectal defects <ul style="list-style-type: none"> Anal stenosis Anal atresia Imperforate anus Anterior displaced anus • Neurogenic <ul style="list-style-type: none"> Myelomeningocele Spina bifida • Colonic neuropathies <ul style="list-style-type: none"> Hirschsprung's disease Intestinal neuronal dysplasia • Colonic defects <ul style="list-style-type: none"> Colonic atresia Short colon 	<ul style="list-style-type: none"> • Idiopathic or functional 90-95% • Anal lesions <ul style="list-style-type: none"> – Anal fissures – Abscess – Strictures due to IBD, TB – Anal surgery/trauma/sexual abuse • Neurological conditions <ul style="list-style-type: none"> – Cerebral palsy – Hypotonia – Mental retardation – Tumor of spinal cord – Tethered cord • Metabolic <ul style="list-style-type: none"> – Hypokalemia – Hypomagnesemia – Hypophosphatemia – Hypercalcemia – Cystic fibrosis • Endocrine <ul style="list-style-type: none"> – Hypothyroidism – Multiple endocrine neoplasia IIB (MEN) – Diabetic mellitus – Hyperparathyroidism • Drug induced <ul style="list-style-type: none"> – Antimotility drugs – Anticholinergics – Antidepressants – Antihypertensives – Anticonvulsants – Opiates – Codeine – Antacids – Phenothiazines – Methylphenidate • Food allergy <ul style="list-style-type: none"> – Milk – Celiac disease • Low fiber diet • Psychiatric problems

of constipation. These children may have enuresis, UTI and behavioral problem. Children with constipation may appear quiet, withdrawn, embarrassed, agitated, clinging to mother and angry on examination as compared to children with other gastrointestinal disorders. The history of functional bowel disorder may be positive in parents at times.²²

CLINICAL APPROACH TO CONSTIPATION

History

Detail history is required to find out precipitating factors for constipation in children. While taking history special

attention should be paid towards the toilet habits, which include characteristics of stools in the toilet, in the underwear and stool withholding maneuvers. Age of onset of constipation is also important. Constipation starting from neonatal life gives clue towards developmental anomalies of anorectal area or colon. Delayed passage of meconium after 48 hours of birth gives clue of Hirschsprung's disease. Associated abdominal pain may be the sole symptom of constipation in 50 percent children with RAP. It is important to enquire about dietary habits of the child. Consumption of excess of milk, juices and/or other drinks, junk foods and bakery products may lead to constipation. In the modern era children largely depend upon low fiber diet and this becomes important factor for onset of constipation. Less consumption of cereals, pulses, vegetables and fruits can result in constipation. Inadequate and low fiber diets are responsible for less production of stool. History of medication/drugs should be asked. One must also enquire about the associated conditions like enuresis, UTI or any psychiatric problems. There is loss of appetite due to delayed stomach emptying and slow transit time due to colo-gastric reflex. There may be poor weight gain.^{5-9,23} There is strong association of constipation or other functional GI disorders in the parents or other sibs.

Examination

Patients should be thoroughly examined including growth parameters, nutritional status, general physical examination, neurological examination, abdomen and perianal area. Abdominal examination may reveal a lump in the left iliac fossa or suprapubic area due to retention of fecal matter in the sigmoid and descending colon. Sometimes whole of the colon may be palpable. Perianal examination may reveal anal anomalies or boil or fissure. Rectal digital examination should be carried out. In case of acquired constipation hard fecal matter is felt just at the entry of the finger in the anal canal on digital rectal examination. In case of HD the rectum is empty, whereas the fecal matter is felt high up and on withdrawal of finger fecal matter may gush out. In case of anal stenosis, there will tight opening. In presence of active anal fissure digital rectal examination should be avoided because this can enhance the anal injury. Neurological examination including inspection of lumbosacral spine, lower limbs and perianal sensation testing should be done.

Investigation

In case of functional chronic constipation there is no need of elaborate investigation. The history and examination give clue to the diagnosis of most of the anatomical defects responsible for constipation. History of food allergy especially milk and celiac disease may be responsible for this. There are other causes of constipation in childhood as mentioned in table and should be investigated as below.^{24,27}

Plain X-ray Abdomen

Abdominal radiographs should be done in erect and supine position to see for the extent of fecal load and to delineate the dilatation of rectum and colon. There may be impaction with megarectum and megacolon. In case of HD and other congenital anomalies the rectum and colon may be hugely distended. At times fecoliths may be seen. The spinal abnormalities like spina bifida or neural tube defects can be diagnosed.²⁴⁻²⁷

Endocrine Assessment

Thyroid function tests should be done to rule out hypothyroidism. Serum calcium levels and parathormone levels are required if there is suspicion of hyperparathyroidism. If there are osmotic features rule out diabetes mellitus.

Metabolic Work-up

To rule out certain metabolic disorders as given in table serum potassium, magnesium, phosphate, calcium, sweat chloride and tissue transglutaminase antibodies should be ordered based up the high index of suspicion.

Anorectal Manometry

This is not done routinely but if there is suspicion of HD then it is indicated.

Barium Enema

In HD there is contracted segment and above that there is huge dilatation of bowel due to obstruction.

Rectal Biopsy

This is important to diagnose HD. The absence of intramural ganglion cells is the diagnostic of HD and biopsy should be taken from rectum above the pectinate line.

Transit Time Study

Some of the patients may have delayed transit time of the bowel. This is measured by giving radio-opaque markers and seeing their elimination over the time. The significance of this is not clear in pediatric age group.

Most of the times, detailed clinical examination of patient gives clue to the anatomical defects/neurological causes of constipation. Drugs responsible can also made out on history only. The points to differentiate acquired constipation and Hirschsprung's disease are given in Table 7. The childhood constipation differs from that of adolescent/adulthood constipation and the differences are given in Table 8. A meticulous practical approach to management of chronic constipation is shown in Flow chart 1. The algorithmic approach is based upon clinical presentation, investigations and treatment.

MANAGEMENT OF CHRONIC FUNCTIONAL CONSTIPATION

Certain principles of management of chronic constipation are very important to ensure drug therapy and its compliance. The treatment of functional constipation is discussed under the following headings.

- General measures
- Pharmacotherapy
- Treatment modalities

General Measures

There are many apprehensions in the minds of parents and the child. The children have emotional and behavioral problems, prolonged school absence and social factors and parental conflicts. Based upon these facts the following interventions are very important.^{2,11}

Table 7: Difference between functional constipation and Hirschsprung's disease in children

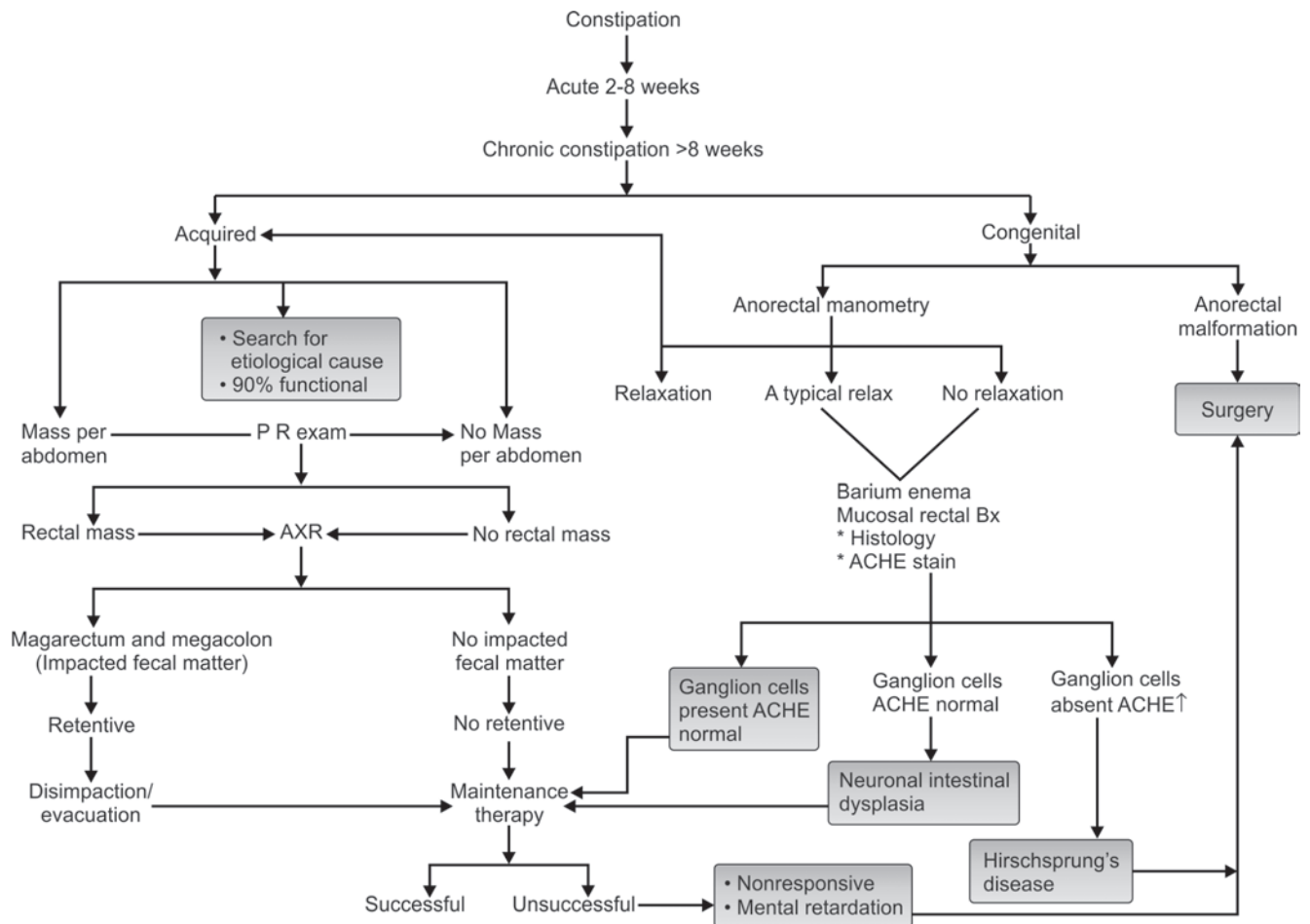
Features	Functional constipation	Hirschsprung's disease
• History		Common
Onset at birth	Never	Unusual
Retentive posturing	Common	Rare
Encopresis	Common	Unusual
Large caliber stools	Common	Common
History of obstruction	Rare	
• Physical examination		
Failure to thrive	Unusual	Common
Distended abdomen	Occasional	Common
Stool in ampulla	Common	Rare
Rectal ampulla	Dilated	Narrow
• Investigations		
X-ray abdomen	Fecal impaction, dilated rectum and colon	Hugely dilated colon with fecal matter
Barium enema	No narrow segment, rather dilated rectum and colon	Narrow segment with proximal dilatation
Rectal biopsy	Normal ganglion cells and ACHE*	Absent ganglion cells and increased ACHE*
Rectal manometry	Normal	Abnormal contraction

* ACHE: Acetylcholinesterase

Table 8: Difference between childhood and adolescent/adulthood with constipation

Features	Children	Adolescents/adults
Occurrence	More common in male	More common in female
To begin with	Toilet training and school entrance	Adolescence, young adulthood
Defecation behavior	Withholding	Straining
Scissoring and to pass stool in standing posture	Common	Sit in squatting position and strain lot
Encopresis	Common	Rare
Use of medications or due to systemic disease	Rare	Common
Barium enema	Rule out Hirschsprung's disease	To rule out intra-abdominal pathology
High fiber diet	Rarely helpful	Helpful
Role of biofeedback	Controversial	Beneficial in pelvic floor dyssynergia
Role of surgery	Only in HD* and in anorectal anomalies but not in functional constipation	May be helpful in slow transit constipation

*HD: Hirschsprung's disease

Flow chart 1: Practical approach to constipation

Education

The actual problem of constipation, its causation and anatomy of large bowel should be explained to parents and the older children. The mechanism of act of defecation and pathophysiology of constipation should also be explained to the parents. This will take care of conflicts in form of blame and guilt between parents and the child. This will encourage the parents to institute the effective therapy.

Behavioral Advice

It is important to gain the trust of the child. Child should be assured of the treatment to take care of his problem. Parents should ignore the failures rather reward for the success. Child should be boosted and encouraged to have more success in the defecation disorder including soiling. This will ensure the meaningful treatment as fear in the mind of the child disappears.

Toilet Training

This is very important component of the treatment where there is deficiency in the toilet training. Child should be encouraged to sit in the toilet in a comfortable position at the time of urge of defecation. This should initially be ensured in the morning, evening and after the meals. Make sure the child sits in the toilet with ease with adequate foot support. This will ensure the smooth flow of the stools.

Reward Schemes

Reward schemes are helpful in the behavioral management of the problem. Small rewards in form of daily requirements of the child are important when the child passes stool successfully.

Reassurance and Encouragement

Parents are to be reassured that constipation is very common problem and outcome of treatment is good if there is good compliance. They should be encouraged for close follow-up.

Diet, Fluids and Exercise

Adequate diet rich in fiber is advised. This will ensure the decrease in transit time. Adequate fluid intake will ensure proper hydration of body and help in evacuation. The daily exercise in form of active participation in outdoor activities will help in better elimination of stools. Toilet training, incentive and reward schemes, desensitization of toilet phobia and cognitive therapies like psychotherapy, cognitive and family therapies do help to have better response and good outcome.

Counseling

Counseling of parents is very important regarding the problem and its treatment. Certain differences among the

child and parents must be taken care of. They should be explained about the availability of treatment. Moreover treatment lies in their hands as they are going to handle the treatment at home. The treatment required is for prolonged period, may be for six months to one year or even longer. The importance of close follow-up is mandatory to ensure successful treatment.

Pharmacotherapy

Various agents used in treatment of constipation are divided in various groups have been given in a tabular form (Table 9).

Osmotic Agents

Lactulose

Lactulose is a very often used to treat constipation in children. Lactulose is a disaccharide of sugars D-galactose and D-fructose and is not absorbed in the intestine. The enzymes in the gut cannot digest it and it reaches the colon as such. There it is acted upon by colonic bacteria. The byproducts of this action lead to increase in fecal bulk and gas stimulates the peristalsis. There are no placebo control trials, however its efficacy in treatment of mild constipation has been reported in children. Lactitol, another form of lactulose, is equally effective. Lactulose can lead to minor side effects in form of abdominal discomfort, flatulence and bloating.³⁵

Polyethylene Glycol

Polyethylene glycol (PEG) 3350 is an osmotic agent. It is not absorbed in the gut due to its large molecule size. This makes the bulk of the stool by not allowing the water absorption. This is very effective. There are case controlled well conducted studies. It is much more superior to lactulose and magnesium hydroxide (milk of magnesia). It is used for disimpaction as well as for maintenance therapy. Its efficacy and safety even for more than 3 months has been well documented. Polyethylene glycol (PEG) electrolyte solution is often used for bowel preparation before colonoscopy and is very effective. It can be used for treatment of constipation but is very cumbersome and may lead to metabolic disturbances, when used for longer time. Polyethylene Glycol (PEG) 3350 is easy to use and very effective as compared to PEG electrolyte solution.²⁹⁻³⁵

Lubricants

Liquid paraffin is a mineral oil and a petroleum derivative. It is popularly used for treatment of chronic constipation. It softens the stool by lubrication and there is osmotic effect also due to conversion of oil to fatty acids. Liquid paraffin is effective for disimpaction as well as for maintenance therapy of chronic constipation as shown in various trials. It is associated with aspiration lipoid pneumonia in younger children. Its use is not recommended for children

Table 9: Commonly used oral laxatives in childhood constipation

<i>Agents</i>	<i>Dosages</i>	<i>Side effects</i>
Osmotic		
Lactulose/lactitol/sorbitol/ mannitol	Maintenance 1-3 ml/kg/day in 2 doses	Bloating, cramps, diarrhea
Magnesium citrate	Maintenance 1-3 ml/kg/day in 2 doses	Hypermagnesemia, hypophosphatemia and secondary hypocalcemia
Magnesium hydroxide (Milk of magnesia)	Maintenance 1-3 ml/kg/day in 2 doses	
Polyethylene glycol (PEG) 3350	Disimpaction: 1.5 g/kg 1 day in 240 ml water X 3-4 days	Nausea, vomiting, cramps and diarrhea
Polyethylene glycol Electrolyte solution	Disimpaction: 14-50 ml /kg/h till clearance Maintenance: 5-10 ml/kg/day	
Lubricant		
Mineral oil (liquid paraffin)	Disimpaction: 15-30 ml/year of age Maintenance: 1-3 ml/kg/day in 2 doses Oral 100 mg twice a day can be used as enema	Aspiration risk Lipoid pneumonia, nausea
Sodium docusate		
Stimulants (given for short course)		
Sodium pecosulphate	5-10 mg daily	Cramps, diarrhea
Bisacodyl oral and enema	5-10 mg daily oral 5 mg per rectally	Cramps, pain abdomen and anal irritation
Glycerine suppository	Pediatric suppository up to 6 years, adult sup- pository >6 years	Anal irritation
Sodium biphosphate enema	Disimpaction: 6 ml/kg/12 hourly 3 times	
Senna	2.5-7.5 ml/day (2-6 years) 5-15 ml/day(6-12 years)	Melanosis coli, hepatitis
Castor oil	Disimpaction: 15-30 ml/day	Cramps, severe diarrhea
Bulk laxatives		
Psyllium (Isbagol), Methylcellulose, Polycarbophil	Maintenance dose: Daily requirement Age in years + 5 = g/day Titrate up to 20 g/day	Bloating
Prokinetic drugs		
Cisapride	0.5-1 mg/kg body weight in diabetes, pseudo- obstruction	Diarrhea

having gastroesophageal reflux and/or aspiration and in children less than 3 years age. Tolia et al studied efficacy of mineral oil versus PEG 3350 and found both are effective for disimpaction and for the maintenance treatment of chronic constipation.²⁸ Compliance was better with mineral oil whereas fecal impaction clearance was good with PEG 3350.

Stimulant Laxatives

These include senna, bisacodyl, sodium dioctyl sulfosuccinate (also a stool softener) and sodium picosulphate. They stimulate the peristalsis and increase the intestinal motility. They are widely used and are safe and effective.

But their use is not based on evidence based medicine. There are no trials on these agents to follow guidelines. Short-term use in the evening to have better clearance in the morning is beneficial in older children. They can lead to colicky abdominal pain. These can be used to prevent relapse intermittently.

Enema

Enema therapy is required when oral medication has failed to give relief to the child with impacted stools. Routinely, should be avoided as this gives a traumatic experience to the child and can exacerbate the stool withholding behavior. There are no trials of enema therapy in children. Phosphate enema can lead to metabolic changes.^{1,11}

Bulk Forming Agents

Low intake of dietary fiber has been well known to lead to constipation in children. The best examples in children are milk based diet and junk food/bakery food. Increase in diet rich in fiber does help to relieve the constipation. The bulk forming laxatives are psyllium (isabgol), methylcellulose, polycarbophil and glucamannon (fiber gel polysaccharide). The role of fiber in chronic constipation has been evaluated and has been found to be a good adjunct to laxative therapy. Certainly diets rich in fiber like vegetables, salads, fruits, pulses with husk and raw grains (dalia) are advised as part of treatment and do help with laxative agents. Wet fiber is preferred over dry fiber in children.

Prokinetic Agents

Cisapride has been found to be helpful but its use has been banned due to side effects. Another drug erythromycin acts by stimulating motilin like receptors on smooth muscle cells and cholinergic neurons in gastrointestinal tract. The trials in small number of patients have shown to be effective but larger trials are required. These are helpful in motility problems has been associated with diabetes mellitus and chronic intestinal pseudo-obstruction.

Probiotics

The role of probiotics has been studied in constipation in relation to irritable bowel syndrome but its efficacy has not been defined in childhood chronic constipation. Studies are required to define efficacy in childhood constipation.

Newer Drugs

The newer drugs include tegaserod, prucalopride and alvimopan. These increase the peristalsis and the secretions to relieve the constipation but trials in children are not available. Tegaserod is banned due to its side effects.

Treatment Modalities

Acute Simple Constipation

This is very common in children, usually mild and easy to treat. Enough fluids and carbohydrate rich diet takes care of constipation in infants. Parents must be educated and reassured that it is not pathological. One has to eliminate the precipitating factor. Treat local causes like anal fissure, boil or dermatitis effectively. Procedures like enemas, finger evacuation/disimpaction, finger dilatation and frequent use of suppositories should be avoided. But encourage use of high fiber diet in terms of cereals, pulses, vegetables and fruits. Adequate fluid intake is advised to keep proper hydration. Initially laxatives can be used. Encourage toilet training simultaneously. Laxatives can be given for 7 to 10 days but prolonged use should be discouraged. If this is not properly treated can result into

chronic constipation¹¹ and may require therapy for longer time.

Chronic Constipation

Treatment of chronic constipation is possible by multimodality approach¹ and is given in Flow chart 3.

Mild Chronic Constipation

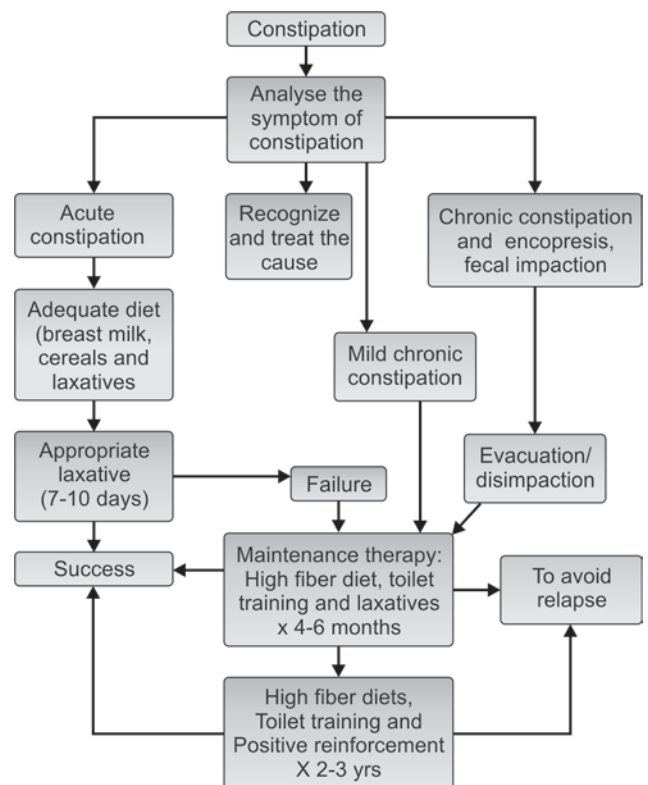
The uncomplicated chronic constipation without palpable fecal masses, megarectum or megacolon and encopresis is treated as the management protocol given under maintenance phase of treatment (Flow chart 2). There is no need of evacuation since there is no impaction.

Chronic Constipation with Impaction and Encopresis

Bowel Disimpaction/Evacuation

This is very important to have clean bowel free of retained/impacted stools. This will also take care of overflow incontinence/soiling. If initial disimpaction is not done, the treatment with oral laxatives result into paradoxically increase in overflow incontinence, increase in abdominal pain and bloating. These cases may land in the emergency ward with acute abdomen. Thus disimpaction is mandatory before starting the laxatives in maintenance phase of treatment. The disimpaction can be done by oral route, rectal route, combination of oral and rectal routes and surgical methods.¹¹ But oral route is preferred.

Flow chart 2: Management of constipation summarized



Oral Route

Total bowel wash is very effective to clear whole of colon. This can be done with normal saline or polyethylene glycol electrolyte solution in the dose of 14 to 40 ml/kg/hour till the returns are clear. Metochlopramide (5-10 mg) should be given ½ hour before the lavage to avoid vomiting. Sodium phosphate solution can be used. In case child is not able to take enough fluids orally it can be given through nasogastric tube. Clearance of colon can be ascertained by examination of abdomen for fecal masses, per rectal digital examination and X-ray abdomen.²⁸⁻³⁴

Recently it has been shown that polyethylene glycol (PEG) a non-electrolyte substance is very effective in disimpaction of the fecal mass in children. This is an osmotic agent. The dose of PEG is 1.5 g/kg/day for 3 to 4 days. This can be dissolved in 240 ml water and given orally. This is quite effective, safe and easy to use orally without much side effects. In case loose stools occur, the dose of PEG can be lowered and adjusted accordingly. The results are better with PEG as compared to lactulose.³⁵

Rectal Route

Enemas: Three hypertonic phosphate enemas 12 hourly can clear the rectum effectively. The dose recommended is 6 ml/kg/day. When the weight of the child is above 20 kg the adult dose can be given. Occasionally hypernatremia, hyperphosphatemia, hypocalcemia, hypokalemia and dehydration have occurred with hypertonic enema. Saline enema is less effective but can be used. This takes longer time to clean the colon. Plain tap water and soap water enemas are not to be used in children.^{1,11}

Suppository: Glycerine or bisacodyl suppositories can be tried in younger infants and may evacuate rectum effectively. It should not be repeated often since it can traumatize the anorectal area. The stool withholding practice by the child is exaggerated further and adds to the misery.

Purgation: Large dose of mineral oil (liquid paraffin) or castor oil or other osmotic agents can effectively evacuate rectum. Usually repeated doses are required. These are not used in children.²⁸

Surgery: Surgical disimpaction is required very rarely in severe constipation, failed medical treatment, mental retardation and fearful situation with poor compliance. Surgery is the definite treatment of Hirschsprung's disease (HD) and other anorectal congenital anomalies in children.^{36,37}

Maintenance Therapy: The goals of maintenance therapy are (1) to maintain adequate frequency, (2) to avoid continued passage of large stools and (3) to prevent withholding/retention of stools. Retraining medications include stool softeners or bulk-forming agents or osmotic agents. The laxatives used are milk of magnesia, liquid paraffin,

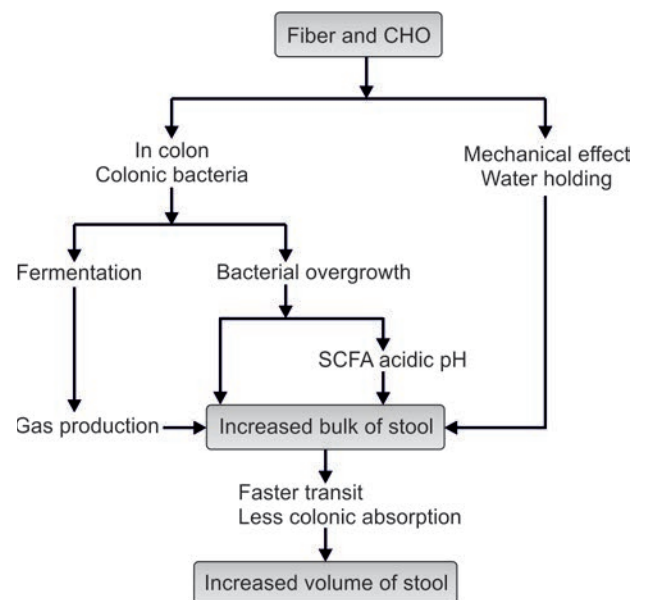
lactulose, lactitol, etc. in the dosage of 1-3 ml/kg body weight. These should always be given twice a day. Recently reported PEG for maintenance phase in the dose of 0.25 to 1g/kg/day has been shown to be very effective and safe even for long term use. The maintenance therapy has to continue for 6 months or even more depending upon the response. Routine use of bisacodyl, castor oil, senna and phenolphthalein is not recommended in children. These stimulate the peristalsis, active electrolyte transport and fluid movements.^{11,38-41}

Cisapride a prokinetic agent can be used in paraplegics, pseudo-obstruction, diabetics, chronic constipation, etc.⁴² Combination of various agents is effective to avoid recurrence of constipation. The most commonly used drugs/agents along with dosage and side effects are given in Table 8.

Dietary Modification

Encourage breastfeeding during early infancy and cereal supplementation should be started after 6 months of life. Diets rich in high fiber are bran based cereals, pulses, fruits, vegetables, etc. For older children and adults daily intake of 20 g of bran is quite effective to avoid constipation. In younger children the fiber requirement can be calculated as age in years plus 5. This gives the daily requirement of fiber in grams for that particular age (e.g. for 5 years + 5 = 10g).⁸ Intake of plenty of fluids is encouraged. Excess of drinks in form of milk, juices and cold drinks are to be avoided. Bakery products and junk foods to be discouraged.⁴³⁻⁴⁵ Mechanism by which dietary unabsorbed carbohydrates known as prebiotics increase the stool bulk is given in Flow chart 3.

Flow chart 3: Mechanism of action of fiber and carbohydrates



Retraining/Toilet Training

There should be positive reinforcement for toilet sitting and defecation. Toilet timing should be regular. Child should sit in squatting position for 5 to 10 minutes once or twice a day after the meals to take advantage of gastrocolic reflex. For proper sitting in the English type of latrines adequate foot rest should be provided to the children, so that the flexion of knee joints and hip joints is possible. Idea is to straighten the anorectal angle, so that stools can flow out easily. Positive reinforcement at home and by the physician is very important. Parents should be prepared to have verbal acclaim and selective awards for desired behavior, initiation of toileting, use of toilet, production of stool, acknowledging the cleaning after defecation and for repeated successes.⁵

Anal Fissure

In toddlers anal fissure is very important leading cause of retention and constipation. It should be taken care by giving sitz bath twice a day for two weeks. This will ensure the healing of the fissure. Xylocaine jelly as local application morning evening will help to provide relief of pain.

Biofeedback

Biofeedback is required when other measures are not working and there is anorectal dyssynergia. This helps in relaxation of external anal sphincter (EAS) and levator ani muscles. This is only possible above 5 years of age because cooperation of patient is very important. It is effective in 50 to 80 percent patients. Take the benefit of conditioning reflex in morning and evening like to move in front of toilet, to drink water, put the tap on and sitz bath. Multidisciplinary behavioral treatment is effective in chronic constipation and defecation process in children.^{9,46-49}

Follow-up

Long follow-up is required. In case the progress is very good the treatment can be weaned off after 6 months, but rest of the protocol in terms of high fiber diet and toilet training should continued for 2 to 3 years to avoid relapse. Appropriate psychiatric consultation should be taken when required. If there is atypical presentation or poor response pathological cause must be ruled out.⁵⁰

Outcome and Prognosis

Outcome with appropriate above mentioned therapeutic modalities is excellent in 45 to 100 percent of individuals. The quality of life and nutritional status improves significantly. Moderate response may be seen in 20 to 30 percent whereas 25-35 percent may have failure. Good prognostic indicators are better compliance, adequate intake of high roughage diet and self-confidence to

achieve the success. Poor prognostic indicators are hearing disabilities, disobedience, fearlessness, school time soiling, teen age occurrence, mental retardation, severe motor disability, associated disorders and neurogenic cause. In a recent study this has been shown that 30 percent of children suffering from constipation continue to be constipated during puberty. Recently reported systematic review articles on various aspects of chronic functional constipation have revealed that there is no evidence based treatment though use of PEG 3350 has been shown to be superior. The quality of life certainly improves with effective therapy.⁵¹⁻⁵⁷

Prevention

Prevention of colonic dysfunctions have received much less attention but attending pediatrician can play important role by providing anticipatory counseling in terms of appropriate feeding advise, high fiber diet, interpretation of normal bowel habits, counseling life issues of the child and early detection of problem and intervention.

SUMMARY

Constipation is a common problem in children and occurs more often in boys as compared to girls. Functional constipation occurs in 90 to 95 percent children whereas secondary causes are uncommon. In toddlers and school going children the anal fissure and painful act of defecation are important triggering factors to develop constipation. The low fiber diet in form of junk foods, soft beverages and bakery products have contributed lot in perpetuation of constipation. In case of functional chronic constipation there is no need to do many investigations. On examination detection of fecal mass per-abdomen or per-rectally is enough, at times plain X-ray abdomen may be required and will show impacted fecal matter and dilated rectum and colon. The acute constipation is simple and easy to treat. On the contrary the chronic constipation is usually associated with complications and is difficult to treat. The chronic constipation with impaction and encopresis requires evacuation followed by maintenance laxative therapy for 6 months in order to avoid further retention. The initial counseling, dietary advise to take fiber rich diet and toilet training are also very important components of treatment. The uncomplicated chronic constipation can be managed with maintenance therapy. The regular follow-up and adequate laxative treatment to ensure passage of soft stool without straining have key role in the success. After 6 months of rigorous drug therapy and the fiber rich diet, toilet training and reinforcement should continue for 2 to 3 years to avoid relapse of constipation later. The quality of life and growth and development improves significantly with meticulous multimodality approach.

Key Words: Constipation, acute or chronic, encopresis, definition and criteria, pathophysiology, impaction, approach, disimpaction, polyethylene glycol, enemas, lactulose, liquid paraffin, Hirschsprung's disease, fiber rich diet, biofeedback.

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Diagnosis and Management of Gastroesophageal Reflux Disease

Manpreet Sethi, SK Mittal

Gastroesophageal reflux (GER) is defined as the passage of gastric contents into the esophagus with or without regurgitation and vomiting. GER is a normal physiological phenomenon and it occurs several times a day in healthy infants, children and adults. Most episodes of GER in healthy individuals last <3 minutes, occur in the postprandial period and cause few or no symptoms.¹ This is referred to as physiological GER. In contrast, gastroesophageal reflux disease (GERD) is said to be present when GER leads to troublesome symptoms and/or complications. Further, when there is an underlying anomaly such as hiatus hernia, short esophagus, etc. the GER is referred to as pathological reflux.

DIAGNOSIS OF GASTROESOPHAGEAL REFLUX DISEASE

History and Physical Examination

Gastroesophageal reflux (GER) or Gastroesophageal reflux disease (GERD) may present with a variety of symptoms and signs, which are not limited only to the gastrointestinal tract (Table 1).

Regurgitation, irritability, and vomiting are common in infants with physiologic GER or GERD² but are indistinguishable from regurgitation, irritability, and vomiting caused by food allergy, colic, and other disorders. Individual symptoms in children generally are not highly predictive of findings of GERD by objective studies. For example, in a study of irritable infants younger than 9 months of age, regurgitation >5 times per day had a sensitivity of 54 percent and specificity of 71 percent for a reflux index (RI) >10 percent by esophageal pH testing, whereas feeding difficulties, which are more difficult to define as an entity, had a sensitivity of 75 percent and specificity of 46 percent.³ Among older children, not all of the children with GER have heartburn or irritability. Conversely,

heartburn and irritability can be caused by conditions other than GER.

Some of the symptoms are more suggestive of underlying GERD. These include persistence of vomiting after 6 months of age, crying during or after feeds, neonatal

Table 1: Symptoms and signs that may be associated with gastroesophageal reflux

Gastrointestinal symptoms

1. Recurrent regurgitation with/without vomiting
2. Heartburn
3. Feeding difficulties
4. Ruminative behavior
5. Dysphagia
6. Hematemesis

Respiratory symptoms

1. Neonatal apneas
2. ALTE, e.g. SIDS
3. Recurrent aspiration pneumonias
4. Reactive airway disease/wheezing
5. Stridor
6. Hoarseness
7. Recurrent laryngitis/tracheitis (specially in post-TEF repair cases)
8. Chronic sinusitis

Neurological symptoms

1. Dystonic neck posturing (Sandifer's syndrome)

Others

1. Anemia
2. Failure to thrive
3. Dental erosions

Table 2: Warning signals in children with persistent vomiting warranting search for causes other than GER or complicated GERD

- Vomiting—bilious or blood stained
- Forceful or projectile vomiting
- Associated fever, diarrhea, lethargy, dehydration
- Abdominal distension, constipation, abdominal colics
- Associated dysphagia
- Failure to thrive
- Neurological s/s like seizures, micro/macrocephaly
- Developmental delay.

apnea in term infants, recurrent aspiration pneumonias, nonnocturnal, nonseasonal wheezing.

GERD should be suspected in infants and children with symptoms mentioned earlier; but none of the symptoms are specific to GERD alone; so the major role of history and physical examination in the evaluation of GERD is to rule out other and more worrisome disorders that present with vomiting (Table 2) and to identify complications of GERD such as esophageal stricture presenting as dysphagia.

Because individual symptoms do not consistently correlate with objective findings or response to medical treatment, parent- or patient-reported questionnaires based on clusters of symptoms have been developed to diagnose GERD. Orenstein et al⁴ developed a diagnostic questionnaire for GERD in infants. A score of >7 (of 25 possible) on the initial instrument demonstrated a sensitivity of 0.74 and specificity of 0.94 during primary validation. However, when applied to a population in India, it had a sensitivity and specificity of only 43 percent and 79 percent, respectively, compared with pH-monitoring results.⁵

A 5-item questionnaire developed for children 7 to 16 years of age had a sensitivity of 75 percent and a specificity of 96 percent compared with pH monitoring during primary validation.⁶

A simplified approach to diagnosis of GERD based on symptoms and signs has been suggested and is given in Flow charts 1 and 2.

Diagnostic Tests for GERD

A variety of diagnostic tests are available (Table 3). None of them is hundred percent reliable, nor applicable in all circumstances. Clinicians must use their discretion while ordering these tests.

The diagnosis of GERD is inferred when tests show excessive frequency or duration of reflux events, esophagitis, or a clear association of symptoms and signs with reflux events, in the absence of alternative diagnoses. Although many tests have been used to diagnose GERD, few studies compare their utility. Importantly, it is not known whether tests can predict an individual patient's response to therapy. Tests are useful to document the presence of pathologic reflux or its complications, to establish

Table 3: Diagnostic tests available for GER/GERD

1. Upper GI barium studies
2. Esophageal and gastric ultrasonography
3. Nuclear scintigraphy (milk scan)
4. Esophagoduodenoscopy and biopsy
5. Esophageal 24 hr pH monitoring
6. Esophageal motility studies
7. Esophageal impedance
8. Therapeutic trial.

a causal relation between reflux and symptoms, to evaluate therapy, and to exclude other conditions. Because no test can address all of these questions, tests must be carefully selected according to the information sought, and the limitations of each test must be recognized.

Barium Contrast Radiography

Although simple and easily available, the upper GI series is neither sensitive nor specific for diagnosing GERD. The sensitivity, specificity and positive predictive values range from 29 percent to 86 percent, 21 percent to 83 percent, and 80 percent to 82 percent respectively when compared with esophageal pH monitoring.^{7,8} The brief duration of the upper GI series produces false negative results whereas the frequent occurrence of nonpathological reflux during the test produces false positive results. It involves radiation hence, is not a preferred test. However, the upper GI series is useful in settings where anatomical abnormalities like strictures, hiatus hernia, achalasia, tracheoesophageal fistula, intestinal malrotation or pyloric stenosis are suspected as part of the differential diagnosis of infants and children with persistent vomiting.

Esophageal and Gastric Ultrasonography

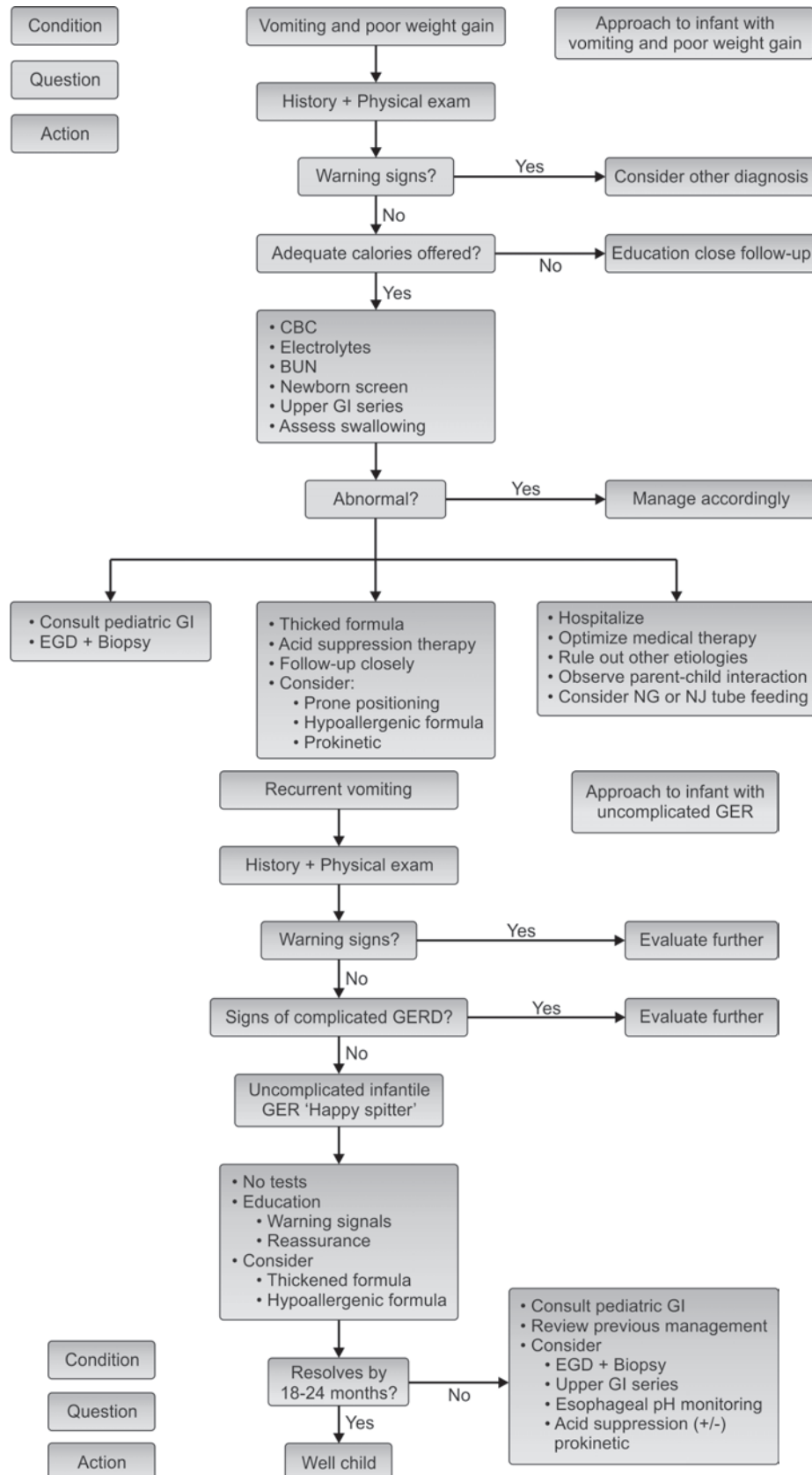
Ultrasonography is not recommended as a test for GERD but can provide information not available through other technology. Ultrasonography of the gastroesophageal junction can detect fluid movements over short periods of time and thereby can detect nonacid reflux events. It can also detect hiatus hernia, length and position of the LES relative to the diaphragm, and magnitude of the gastroesophageal angle of His. Barium upper GI series can also provide the same information. When compared with the results of 24-hour esophageal pH testing as a diagnostic test for GERD, the sensitivity of color Doppler ultrasound performed for 15 minutes postprandial is about 95 percent with a specificity of only 11 percent, and there is no correlation between reflux frequency detected by ultrasound and reflux index detected by pH monitoring.⁹

Nuclear Scintigraphy (Milk Scan)

In gastroesophageal scintigraphy, food or formula labeled with 99technetium is introduced into the stomach and

Flow chart 1: Simplified approach to diagnosis of GERD based on symptoms and signs

[(Adapted from Joint Recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) 2009)]



areas of interest—stomach, esophagus, and lungs are scanned for evidence of reflux and aspiration. The nuclear scan evaluates only postprandial reflux and demonstrates reflux independent of the gastric pH. While performing the test it is important to remember that the amount of milk/formula to be given must be roughly equal to the amount of the normal feed for that infant and to wait for about half an hour before scanning the baby. The advantages of this technique are that it demonstrates both acidic and nonacidic reflux, can evaluate gastric emptying (which may be delayed in children with GERD), and may even demonstrate aspirations. Moreover, it is noninvasive and radiation free. However, lack of standardized techniques and the absence of age-specific norms limit the value of this test. Sensitivity and specificity of a 1-hour scintigraphy for the diagnosis of GERD are 15 percent to 59 percent and 83 percent to 100 percent, respectively, when compared with 24 hour esophageal pH monitoring.^{10,11} Late postprandial acid exposure detected by pH monitoring may be missed with scintigraphy. Gastroesophageal scintigraphy scanning can detect reflux episodes and aspiration occurring during or shortly after meals, but its reported sensitivity for microaspiration is relatively low. Evidence of pulmonary aspiration may be detected during a 1-hour scintigraphic study or on images obtained up to 24 hours after administration of the radionuclide. A negative test does not exclude the possibility of infrequently occurring aspiration. Gastric emptying studies have shown prolonged half emptying times in children with GER. Delayed gastric emptying may predispose to GERD. Tests of gastric emptying are not a part of the routine examination of patients with suspected GERD, but may be important when symptoms suggest gastric retention. Despite its limitations, this can be useful test in infants, provided it is done and interpreted properly.

Endoscopy and Biopsy

The role of endoscopy and biopsy in the evaluation of GERD is primarily to demonstrate the effects of GERD on the esophagus in the form of reflux esophagitis and not to demonstrate or document reflux directly. It therefore, has limited application in the diagnosis of GERD. The main indications for endoscopy and biopsy are situations where the complication of reflux esophagitis is suspected, such as older children with recurrent abdominal pain, heartburn and chest pain or infants and younger children with alarm symptoms like irritability, crying excessively during feeds, unexplained anemia, failure to thrive, etc. It is also useful in evaluating empiric therapy failure, for preoperative evaluation and to rule out other conditions in the differential diagnosis such as eosinophilic or infective esophagitis, Crohn's disease, Barrett's esophagus, etc.¹² It is not useful in infants younger than 6 to 9 months of age.

Recent global consensus guidelines define reflux (erosive) esophagitis as the presence of endoscopically visible

breaks in the esophageal mucosa at or immediately above the gastroesophageal junction.¹² Mucosal erythema or an irregular Z-line is not a reliable sign of reflux esophagitis. Grading the severity of esophagitis, using a recognized endoscopic classification system, is useful for evaluation of the severity of esophagitis and response to treatment.¹³ The presence of endoscopically normal esophageal mucosa does not exclude a diagnosis of nonerosive reflux disease (NERD) or esophagitis of other etiologies.¹⁴ Histology may be normal or abnormal in NERD because GERD is an inherently patchy disease.¹⁴ Therefore, multiple biopsies must be obtained to exclude reflux esophagitis. Histological findings of eosinophilia, elongation of papillae, basal hyperplasia, and dilated intercellular spaces (spongiosis) are usually suggestive of reflux esophagitis, although not very specific of this condition.¹⁴ Taken with multiple esophageal biopsies, endoscopy provides more than 80 percent sensitivity and specificity for the diagnosis of reflux disease.

When biopsies from esophageal mucosa show columnar epithelium, the term Barrett's esophagitis should be applied and the presence or absence of intestinal metaplasia specified.^{14,15} BE occurs with greatest frequency in children with underlying conditions putting them at high risk for GERD. The primary role for esophageal histology is to rule out other conditions in the differential diagnosis, such as eosinophilic esophagitis, Crohn's disease, Barrett's esophagus, and infection.

Esophageal pH Monitoring

Intraluminal esophageal pH monitoring measures the frequency and duration of acid esophageal reflux episodes. Although not hundred percent reliable, it is considered the 'gold standard' for the diagnosis of GER. It only demonstrates GER and not necessarily GERD unless the reflux symptoms are correlated with acid reflux episodes with the help of symptom diary.

Most commercially available systems include a catheter for nasal insertion with one or more pH electrodes (antimony, glass, or ion-sensitive field effect) arrayed along its length and a system for data capture, analysis, and reporting. The recording device is a small box with high portability and allows maximum normal activity. Prokinetic agents should be discontinued at least 48 hours before, H-2 antagonist at least 3 to 4 days and antacids at least 24 hours before the investigation. Calibration is done before the procedure. For standard recording, the pH electrode is placed in adults, 5 cm above the lower esophageal sphincter under fluoroscopy. In children it may be placed about 3 to 5 cm above GE junction and the position be checked with a plain X-ray chest. The location of the tip of the probe should be at the third vertebra above the diaphragm. Patients are allowed normal diet and unrestricted activity for a 24 hr recording period. Parents are instructed to record activities and events like

eating, drinking, change of position and occurrence of symptoms and a symptom/activity diary is maintained. Data is collected in the recorder for 24 hours, then downloaded into a computer and finally graphic and numerical displays can be presented. It must be noted here that it is important to actually see the record to ensure absence of artifacts and to correlate with symptom diary. Only those episodes are relevant which are associated with occurrence of symptoms. Recordings of less than 24 hours are not that helpful.

Interpretation of 24 hours esophageal pH monitoring

- A pH of 4 is regarded as the cut-off level for acid GER

The standard parameters calculated are:

- Total number of episodes with a pH <4
- No. of episodes lasting >5 minute with a pH <4.0
- Percentage of time related to the total duration of the investigation with a pH <4 (reflux index).

In pH studies conducted with antimony electrodes, a RI >7 percent is considered abnormal, a RI <3 percent is considered normal, and a RI between 3 percent and 7 percent is indeterminate.^{1,16} In infants up to 18 months of age an RI of >10 is taken as abnormal.

The sensitivity and specificity is quoted as 87 to 93 percent and 93 to 97 percent respectively. In adult group of patients, the reproducibility of the test varies from 77 to 85 percent.^{17,18} It does not detect alkaline reflux.

The advantages of esophageal pH monitoring are that it detects episodes of acid reflux, determines association of acidic GER with symptoms, can assess the adequacy of anti-secretory treatment and helps to select those children with wheezing or respiratory symptoms in which acid reflux may be an aggravating factor. However, its disadvantages include nondetection of nonacidic or weakly acidic reflux episodes. In children with documented esophagitis, normal esophageal pH monitoring suggests a diagnosis other than GERD.

Wireless capsule pH monitoring is a relatively new modification of the conventional pH probe. It offers the advantage of being more patient friendly with greater comfort in carrying out daily activities. Moreover, it allows for a longer, 48 hours period recording.¹⁹ However, its limitations include an endoscopic placement, greater cost and variability in the records obtained on day1 and day 2.

Double lumen esophageal pH monitoring (where one port is placed higher—near the upper esophageal sphincter) allows demonstration of high reflux and is useful in correlating upper respiratory symptoms with Gastroesophageal reflux.

Motility Studies

Esophageal manometry measures esophageal peristalsis, upper and lower esophageal sphincter pressures, and the coordinated function of these structures during

swallowing. Although esophageal manometry has been an important tool in studying the mechanisms of GERD but GERD cannot be diagnosed by esophageal manometry. Manometric studies were critical in identifying TLESR (transient relaxation of lower esophageal sphincter) as a causative mechanism for GERD. Recent studies indicate that there is no role for manometry in predicting outcome of fundoplication. Manometric studies are also important in confirming a diagnosis of achalasia or other motor disorders of the esophagus that may mimic GERD. Esophageal manometry may be abnormal in patients with GERD, but the findings are not sufficiently sensitive or specific to confirm a diagnosis of GERD, nor to predict response to medical or surgical therapy. It may be useful in patients who have failed acid suppression and who have negative endoscopy to search for a possible motility disorder, or to determine the position of the LES to place a pH probe. It is also useful before planning a fundoplication.

Combined Multiple Intraluminal Impedance (MII) and pH Monitoring

Multiple intraluminal impedance (MII) is a relatively new procedure in which esophageal impedance tracings are analyzed for the typical changes in impedance caused by the passage of liquid, solid, gas, or mixed boluses. If the impedance changes of a liquid bolus appear first in the distal channels and proceed sequentially to the proximal channels, they indicate retrograde bolus movement, which is GER. The upward extent of the bolus and the physical length of the bolus can also be evaluated.²⁰ MII can detect extremely small bolus volumes.

MII and pH electrodes can and should be combined on a single catheter. The combined measurement of pH and impedance (pH/MII) provides additional information as to whether refluxed material is acidic, weakly acidic, or nonacidic. Evaluation of MII recordings is aided by automated analysis tools. Normal values for all of the age groups have not yet been established. The combination of pH/MII with simultaneous monitoring of symptoms using video-polysomnography or manometry has proven useful for the evaluation of symptom correlations between reflux episodes and apnea, cough, other respiratory symptoms, and behavioral symptoms.²¹ The technology is especially useful in the postprandial period or at other times when gastric contents are nonacidic.

Tests on Ear, Lung and Esophageal Fluids

Finding of lipid-laden macrophages in bronchoscopically obtained alveolar aspirate (BAL) suggests aspiration of gastric contents and can be related to presence of GERD.

Recent studies have suggested that finding pepsin, a gastric enzyme, in middle ear effusions of children with chronic otitis media, indicates that reflux is playing an etiologic role.²² However, this relation has not been validated in controlled treatment trials.

Empiric Trial of Acid Suppression as a Diagnostic Test

In adults, empiric treatment with acid suppression (usually with proton pump inhibitors like Omeprazole), without diagnostic testing, has been used for symptoms of heartburn, chronic cough, noncardiac chest pain, and dyspepsia. However, empiric therapy has only modest sensitivity and specificity as a diagnostic test for GERD, depending upon the comparative reference standard used (endoscopy, pH monitoring, symptom questionnaires),²³ and the appropriate duration of a “diagnostic trial” of acid suppression has not been determined. The 2-week “PPI test” lacks adequate specificity and sensitivity for use in clinical practice. In an older child or adolescent with symptoms suggesting GERD, an empiric PPI trial is justified for up to 4 weeks. Improvement following treatment does not confirm a diagnosis of GERD because symptoms may improve spontaneously or respond by a placebo effect.

When to Perform Diagnostic Tests

There is no unanimity on the indications for undertaking diagnostic evaluations for suspected GERD. In general, infants with just regurgitations or vomiting and continuing to gain weight do not need any investigations unless danger signs are present as mentioned earlier. Generally agreed indications for undertaking diagnostic evaluation for GERD are mentioned in Table 4.

Generally, in children younger than 2 years, the indications for work up/investigations for GER include situations where complications of GERD are suspected clinically. These may include a generally unhappy baby, irritability during and after feeds, persistent vomiting, recurrent pneumonias, chronic cough, or a child who is failing to thrive.

Similarly, in children older than 2 years, there are certain features that may warrant investigations for GER. These include persistence of vomiting since the child was less than 2 years, new onset vomiting, or heartburn not responsive to 4 weeks of medical therapy. Investigations are also called for in cases where there is a suspicion of complications of GER such as undiagnosed anemia, dysphagia, odynophagia, recurrent pneumonias and nonseasonal asthma.

Which Test to Perform?

It is advisable in such a scenario, to allow clinical presentation to dictate the diagnostic approach. For instance, in case of persistent vomiting or dysphagia, anatomical causes or severe esophagitis are to be investigated, preferably through barium studies and EGD. Alternatively, if the clinical presentation is in the form of wheezing, apnea, or recurrent pneumonia, investigation into such being secondary to reflux are advisable, with pH monitoring and nuclear scans. If seizure like activities are observed, especially with normal EEGs, it may be advisable to investigate the factum of reflux with pH monitoring and videographic recording. Lastly, if the presentation is of a feeding problem with a persistent failure to thrive, or persistent or recurrent anemia, reflux esophagitis should be investigated through an EGD along with biopsy.

Evaluation of Children with Recurrent Respiratory Symptoms and Suspected GER

Some of the children with chronic, persistent asthma may have an underlying GER and may benefit from therapy aimed to decrease acid reflux. However, as only a small number of asthmatic children benefit from GER therapy, it is important to carefully select patients for GERD evaluation and management (Flow chart 2).

While investigating possible causes of recurrent pneumonia and suspected GER, it is advisable to exclude other potential causes, such as anatomical abnormality, aspiration during swallowing, foreign body, cystic fibrosis or immunodeficiency, neurological impairments, etc. Tests useful in differentiating cases of recurrent pneumonia and suspected GER with these others, include flexible bronchoscopy with BAL for lipid-laden alveolar macrophages, nuclear scintigraphy, VSS (video fluoroscopic swallowing study), or FEEST (flexible endoscopic evaluation of swallowing with sensory testing), the latter two being useful for effectively evaluating airway protective mechanisms.

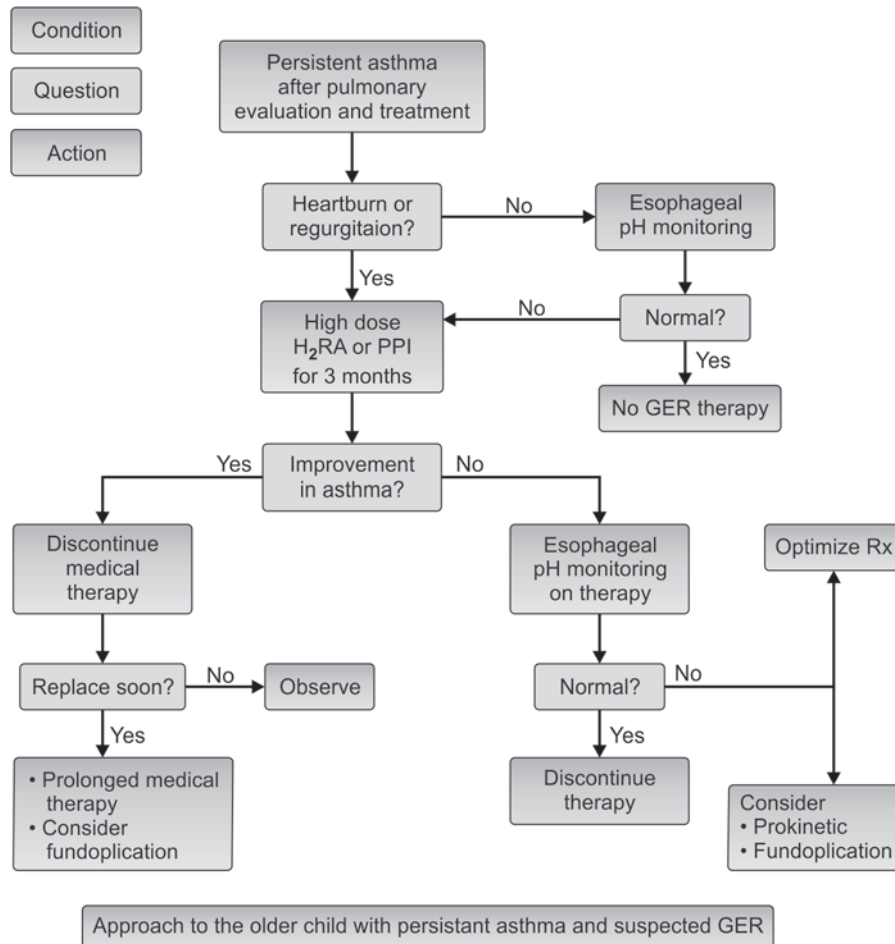
Management of (Physiological) GER

Regurgitation or vomiting of feeds is very common in infants being present in more than 70 percent infants. It reaches its peak at about 3 to 4 months of age and then gradually declines. This does not affect the health of infants and apart from causing nuisance to mother it causes no harm to the infant. As such therefore, it does not require any specific treatment/management. Mothers need to be reassured and the infant followed up for adequate weight gain. Advice regarding burping should be given and may help in decreasing visible vomiting.

However, if the mother is really concerned then non-pharmacological methods of management can be tried. These include changes in posture and thickening of feeds.

Table 4: Indications for undertaking diagnostic evaluation for GERD

- Uncertain diagnosis
- Atypical symptoms
- Symptoms associated with complications
- Inadequate response to therapy
- Recurrent symptoms
- Prior to anti-reflux surgery

Flow chart 2: Simplified approach to diagnosis in an older child with asthma and suspected to have GER

Positioning Therapy for Infants

Several studies in infants have demonstrated significantly decreased acid reflux in the flat prone position compared with flat supine position.^{24,25} However, there are significant concerns regarding the association of SIDS with the prone position and therefore, prone position is recommended only in the awake infant who can easily be observed and specially in the postprandial period. During sleep, only the supine position is recommended unless the infant has certain upper airway disorders where the risk of death from GERD may outweigh the risk from SIDS.

Also, to be noted is the fact that the amount of reflux in supine infants with head elevated is equal to or greater than in infants supine and flat.^{24,25}

The semi-supine positioning as attained in an infant car seat exacerbates GER.²⁴ Although the full upright position appears to decrease measured reflux, one study suggested that using formula thickened with rice cereal is more effective in decreasing the frequency of regurgitation than upright positioning after feeds.²⁶

In older children, the left lateral position with head high is considered effective and better than the supine position for the management of reflux.

Feeding Changes in Infants

Breast-fed and formula-fed infants have a similar frequency of physiologic GER, although the duration of reflux episodes measured by pH probe may be shorter in breast-fed infants. In any case, most breast-fed infants can be safely managed on advise to be burped adequately, if required, to be done also in the middle of feeding in addition to be done at the end of feeding and before returning the baby to the bed. Physiological GER should never become an indication to change to formula feeding.

Top fed infants with physiological GER, may benefit with thickening of feeds. Rice cereal is a good thickening agent. Adding thickening agents such as rice cereal to formula does not decrease the time with pH < 4 (reflux index) measured by esophageal pH studies, but it does decrease the frequency of overt regurgitation.^{27,28} Rice cereal is the most commonly used thickening agent for formula. Thickening a 20-kcal/oz infant formula with 1 tablespoon of rice cereal per ounce increases the energy density to ~34 kcal/oz (~1.1 kcal/mL). Thickening with 1 tablespoon per 2 oz of formula increases the energy density to ~27 kcal/oz (~0.95 kcal/mL). Although the actual number of esophageal reflux episodes may not decrease, the reduction in

regurgitation may be a welcome improvement in quality of life for caregivers.

A subset of top fed infants with allergy to cow's milk protein experience regurgitation and vomiting indistinguishable from that associated with physiologic GER. In these infants, vomiting frequency decreases significantly (usually within 2 weeks) after the elimination of cow's milk protein from the diet, and reintroduction causes recurrence of symptoms. Breast-fed infants with regurgitation and vomiting may benefit from a trial of withdrawal of cow's milk and eggs from the maternal diet.

Lifestyle Changes in Children and Adolescents

Current evidence generally does not support (or refute) the use of specific dietary changes to treat reflux beyond infancy. Expert opinion suggests that children and adolescents with GERD should avoid caffeine, chocolate, alcohol, and spicy foods if they provoke symptoms. In an overweight individual, weight loss does decrease reflux, and is therefore recommended. Smoking should be avoided in those with GERD because it has been linked to adenocarcinoma of the esophagus in adults. Some studies have shown that chewing sugarless gum after a meal decreases reflux.²⁹

Pharmacologic Therapies

Prokinetics

Prokinetics are a group of drugs, which decrease esophageal motility, increase LES pressure and increase gastric emptying. Thus, they counter the pathophysiological mechanisms of reflux. Although a number of prokinetic agents are available in the market, none of them has been proven to be effective and safe.

Available prokinetic agents include dopamine receptor blockers (Metoclopramide, Domperidone); serotonin receptor (5HT₃,4) agonists (Cisapride, Mosapride), and drugs with both effects (Itopride).

Domperidone and metoclopramide are antidopaminergic agents that facilitate gastric emptying and also increase the LES tone. However, no RCT is available to demonstrate their clinical efficacy in children with GERD. They are poorly active and are associated with side effects like lethargy, irritability, gynecomastia, galactorrhea, and extrapyramidal reactions. They may be used for short-term but their long-term use is therefore not recommended.

Cisapride is a mixed serotonergic agent that facilitates the release of acetylcholine at synapses in the myenteric plexus, thus increasing gastric emptying and improving esophageal and intestinal peristalsis. Clinical studies of cisapride in children with GERD showed significant reduction in the RI but with less consistent reduction in symptoms.³⁰ However, cisapride was found to produce prolongation of the QTc interval on electrocardiogram, a finding increasing the risk of sudden death, its use has

become restricted. Moreover, it is not recommended to be used along with some other drugs like macrolides, antifungals, and antivirals that are also metabolized through cytochrome P450. Mosapride on the other hand has a better safety profile (than cisapride) vis a vis cardiac arrhythmias and shows no interaction with other cytochrome P 450 inhibitors like macrolids, antifungals, antivirals, etc. Although used commonly in adults, its dose and use in children is not yet clearly defined. Also no RCT is yet available regarding its efficacy and safety in children.

Other prokinetic drugs like bethanechol³¹ (a direct cholinergic agonist), erythromycin (a dopamine receptor antagonist) have uncertain efficacy and a high incidence of side effects limiting their use in clinical practice.³³

Baclofen, a γ -amino-butyric-acid receptor agonist, reduces both acidic and nonacidic reflux and also increases gastric emptying in children. However, it has unacceptable side effects like drowsiness, dizziness, fatigue and lowers seizure threshold that preclude its routine use.¹

Histamine-2 Receptor Antagonists (H2RA)

Histamine-2 receptor antagonists (H2RAs) decrease acid secretion by inhibiting histamine-2 receptors on gastric parietal cells. Gastric pH begins to increase within 30 minutes of administration and the effect lasts for 6 hours. Tachyphylaxis or diminution of the response has been observed after 6 weeks of administration of H2RA drugs, hence their long-term use is not recommended. Also, the efficacy of H2RA in achieving mucosal healing is greater in mild esophagitis than in severe esophagitis. It is therefore, suggested that H2RA maybe used in older children and adolescents for the treatment of GERD symptoms and for healing esophagitis although H2RA are less effective than PPI for both symptom relief and healing of esophagitis.³²

Side effects of H2RA in infants include irritability, head banging, headache, and somnolence. The commonly used H2RA include Ranitidine, Famotidine, Cimetidine and Nizatidine. The usual dose of Ranitidine is 2 mg/kg/day in 2 divided doses.

Proton Pump Inhibitors

Proton pump inhibitors (PPIs) inhibit acid secretion by blocking Na⁺-K⁺-ATPase, the final common pathway of parietal cell acid secretion, often called the proton pump. The superior efficacy of PPIs is largely because of their ability to maintain intragastric pH at or above 4 for longer periods and to inhibit meal-induced acid secretion, a characteristic not shared by H2RAs. In contrast with H2RAs, the effect of PPIs does not diminish with chronic use. The potent suppression of acid secretion by PPIs also results in decrease of 24-hour intragastric volumes, thereby facilitating gastric emptying and decreasing volume reflux.^{32,33} Side effects of PPIs include constipation, diarrhea, dizziness, headache and their long-term use may be associated with side effects of acid

suppression like malabsorption of nutrients and drugs and microbial overgrowth.

PPIs currently approved for use in children are omeprazole, lansoprazole, and esomeprazole. No PPI has been approved for use in infants younger than 1 year of age. The dose of omeprazole is 1 to 3.3 mg/kg/day given once or divided twice a day. That of lansoprazole is 1.4 mg/kg/day OD. In clinical trials they have proved to be equally efficacious. Ease of administration of lansoprazole in young children, with the availability of easily dissolvable tablets makes it a preferred drug for them.

Other Agents

Antacids directly buffer gastric contents, thereby reducing heartburn and healing esophagitis. On-demand use of antacids may provide rapid symptom relief in some children and adolescents with NERD. Although, this approach appears to carry little risk, long-term use of antacids containing aluminum hydroxide is associated with side effects like increased plasma aluminum levels and those containing calcium carbonate with milk alkali syndrome (a triad of hypercalcemia, alkalosis and renal failure). Moreover, these agents have a short duration of action and need to be given 3 to 4 times a day. These agents therefore, have limited use and are beneficial only for immediate relief in older children and adolescents on a need basis. Their routine or long-term use in the management of GERD is not recommended.¹

Surface protective agents mostly comprise of alginate or sucralfate. Alginates are insoluble salts of alginic acid, a component of algal cell walls. Sucralfate is a compound of sucrose, sulfate, and aluminum, which, in an acid environment, forms a gel that binds to the exposed mucosa of peptic erosions. Although these agents have shown to be effective in decreasing symptoms and healing of nonerosive esophagitis in adults, the available data of their safety and efficacy in children is inadequate to warrant their routine use in the management of GERD in children.

Supplementary Feedings

Infants with GERD who are unable to gain weight despite conservative measures (and pharmacological treatment) and in whom nasogastric or nasojejunal feeding may be beneficial are rare. Similarly, nasojejunal feeding is occasionally useful in infants with recurrent reflux-related pneumonia to prevent recurrent aspiration.

SURGICAL THERAPY

Fundoplication decreases reflux by increasing the LES baseline pressure, decreasing the number of TLESRs and the nadir pressure during swallow-induced relaxation, increasing the length of the esophagus that is intra-abdominal, accentuating the angle of His, and reducing an HH if present.³⁴ Fundoplication usually eliminates

reflux, including physiologic reflux. Fundoplication does not correct underlying esophageal clearance, gastric emptying, or other GI dysmotility disorders.¹

Surgical treatment of gastroesophageal reflux should be considered for the following patients:

- Infants and children who have failed medical therapy for gastroesophageal reflux (typically over 12 week) and those who cannot be weaned off of acid-reducing medications
- Those with an atypical presentation, especially respiratory, whose symptoms are clearly associated with gastroesophageal reflux (e.g. obstructive apnea temporally associated with reflux during pH monitoring. However, a period of medical therapy (including acid blockade) under close monitoring conditions should be attempted in many cases prior to recommending a surgical approach
- Patients with complications of gastroesophageal reflux, such as aspiration, stricture of the esophagus, or Barrett esophagus should be considered for surgical treatment
- Patients with neurologic impairment that requires feeding gastrostomy who are found to have pathologic reflux and remain medication dependent should also be considered for surgery.
- Patients with chronic reflux and recurrence of anastomotic stricture after repair of esophageal atresia should be considered for surgical treatment.

A large open RCT compared the efficacy and safety of laparoscopic fundoplication versus esomeprazole (20 mg q.i.d) for treatment of adults with GERD.³⁵ Short-term outcomes were reported in an interim analysis of data at 3 years. More than 90 percent of both the surgically and medically treated adults showed good to excellent symptom control; 10 percent of the surgical group had dysphagia whereas dysphagia was uncommon in the medically treated group. Quality of life measures were similar in both groups.³⁵

SUMMARY

While gastroesophageal reflux is very common in infants in first 6 months of life, in most it is self-limiting. At this age it is important to consider and exclude other, more ominous, causes of vomiting. Infants with GER, who continue to gain weight adequately, require no investigations or management. Diagnosis of GERD is essentially clinical, based on high index of suspicion and careful analysis of myriad of signs and symptoms present in the child. Investigative modality should be carefully selected depending on the age of the child and type of symptom complex. Medical management with prokinetics and or acid suppression therapy is helpful in most of the cases. PPIs are the most useful acid suppression drugs which can be used over a long period of time safely. Surgery is rarely required unless there is an underlying anatomical abnormality.

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Pediatric Liver Transplantation

Nishant Wadhwa

INTRODUCTION

Liver transplantation (LT) has been very successful in treating children with end-stage liver disease, and offers the opportunity for a long-term healthy life. The survival rates have improved significantly over the last decade mainly due to the advances made in the surgical techniques, better postoperative care and newer immunosuppressive drugs.¹ The improved results have also led to an increasing awareness of this treatment modality in the developing world with successful LT having been reported in both adults and children from various centers across India. The history of pediatric liver transplantation across the globe has clearly shown that success is dependent on strict and integrated collaboration between referring pediatricians, pediatric transplant hepatologists, transplant surgeons, nurses, transplant coordinators, psychologists and social workers.

INDICATIONS

The main indications for LT are listed in Table 1. Biliary atresia constitutes the most common indication for LT in the pediatric age group world over.² Most of these infants usually have undergone a Kasai's procedure, which has failed or have been diagnosed late in the course of the disease when cirrhosis has already set in, thus requiring a transplant as a primary procedure. In conditions such as Bile duct paucity, progressive familial intrahepatic cholestasis, LT is indicated to eliminate severe debilitating symptoms such as pruritis and associated failure to thrive and poor quality of life. Children affected with these diseases are also at a higher risk of developing liver carcinoma.³

Metabolic diseases are the second most common indication for LT. These are divided in two groups depending on the presence or absence of structural damage to

the liver. In the first group are diseases such as Wilson's disease, tyrosinemia, which have a potential to progress to end stage liver failure and acute liver failure. Diseases such as Crigler-Najjar syndrome-I, ornithine transcarbamylase (OTC) deficiency, LT helps restore the deficiency of single enzyme leading to normal life expectancy. In Primary hyperoxaluria type-I, combined liver and kidney transplantation is considered when irreversible kidney damage from oxalic acid accumulation has developed.^{4,5} While liver transplantation has been suggested for organic acidemia, LT in these diseases does not correct the enzyme deficiency in other organs besides liver. Although the quality of life is improved, the patients remain at risk of severe extrahepatic disease complications.⁶

Children in acute liver failure (ALF) constitute an important subgroup who benefit immensely with a LT. There are specific criteria laid down for identifying children with ALF in whom survival is unlikely without LT (Tables 2 and 3). There are separate criteria for Acetaminophen induced liver failure and nonacetaminophen induced cases.⁷ The positive predictive value of these criteria in predicting mortality in the absence of LT has been 70 to 100 percent in various studies.

Hepatoblastoma is the most common liver tumor in children and, when nonresectable, is an indication for total hepatectomy and liver transplantation. Children with hepatoblastoma are initially treated with chemotherapy and then evaluated for resection or transplantation. Hepatocellular carcinoma in children is rare and is often secondary to congenital liver disease. The development of hepatocellular carcinoma has been reported in biliary atresia, Alagille's syndrome, progressive intrahepatic cholestasis. In children with tyrosinemia, there is a 33 percent incidence of hepatocellular carcinoma before 2 years of age.

CONTRAINDICATIONS

The following are the contraindications to LT in children:

- Nonresectable extrahepatic malignant tumor
- Concomitant end-stage organ failure that cannot be corrected by a combined transplant
- Uncontrolled sepsis
- Irreversible serious neurological damage.

PRETRANSPLANT EVALUATION

The primary goal of the evaluation process is to identify appropriate candidates for liver transplantation and to establish a pretransplantation plan. Liver transplantation is a life saving procedure and is opted for in a situation when all other modes of therapy are redundant and found ineffective. Hence, a thorough assessment prior to a transplant is a must. The aim of this assessment is:

- To confirm the diagnosis and severity of disease
- To define the patients general medical status
- To determine eligibility and priority for transplant
- To exclude contraindications to transplantation
- To identify active infections and assess the immunological status of the child
- To rule out cardiac malformations that might need to be corrected before transplantation
- To arrange interim supportive care
- To establish a pretransplant therapeutic plan: immunizations, when possible, nutritional support to optimize growth, dental care.

Table 1: Indications for LT in children

Extrahepatic cholestasis	Biliary atresia
Intrahepatic cholestasis	Nonsyndromic bile duct paucity
	Progressive intrahepatic cholestasis (PFIC)
	Syndromic bile duct paucity (Alagille's syndrome)
Metabolic diseases	Wilsong's disease
	Tyrosinemia
	Inborn errors of bile acid metabolism
	Disorders of urea cycle
	Primary hyperoxaluria type-I
	Organic acidemia
	Disorders of carbohydrate metabolism
	Crigler-Najjar syndrome type-I
Acute liver failure	
Others	Primary liver tumor
	Cystic fibrosis

- To inform parents about the transplantation procedure and on the post-transplantation period in order to motivate and prepare them to accept and deal with all issues and possible complications of the procedure.
- To assess the socioeconomic and educational status of the family and evaluate logistic issues.

Hepatic function is assessed by measurement of albumin and prothrombin time (synthetic function) and bilirubin, transaminases, alkaline phosphatase and gamma-glutamyl transpeptidase. Doppler ultrasonography and/or MR or conventional angiography is used to delineate the vascular anatomy. A nutritional, developmental, cardiac and dental assessment is performed in all children. Serological examination is performed to document immunity to viral pathogens, important ones being CMV, EBV, HSV I and II. The important aspects of preparation are:

NUTRITIONAL REHABILITATION

The preoperative nutritional status has an important bearing on the post-transplant outcome of the child. Modular feeds allowing protein, carbohydrate and fat content to be individually prescribed for each child are recommended. In children with chronic liver disease optimum nutritional status may sometimes be achieved only by nasogastric/nasojejunal feeds including night-time feeds.

IMMUNIZATION

A complete immunization history of the child is a must. Any pending vaccines need to be expatiated prior to transplant ensuring that all the live vaccines have been

Table 2: King's college criteria for non-acetaminophen induced ALF

- PT >100 seconds irrespective of coma grade OR
- Any three of the following, irrespective of coma grade:
- Drug toxicity, indeterminate cause of ALF
 - Age <10 years or >40 years†
 - Jaundice to coma interval >7 days
 - PT >50 seconds (INR >3.5)
 - Serum bilirubin >17.5 mg/dl

Table 3: King's college criteria for acetaminophen induced ALF

- Arterial pH <7.3 (following adequate volume resuscitation) irrespective of coma grade OR
- PT >100 seconds (INR >6.5) + serum creatinine >3.4 mg/dl in patients in grade III/IV coma

administered at least six weeks prior to the transplant in all children with chronic liver disease. However in children undergoing emergency liver transplantation, completing the immunization with live vaccines is not possible.

TREATMENT OF HEPATIC COMPLICATIONS

Ascites and fluid retention is managed by restricted sodium and fluid intake and the use of diuretic therapy. Bleeding varices are treated with intravenous somatostatin or octreotide, endoscopic band ligation or transjugular intrahepatic portal shunts. It is preferable to employ band ligation instead of sclerotherapy because of the potential risk of portal vein thrombosis and ulceration. Hepatic encephalopathy is treated by low-protein diet and oral lactulose. The role of branched chain amino acids remains controversial and use of extracorporeal liver assist devices as a bridge to transplantation is not yet fully established in children.

COUNSELING

Education and counseling of the family and the child is of paramount importance to sustain them through the stressful procedure, the prolonged postoperative period and the life-long immunosuppressive therapy with its attendant risks and side effects.

DONOR SELECTION

Most of the transplantation in developing countries like India constitutes. Living related transplants (LDLT) due the poor availability of cadaver organs. While a lot has been done to increase awareness on organ donation, LDLT continues to be the way forward. In living-donor transplantation, the evaluation and selection of a donor, usually a parent or first-degree relative is performed on the assumption that donor safety can be assured and that the donor's liver function is normal. Donors should be 18 to 55 years of age, and have an ABO-compatible blood type. Following a satisfactory medical and psychological examination by physicians who are not directly involved with the transplantation program, vascular imaging is performed to assess the hepatic arterial anatomy. Donor safety has been excellent in all living donor series.

PROCEDURE

The first description of the procedure in which segments 2 and 3 were procured from a living donor (the mother), and transplanted in a child affected by biliary atresia, dates back to 1988.^{8,9} Living-related liver transplants soon came to account for a substantial number of pediatric cases performed in many centers throughout the world, and the only possibility for liver transplants in countries where cadaveric organ procurement was not allowed until just a few years ago.¹⁰

Living-related liver transplantation has been widely debated with regard to the ethics of performing major surgery on a healthy person. The validity of this procedure is broadly recognized, and over 1200 cases have been performed worldwide, with a donor mortality and morbidity of approximately 0.2 and 10 percent, respectively. Morbidity relates mainly to biliary fistulas, incisional hernias, and bleeding. In the majority of cases, living-related transplants register an excellent outcome for pediatric recipients, thanks to the possibility of performing the transplant before the child's clinical condition deteriorates. Centers with most experience in this area report survival rates between 80 and 90 percent after 1 year.¹¹⁻¹⁶

Postoperative Care

The care of a child after liver transplantation involves a dedicated transplant team. Main issues revolve around graft function in the postoperative period [PT (INR), PTT and other liver function tests] in addition to maintenance of hemodynamic parameters, intake output, abdominal drain output, biliary output and oxygenation to ensure adequate blood flow to liver graft. Strict aseptic precautions must be followed in caring for transplant patients.

Primary nonfunction must be closely monitored for in the first 24 hours (rising transaminases, profound hypoglycemia and acidosis, coagulopathy, oliguria) requiring emergency retransplantation. Hyperacute rejection is rare but can occur (humoral rejection). Five to twenty percent patients will have vascular occlusion with associated graft loss. Vena cava, portal vein and more commonly hepatic artery may get occluded by intramural thrombus, or less commonly by extrinsic compression or vessel kinking. Vessels smaller than 3 mm diameter tend to have higher incidence of arterial thrombosis. Signs and symptoms consist of hepatic failure, increased transaminases and bilirubin levels with worsening coagulopathy. Portal thrombosis presents with fulminant necrosis, intestinal edema with ascites. Doppler ultrasonography and angiography are useful tools. Bile leak and postoperative bleeding must be closely monitored. Early nutrition is important.

About 20 to 50 percent of patients develop at least one episode of acute rejection in the first weeks after liver transplantation. The clinical picture of rejection includes fever, irritability, malaise, leukocytosis, often with eosinophilia, and increased γ -GT, bilirubin, and transaminases. A liver biopsy is required to confirm rejection. The histological triad of endothelialitis, portal triad lymphocyte infiltration with bile duct injury, and hepatic parenchymal cell damage characterizes acute rejection.¹⁷

The primary treatment of rejection is a short course of high-dose steroids. Bolus doses administered over a 3 to 6 day period with a rapid taper to baseline therapy are successful in the majority of cases. When refractory or recurrent rejection occurs, conversions from cyclosporine

to tacrolimus, or antilymphocyte therapy using the monoclonal antibody, ornithine-ketoacid transaminase orthoclone, have been successfully used.^{18,19}

The usual immunosuppressive regimen consists of Calcineurin inhibitors—Cyclosporine or Tacrolimus and prednisolone along with Mycophenolate mofetil (MMF). Tacrolimus based immunosuppression is preferred as it has been associated with less acute rejection and better long-term graft survival rates.

Duration of mechanical ventilation in transplant recipient depends upon age and preoperative condition of the patient. A child with fulminant hepatic failure may require a longer duration of ventilation depending on the neurological state. On the other hand, patients with normal pulmonary function preoperatively may require short-term or no ventilation. Infants and small children are more likely to need postoperative ventilation.

Ventilatory management aims at avoiding the respiratory complications of atelectasis, effusions and pneumonia. Some smaller patients may require a higher end expiratory pressure to compensate for a distended abdomen pushing onto the diaphragm. In a single center series the mean time to extubation was 11.1 ± 15 hours and the mean duration of ICU stay was 7.2 ± 5.5 days.²⁰ Pain control is commonly achieved by opioid infusions titrated to effect. Judicious use of muscle relaxants might be needed. Atracurium (a nondepolarizing muscle relaxant metabolized by nonenzymatic hydrolysis (Hoffman elimination) can be safely used. General principles of respiratory care apply in all mechanically ventilated patients.

Close monitoring, early detection and treatment of complications remains the key to success in addition to supportive management by the liver transplant team.

Immunosuppressive drugs used to prevent rejection inhibit activation of T lymphocytes, medullar cell proliferation and macrophage function, therefore creating an optimal environment for the development of infections. Infectious complications represent a common source of morbidity and mortality after transplantation. Bacterial infections occur in the immediate post-transplantation period and are most often caused by Gram-negative enteric organisms, enterococci, or staphylococci. Replacing or removing all of the intraoperative lines soon after transplantation can minimize sepsis originating at sites of invasive monitoring lines. The use of prophylactic antibacterial antibiotics is discontinued as soon as possible to avoid the development of resistant organisms.

Early and severe viral infections are caused by viruses of the herpes family, including Epstein-Barr virus (EBV), cytomegalovirus (CMV), and herpes simplex virus.²¹ The risk of developing either CMV or EBV infection is influenced by the preoperative serological status of the transplant donor and recipient.^{22,23} Seronegative recipients receiving seropositive donor organs are at greatest risk. Various prophylactic protocols, including intravenous IgG

and hyperimmune anti-CMV IgG, associated with acyclovir or ganciclovir have been used to decrease the incidence of symptomatic CMV and EBV infection, although seroconversion in naive recipients inevitably occurs.^{22,24} The suspicion of CMV infection is suggested by the presence of fever, leukopenia, maculopapular rash and hepatocellular abnormalities, respiratory insufficiency, or gastrointestinal hemorrhage. Hepatic biopsy or endoscopic biopsy of colonic or gastroduodenal sites allows early diagnosis with immunohistochemical recognition. Nowadays, the availability of specific antiviral drugs like ganciclovir, foscarnet and more recently valaciclovir, have radically modified the prognosis of CMV infection.

Herpes simplex virus infections, similar to those seen in nontransplant patients, require treatment with acyclovir when diagnosed. EBV infection represents a potential risk for the pediatric transplant recipient. EBV infection has a variable clinical picture including a mononucleosis-like syndrome, hepatitis-simulating rejection, extranodal lymphoproliferative infiltration, peritonitis or lymph node enlargement, or encephalopathy. Monitoring of EBV blood viral load by quantitative polymerase chain reaction (PCR) is the best predictor of risk. When evidence of active infection exists, an acute reduction in immunosuppression is mandatory. Other post-transplantation infectious complications include adenovirus hepatitis, varicella, and enterovirus induced gastroenteritis. *Pneumocystis carinii* infection has been nearly eliminated by the prophylactic administration of sulfisoxazole and trimethoprim or aerosolized pentamidine.

Outcome Following LT

The overall results following LT are rewarding. The European Liver Transplantation Registry (ELTR) reports liver transplantation activity in Europe, and represents 5895 children transplanted between 1988 and 2005. Overall 1 year patient and graft survival was 84 and 73 percent, respectively, in patients older than 2 years at the time of transplantation, and 81 and 71 percent, respectively, in children <2 years of age. Ten-year patient and graft survival rates for the same age groups were 75 and 61 percent, and 74 and 60 percent, respectively. Similarly, united network for organ sharing in America (UNOS) reported survival rates of the 9064 pediatric patients transplanted between 1997 and 2004. Overall 1 year patient and allograft survival reported to the studies of pediatric liver transplantation (SPLIT) registry, representing 1611 patients, reached 88 and 82 percent, respectively, while these were 83 and 74 percent, respectively, 4 years after transplantation. Specific factors influencing early survival include age, diagnosis, severity of illness, and possibly allograft type.²⁵

In India the first successful pediatric LT was performed in the year 1998. Subsequently more than 150 liver transplants have been performed at various centers

across the country. At present the success rates reported are comparable to the best centers in the west.^{26,27} The surgical expertise gained over the last few years combined with the advancements made and lessons learnt in the medical management have contributed in a big way to this achievement.

However, there is a paucity of reliable cadaver organ supply, primarily due to low awareness about organ donation. This has necessitated the development of living related liver transplantation in a big way. With an appropriate brain death law already in place, sufficient public and professional education is needed to develop cadaver donation. However, with excellent results of LDLT's, this problem is somewhat offset till the time there is more awareness and acceptability towards organ donation in India. The faith and support of the medical fraternity and the public at large has helped in making LT a practically feasible and economically viable treatment modality.

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INTRODUCTION

Acute liver failure (ALF) in children is a devastating multi-organ syndrome characterized by sudden and severe liver cell dysfunction in a previously healthy child. This catastrophic illness can rapidly progress to coma and death due to cerebral edema and multiorgan system failure. Excellent intensive care is critical in management of patients with ALF. All pediatric health care providers must be aware of this entity, because early identification and immediate initiation of appropriate supportive therapy will maximize potential for recovery.

There have been recent elaborate reviews and publications on the causal factors, diagnosis, and management of this complex and life-threatening syndrome. In this chapter, we summarize these changes and explain the present best approach to its management.

DEFINITION AND CLASSIFICATION

Since the initial definition of FHF by Trey and Davidson 30 years ago,¹ several classifications have been proposed (Table 1). However, none of these systems have been accepted universally, and overlap in terms and time intervals among them is a source of obvious confusion.

The pediatric acute liver failure (PALF) study group was formed in 2000 as a multisite, multinational consortium to prospectively study ALF in children from birth up to 18 years of age.^{2,3} A consensus reached by 21 PALF investigators defined liver failure as:

- No evidence of a known chronic liver disease
- Hepatic-based coagulopathy that is not corrected within 8 hours by parenteral administration of vitamin K
- Hepatic encephalopathy must be present if the uncorrected prothrombin time (PT) or international

Table 1: Definitions and classifications of acute liver failure

<i>Trey and Davidson</i> ¹	<i>Fulminant hepatic failure: development of HE within 8 weeks of onset of symptoms</i>
<i>O'Grady et al London</i> ⁴ (includes only patients with encephalopathy)	<i>Subclassification depending on the interval between jaundice and HE</i> <i>Hyperacute liver failure: 0 to 7 days</i> <i>Acute liver failure: 8 to 28 days</i> <i>Subacute liver failure: 29 to 72 days</i> <i>Late-onset acute liver failure: 56 to 182 days</i>
<i>Bernuau et al Paris</i> ⁵	<i>Severe acute hepatic failure: Prothrombin time or factor V concentration below 50% of normal with or without HE</i> <i>Subclassification</i> <i>Fulminant hepatic failure: HE within 2 weeks of onset of jaundice</i> <i>Subfulminant hepatic failure: HE between 3 and 12 weeks of onset of jaundice</i>
<i>International Association for the study of the liver</i> ⁶ (occurrence of HE within 4 weeks after onset of symptoms)	<i>Subclassification</i> <i>Acute liver failure—hyperacute: within 10 days</i> <i>Acute liver failure—fulminant: 10 to 30 days</i> <i>Acute liver failure—not otherwise specified</i> <i>Subacute liver failure—development of ascites and/or HE from 5 to 24 weeks after onset of symptoms</i>

FHF—fulminant hepatic failure; HE—hepatic encephalopathy.

normalized ratio (INR) was between 15 and 19.9 seconds or 1.5 to 1.9, respectively

- Hepatic encephalopathy was not required if the PT or INR was greater than or equal to 20 seconds or 2.0, respectively.

This definition is different from adults, as encephalopathy is not necessary because in infants early stages of encephalopathy are difficult to assess, and encephalopathy may not be apparent until terminal stages of ALF.

Also there has been confusion regarding the term used to denote this disease entity like fulminant hepatic failure and fulminant hepatitis or necrosis. It has now been recommended that acute liver failure is a better overall term which includes all durations up to 26 weeks.³

ETIOLOGY AND EPIDEMIOLOGY

ALF can be classified into seven categories: metabolic, infective, toxic, autoimmune, malignancy-induced, vascular-induced, and undetermined. In infants, metabolic disease is the most frequent cause of FHF, whereas in

children, viral FHF is most frequently seen. Whatever the age, undetermined FHF is frequently observed (Table 2).

In the largest study on acute liver failure in children, the pediatric ALF database till December 2006 has enrolled 548 cases, 38 percent of which occurred in children less than 3 years of age. Etiologies were: acetaminophen overdose in 12 percent of cases, metabolic causes in 10 percent of cases, viral hepatitis in 6 percent of cases, ischemia in 4 percent of cases, nonacetaminophen drug-induced liver injury in 4 percent of cases, and other causes in 15 percent of cases; 49 percent were considered indeterminate. While in Indian studies infectious hepatitis is the most important cause of ALF in majority of the cases⁷⁻¹¹ (Table 3).

PATHOGENESIS

The specific pathogenesis of the liver injury is dependent to a large degree on the etiology. But hepatocellular injury is central to FHF, irrespective of the causative agent. The initial insult and interplay of cytokines lead to hepatocyte necrosis or apoptosis.¹²

Table 2: Diagnostic priorities of etiology of FHF by age

	<i>Infectious disease</i>	<i>Cardiovascular</i>	<i>Drugs/toxins</i>	<i>Metabolic/immune</i>
Infant	Herpes simplex Parvovirus Enterovirus EBV Hepatitis B Measles HHV-6	Asphyxia Myocarditis	Paracetamol overdose	Fatty acid defects Mitochondrial defects Galactosemia tyrosinemia Neonatal hemochromatosis Fructose intolerance Niemann-Pick type C
Child	Hepatitis A,B,C,D,E Leptospirosis EBV	Cardiomyopathy Budd-Chiari syndrome Myocarditis	INH Valproic acid Halothane Acetaminophen Vitamin A toxicity	Autoimmune disease Wilson's disease Leukemia Fatty acid oxidation defects Hemophagocytic syndrome Mitochondrial defects NK cell dysfunction
Adolescent	Hepatitis A,B,C,D,E Dengue fever	Congestive heart failure Heat stroke Shock	Acetaminophen MAO inhibitor Tetracycline Mushroom poisoning	Wilson's disease Autoimmune disease Fatty liver of pregnancy Protoporphyrria

EBV—Epstein-Barr virus; INH—isoniazid; Hep—hepatitis; MAO—monoamine oxydase.

Table 3: Indian studies on children with acute liver failure

<i>Year of study</i>	<i>Place of study</i>	<i>n</i>	<i>Etiology being infectious hepatitis</i>
1996	AIIMS, New Delhi	n = 40	75%
1999	Pune	n = 36	61%
2002	Chandigarh	n = 67	94%
2004	SGRH, New Delhi	n = 32	62%
2007	Kolkata	n = 45	66%

An important feature of acute liver injury is the general loss of Kupffer cell function that results in reduced clearance of endotoxin and other substrates regularly presented to hepatocytes by means of the portal system, thus increasing the risk of infection and inflammation.¹³

The site of injury in the liver plays an important role in determining the ability of the liver to regenerate. Arterial blood and portal blood rich in oxygen and nutrients are supplied in the portal tract where the liver progenitor cells, ductal hepatocytes, or oval cells are present. Injury to the portal zone inhibits the regenerative response, while injury to the central zone with sparing of the portal zone permits more frequent spontaneous recovery.¹⁴

With severe hepatocellular injury, liver metabolic functions are impaired. Patients have compromised glucose homeostasis, increased lactate production, impaired synthesis of coagulation factors, and reduced capacity to eliminate drugs, toxins, and bilirubin. As a result, patients develop coagulopathy, hypoglycemia, and acidosis, all of which increase the risk of gastrointestinal bleeding, seizures, and myocardial dysfunction. With ALF, actin scavenger function is compromised by depleted gelsolin.¹⁵ Consequently, actin polymerization occurs, and microvascular function is compromised. The clinical effects of this microvascular injury are manifested by cardiovascular compromise, oxygen exchange abnormalities leading to acute respiratory distress syndrome, renal dysfunction, and disseminated intravascular coagulation (Fig. 1).

CLINICAL FEATURE

The chaos surrounding the patient with ALF makes the initial assessment challenging, but a detailed history and physical examination cannot be overlooked or abbreviated. If a specific diagnosis can be secured, an effective treatment could alter the natural history of the disease.

In viral-induced FHF, jaundice is preceded by symptoms such as fever, myalgia, arthralgia, and nausea. Thereafter, jaundice worsens, liver enzymes become increasingly elevated, and prothombin time becomes prolonged before

hepatic encephalopathy appears, underscoring hepatic dysfunction secondary to significant viral destruction of the liver.

Hepatic encephalopathy (HE) is a neuropsychiatric syndrome associated with hepatic dysfunction and is classified into four grades using a modification of the West Haven criteria^{16,17} (Tables 4 and 5). The patient should be clinically assessed initially and then multiple times during the day for each component of the HE score, as clinical progression can be devastatingly rapid.

Hepatic encephalopathy pathophysiology is complex and multifactorial. Various theories deserve mention:^{18,19}

- The hyperammonemia theory, in which hyperammonemia is thought to have a direct effect on neuronal membranes,
- The false-neurotransmitter theory, in which liver failure causes an increase in aromatic amino acids, decrease in branched-chain amino acids, which results in alterations to brain metabolism.
- The GABA-benzodiazepine theory, which is characterized by increased levels of neuroinhibitory GABA and a synergistic neuroinhibitory effect with benzodiazepine receptor ligands, explaining why, in some cases, use of flumazenil has been shown to reverse encephalopathy without affecting outcome.
- Other theories—abnormal histamine and serotonin neurotransmission, endogenous opioids, neurosteroids, inflammatory cytokines, and potential manganese toxicity.

Ammonia, infection/inflammation, and hyponatremia are the main contributors to the development of brain edema in acute liver failure. Higher arterial ammonia levels were found to be predictive of higher mortality and are associated with more complications including cerebral edema, seizures, and ventilation requirement.²⁰

The World Congress of Gastroenterology has proposed three main categories of HE based on the underlying liver dysfunction.²¹ Type A HE is associated with acute liver failure and progresses rapidly to seizures,

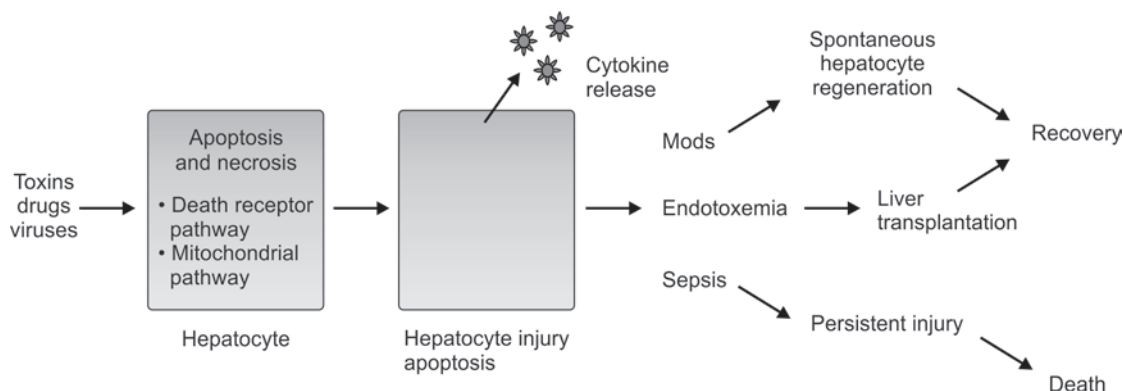


Fig. 1: Pathogenesis of acute liver failure.

Table 4: Stages of hepatic encephalopathy

	<i>Stages</i>			
	<i>I</i>	<i>II</i>	<i>III</i>	<i>IV</i>
Symptoms	Periods of lethargy, euphoria; reversal of day-night sleeping; may be alert	Drowsiness, inappropriate behavior, agitation, wide mood swings, disorientation	Stupor but arousable, confused, incoherent speech	Coma IVa responds to noxious stimuli IVb no response
Signs	Trouble drawing figures, performing mental tasks	Asterixis, fetor hepaticus, incontinence	Asterixis, hyperreflexia, extensor reflexes, rigidity	Areflexia, no asterixis, flaccidity
Electroencephalogram	Normal	Generalized slowing, θ waves	Markedly abnormal, triphasic waves	Markedly abnormal bilateral slowing, δ waves, electric-cortical silence

Adapted from the West Haven criteria.

Table 5: Stages of hepatic encephalopathy for infant and child less than 4 years

	<i>Stages</i>		
	<i>I</i>	<i>II</i>	<i>III</i>
Symptoms	Inconsolable crying, inattention to tasks, child is not acting like self to parents		Stupor, somnolence, combativeness
Signs	Normal or hyper-reflexic. Other neurological signs are difficult to test		Hyper-reflexia, extensor reflexes, rigidity
Electroencephalogram	Difficult to test and interpret		Markedly abnormal, triphasic waves

decerebrate rigidity, coma, and frequently death. Type B is associated with portosystemic bypass with no intrinsic liver disease and type C is associated with cirrhosis and portal hypertension.

DIAGNOSTIC WORK-UP

Initial laboratory tests should be focused in three areas:

- General laboratory investigations to assess hematological, renal, and electrolyte abnormalities (Table 6)
- Diagnostic tests: Prioritize for age and history (Table 7)
- Liver tests: Liver status can be assessed by serial measurement of serum aminotransferase levels, total and direct bilirubin, ammonia, prothrombin time, partial thromboplastin time, lactate and ammonia. A decrease in liver size at a time when the serum bilirubin is rising and serum aminotransferase levels are falling reflects generalized hepatocellular necrosis and parenchymal collapse. To determine if there is evidence of significant liver synthetic dysfunction, factors V, VII, VIII, and fibrinogen should be measured, recognizing that factor VIII levels will be normal even in the face of ALF and also it can differentiate it from DIC, where there will be low factor VIII level.

Table 6: General laboratory investigation

<i>Systems</i>	<i>Laboratory investigations</i>
Hematological	Complete blood cell count with platelets PT—International normalized ratio, aPTT fibrinogen, D—dimer
Electrolytes	Blood glucose, lactate, arterial ammonia, serum osmolarity. Blood gas with pH, Na, K, Ca, Mg, Cl, HCO ₃ , BUN, Cr
Sepsis	CRP, urinalysis and microscopic analysis, blood cultures, urine cultures
Imaging and other testing	Chest radiograph, ECG Abdominal ultrasound with Doppler study of the liver
CNS	EEG, ICP monitor?

MANAGEMENT (FLOW CHART 1)

Advances in critical care medicine and in management strategies have reduced mortality for ALF to approximately

Flow chart 1: Stepwise treatment protocol in FHF

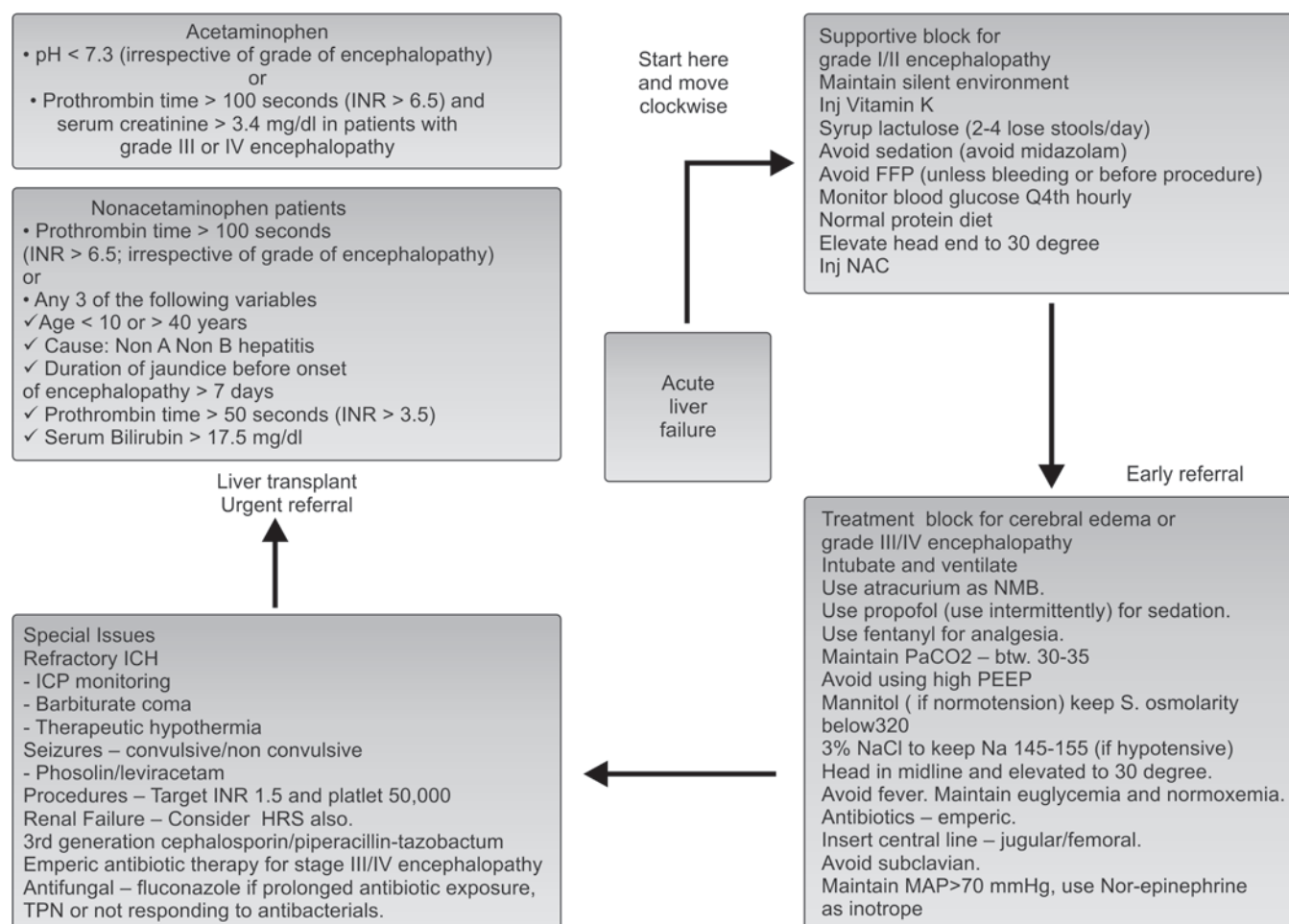


Table 7: Specific diagnostic tests to evaluate etiology of acute liver failure

Cause	Test
Hepatitis A infection	Anti-HAV antibody (IgM)
Hepatitis B infection	Acute infection/ Increased replication Anticore antibody (IgM)/ full hepatitis B virus profile
Hepatitis D infection	Antihepatitis D virus antibody (IgM)
Hepatitis C infection	Antihepatitis C virus antibody (IgM)
Other Infections	HHV-1, 2, 6; CMV; EBV; VZV; echovirus; parvovirus B19
Mushroom poisoning	History, diarrhea
Autoimmune hepatitis	Autoantibodies, immunoglobulins
Wilson's disease	Urinary copper, Kayser-Fleischer rings, Coombs negative hemolytic anemia
Galactosemia	Galactose-1-phosphate uridyl transferase level in the blood
Tyrosinemia	Urinary succinylacetone, wrist radiograph
Neonatal hemochromatosis	Buccal mucosal biopsy, raised ferritin, high transferrin saturation
Hemophagocytic lymphohistiocytosis	Bone marrow aspiration (typical cells)
Mitochondrial hepatopathies	Muscle and liver biopsies for quantitative assay of respiratory chain enzymes
Veno-occlusive disease	Doppler ultrasonography/venography imaging (computed tomography/ magnetic resonance imaging) and histology
Malignancies	Orotic acid
OTC deficiency	Acetaminophen, opiates, barbiturates, cocaine, alcohol
Toxicology screen and drug panel	

33 percent according to the USALF Study Group Registry. This mortality is mainly attributed to three complications in particular: cerebral edema, multiorgan dysfunction syndrome (MODS), and sepsis. The following section will review ICU based management strategies and interventions that have evolved to address the various organ dysfunctions associated with ALF.

PRINCIPLES OF MANAGEMENT

- Monitor and support the patient and organ systems
- Identify and treat complications
- Treat the patient to maximize chances of spontaneous recovery and maintain optimal clinical condition for best post-transplant survival

Although these principles are straightforward, their practical application is more complex and outcomes seem best for patients treated in centers experienced in management of acute liver failure.

Electrolytes and Fluid Therapy

- Hypoglycemia: Hypoglycemia may be present in most of patients with ALF. So regular blood sugar monitoring is mandatory and frequently by finger stick (e.g. every 1-2 hr). Hypoglycemia can worsen hepatic encephalopathy and cause rapid neurological deterioration. Intravenous glucose infusion (6-8 mg/kg/min) is recommended in patients who develop hypoglycemia.
- Dextrose concentration greater than 15 percent—use central line
- Frequent monitoring and correction of other metabolic derangements like hypokalemia, hypophosphatemia, and hypomagnesemia are critical.
- Restrict fluids to 2/3rds maintenance, provided child is hemodynamically stable and avoid fluid overload.
- Use 3 percent NaCl (0.1-1 ml/kg/hour) to maintain Na level between 140 and 150 mEq/L and serum osmolality less than 360 mOsm/L.²²

Ventilation and Monitoring

- Oral intubation is preferred, with a cuffed ETT, due to risk of bleeding and aspiration. Indications of intubation are:
 - > Grade 2 encephalopathy
 - Raised intracranial pressure
 - Rapidly deteriorating course
 - Respiratory failure
 - Cardiovascular collapse
- Aim to oxygenate ($\text{SpO}_2 > 90\%$) and maintain normocarbica (PaCO_2 35-45 mm Hg)
- Avoid high PEEP.
- Excessive hyperventilation should be avoided and not used prophylactic measure but as a transient maneuver to control surges of ICP,²³ as it may paradoxically

compromise the CPP (do not take PaCO_2 level below 30 mm Hg)

- Femoral or jugular central access if vasoactive agents or high concentration dextrose infusions are required.
- The risks and benefits of individual vasopressor agents have not been evaluated carefully, but extrapolation of data from TBI suggests that norepinephrine should be preferred, as it is associated with consistent and predictable increases in CPP.²⁴ Overzealous norepinephrine use should be avoided as this may exacerbate cerebral hyperemia because of the loss of CBF autoregulation in ALF
- Paralyze and sedate with fentanyl/propofol/atracurium.²⁵
- Avoid prolonged propofol infusion (restrict use to <24 hours) in children and in shock.
- Monitor pupils.
- Monitor arterial gases, glucose, sodium, PT (INR) and lactate levels closely.
- Continuous EEG monitoring for nonconvulsive seizure episodes.
- Raise head end of bed to 30 degree (provided patient is not in shock) and keep head in midline.

Cerebral Edema and Intracranial Hypertension

The first line of treatment is to minimize aggravating conditions. Therefore, any precipitating events that can result in hyperammonemia should be avoided. Treatment should include:

- Lowering endogenous nitrogen intake (by limiting bleeding and infection and preventing slowed intestinal transit) or exogenous nitrogen intake (by keeping protein delivery below 0.5 g/kg/day and avoiding unjustified fresh frozen plasma administration)
- Administration of oral or rectal lactulose (4-8 ml/kg, titrated to result in 2 to 4 daily soft stools), is advisable though lactulose use is associated with a small increase in survival but no difference in severity of HE or overall outcome.²⁶
- Neomycin is not recommended and should not be used, as it may precipitate renal failure and has not shown a benefit when combined with lactulose.
- Ornithine aspartate and sodium benzoate have been proposed to decrease serum ammonia, as in Reye syndrome and in urea cycle defects, but hemofiltration remains the main treatment of acute hyperammonemia.
- It is important to consider that minimizing neurosensory and painful stimulation (quiet and darkened room, limited nasopharyngeal aspiration) may help in controlling intracranial pressure (ICP) outburst.
- No consensus exists on the use of invasive ICP monitoring. The ultimate goal of this technique is to maintain adequate cerebral perfusion pressure. However,

an effect on mortality has never been shown.²⁷ Even after a decision is made to proceed with invasive ICP monitoring, the ideal location of placement remains unclear. When invasive monitoring is available the mean arterial pressure (MAP) should be adequate to maintain cerebral perfusion pressure (CPP) between 50 and 80 mm Hg.

- Mannitol can be used as first-line therapy and given as repeated boluses, provided serial serum osmolality remains below 320 mOsm/L, as the equilibrium in osmolality will render the drug ineffective. Its use is limited once patients develop significant renal injury.
- In contrast to mannitol, hypertonic saline can be used as a prophylactic measure with few adverse effects, with a goal of achieving sodium of 145 to 155 mEq/L, provided serum osmolality remains below 360 mOsm/L.¹⁵
 - If osmotic therapies fail to adequately control ICP, other adjunctive measures to reduce ICP include:
 - a. Barbiturate coma (to reduce brain metabolism, although incremental benefit is unclear if the patient is already in stage 4 encephalopathy with coma)
 - b. Paralytic agents
 - c. Phenytoin (may reduce cerebral edema regardless of seizure activity)
- Corticosteroids have been shown to be ineffective in patients with ALF with respect to controlling edema or improving survival
- Moderate hypothermia (32 to 33°C) so far appears to be a formidable tool for managing refractory ICP elevations.²⁸
- Indomethacin (infused intravenously over 1 min) also has been shown to acutely decrease ICP and increase CPP by causing cerebral vasoconstriction. However the use of nonsteroidal drugs in patients with ALF with coagulopathy and renal dysfunction excludes it from routine use without further validation.

Infectious Disease Consideration

Empirical administration of antibiotics is recommended in the following circumstances where infection or the likelihood of impending sepsis is high:²⁹

- Surveillance cultures reveal significant isolates,
- Progression of, or advanced stage (III/IV), hepatic encephalopathy,
- Refractory hypotension;
- Presence of systemic inflammatory response syndrome
- Patients listed for OLT.

Antifungal therapy may be particularly warranted in patients who have had prior antibiotic treatment and for those who have renal failure or the lack of a prompt response to institution of antibacterial therapy and for those patients who are listed for OLT.

The choice of an antimicrobial agent must take into account the need to cover a broad-spectrum of Gram-positive and -negative organisms. In general, third-generation cephalosporin drugs are recommended. Aminoglycosides are to be avoided if possible, owing to their potential for nephrotoxicity. Once speciation from any culture is possible, antimicrobial therapy may be narrowed accordingly.

Selective parenteral and enteral antimicrobial regimen (SPEAR) has shown a 30 percent reduction in the overall frequency of infection compared with those who received antimicrobial treatment when clinically indicated.³⁰ The administration of oral nonabsorbable antibacterials {rifacol} for selective decontamination of the gut does not appear to improve survival in patients already receiving prophylactic systemic antibacterials.³¹

For Gastrointestinal Hemorrhage

- Correct coagulopathy and thrombocytopenia.
- Give vitamin K 5 to 10 mg intravenously.³²
- Ensure packed cells given and more available for transfer, as well as other blood products
- Commence octreotide infusion (0.5-1 mcg/kg/min)
- Consider placing Sengstaken tube (if appropriately trained)
- Patients with ALF in the ICU should receive prophylaxis with H2 blocking agents or PPIs (or sucralfate as a second-line agent) for acid-related gastrointestinal bleeding associated with stress.³

Hematologic Failure: Dealing with Coagulopathy

In the absence of bleeding, it is not recommended to correct homeostasis, because doing so will interfere with the evaluation of liver function (factor V activity, PT). An exception would be if an invasive procedure is planned, such as placement of a central venous catheter. In these cases, procedures can be performed under cover of FFP, platelet or administration of activated recombinant factor VII if profound thrombopenia ($<10,000/\text{mm}^3$) is observed. Although strict guidelines do not exist, a rough target would be to correct the INR to approximately 1.5 and platelet count to approximately $50,000/\text{mm}^3$ before procedures with the use of fresh frozen plasma (FFP) and platelets. Concomitant administration of cryoprecipitate is recommended for patients who have significant hypofibrinogenemia (less than 100 mg/dl). When FFP fails to adequately normalize PT/INR, the use of recombinant factor 7a (rF7) can be considered. FFP or cryoprecipitate should be administered before rF7 (40 $\mu\text{g/kg}$) if fibrinogen levels are less than 100 mg/dl to replete factors involved in the clotting cascade.³³

Acute Kidney Injury

Acute kidney injury is multifactorial in the setting of ALF. Acute renal failure denotes a poor prognosis and

contributes to mortality. Hypovolemia, low systemic vascular resistance, acute tubular necrosis (ATN), GI blood loss and hepatorenal syndrome are among the most important associated entities. Renal toxic agents should be avoided.

Hepatorenal syndrome, defined as a progressive renal insufficiency in patients with liver disease, is characterized by a low urine sodium output and elevated urinary-to-plasma ratios for creatinine and osmolality. In patients with FHF, type 1 hepatorenal syndrome is found and defined as a rapid and progressive renal impairment. The pathogenesis is poorly understood; however, it is characterized by renal cortical vasoconstriction and corticomedullary redistribution of renal blood flow. Hepatorenal syndrome may be precipitated after digestive bleeding, septicemia, and dehydration.

Where available continuous venovenous hemofiltration (CVVHF) is preferred method of renal replacement because of the reduced shifts in blood pressure associated with its use. Anticoagulation of renal replacement circuits can be problematic and the most units avoid systemic heparinization. Due to this knowledge most liver transplant centers use citrate for patient with ALF or postliver transplant.³⁴

NUTRITION

There is a need for nutritional supplementation in ALF, because these patients are catabolic and enteral nutrition should be administered whenever possible, with higher caloric density feeds preferred to avoid excessive free water and hypo-osmolality, which may exacerbate cerebral edema. Parenteral nutrition (35-40 kcal/kg per day) delivered by a dedicated central venous catheter, should be reserved for patients with specific contraindications to enteral nutrition. Normal protein intake recommended till Stage I and II encephalopathy and thereafter restriction is recommended. Excess glutamine supplementation

should be avoided given glutamine's role in the production of ammonia and development of cerebral edema in ALF.³⁵

ETIOLOGY SPECIFIC TREATMENT

Table 8 describes etiology specific treatment.

Liver Support Systems

A support device to replace the acutely failing liver seems a reasonable but elusive goal. The ideal replacement for the failing liver would detoxify, metabolize and synthesize; in short, perform all the liver's many functions. A variety of systems have been tested to date, with no certain evidence of efficacy. Currently available liver support systems are not recommended outside of clinical trials; their future in the management of acute liver failure remains unclear.³⁶

N-acetylcysteine

When used early as an antidote after a single, intentional paracetamol overdose, NAC is extremely effective at replenishing hepatic glutathione stores and preventing severe N-acetyl-p-benzoquinone imine induced hepatotoxicity and liver failure.

N-acetylcysteine is now also used to treat established FHF of any cause, because of its antioxidant effects and improved tissue oxygenation and is efficacious if given early in liver failure.³⁷ The optimal duration of NAC therapy in these patients is unclear; some say till reversal of encephalopathy at a dose of 100 mg/kg/day in 5 percent Dextrose or for 3 days.

Liver Transplantation

Emergency liver transplantation remains the only treatment of end-stage FHF in children. Transplantation decisions rely on the cause and severity of FHF and the

Table 8: Target specific therapy of underlying ALF

<i>Cause</i>	<i>Treatment</i>
Hereditary tyrosinemia	Nitisinone (NTBC) 1 mg/kg/day orally in 2 doses
Neonatal hemochromatosis	Deferoxamine 30 mg/kg/day IV in 3 doses. Selenium 2-3 mcg/kg/day IV N-acetyl-cysteine 140 mg/kg, then 70 mg/kg orally or IV tocopherol polyethylene glycol succinate 20 UI/kg/day orally
Herpetic hepatitis	Acyclovir 150 mg/m ² /day IV
Acetaminophen poisoning	Activated charcoal 1 g/kg orally N-acetylcysteine 150 mg/kg IV in 15 min, then maintenance dose 50 mg/kg over 4 hours, followed by 100 mg/kg administered over 16 hours
Mushroom poisoning	Penicillin G 300,000-1 million units/kg/day IV. Silymarin 30-40 mg/kg/day IV or orally
Hepatitis B	Lamivudine 4 mg/kg/day once daily orally
HSV	Acyclovir 10 mg/kg 8 hourly
Autoimmune hepatitis	Methylprednisolone 60 mg/kg IV

Table 9: Indications to discuss emergency liver transplantation with parents

1. Hepatic encephalopathy grade II with	Factor V activity of <20%
	Worsening prothrombin time
2. Other criteria	Rapid decrease in liver size
	Seizures, ascites, hepatorenal syndrome
	Fibrinogen level of <1g/L, bilirubinemia of >23 mg/dl
	Worsening lactic acidosis and hyperammonemia of >150 mmol/L

Table 10: King’s college hospital and clichy liver transplantation criteria for fulminant hepatic failure

	<i>King’s College criteria</i>
FHF secondary to acetaminophen overdose	pH less than 7.30 (irrespective of encephalopathy grade), Or Hepatic encephalopathy grade III–IV, Prothrombin time over 100 seconds (INR > 6.5), and Serum creatinine over 300 μmol/L (3.4 mg/dl)
FHF with other causes	Prothrombin time over 100 seconds (INR > 6.5) (irrespective of encephalopathy grade), Or any three of the following (irrespective of encephalopathy grade) Age under 10 or over 40 years Non-A, non-B hepatitis or drug-induced origin Duration of jaundice before encephalopathy over 7 days Serum bilirubin greater than 300 μmol/l (17.6 mg/dl) Prothrombin time over 50 seconds (INR > 3.5)
	<i>Clichy criteria</i>
Presence of confusion or coma (stage III–IV HE) associated with	
Factor V level lower than 20% of normal in patients aged less than 30 years	
Factor V level lower than 30% of normal in patients aged over 30 years	

potentialities of spontaneous liver regeneration and the comorbidities, especially the development of permanent neurologic damage. In adults, the most commonly used transplantation criteria are those developed at King’s College in London (Tables 9 and 10) and Beaujon’s Hospital in Paris.³⁸ However, these criteria fail to be adequate in children, mainly due to a very weak negative predictive value. In children, etiology is a critical determinant of outcome. Fulminant Wilson disease and undetermined FHF carry the worst prognosis and require emergency liver transplantation, whereas hepatitis A-induced and acetaminophen-induced FHF have significant spontaneous recovery without transplantation. Other FHF causes have variable outcome, mainly determined by the severity of neurologic involvement.

Liver transplantation may be contraindicated in 11 to 20 percent of cases. For instance, malignant disease, such as leukemia, lymphoproliferative syndrome, lymphohistiocytosis, and some mitochondrial respiratory chain disorders, as well as the patient’s end-stage intracranial

hypertension or uncontrolled multiorgan failure, are contraindications to transplantation due to poor outcome.

OUTCOME

FHF prognosis has significantly improved since the performance of the initial series of emergency liver transplantations, shifting from an overall survival of 15 to >60 percent.³⁹ In children, published experience of emergency liver transplantation in the setting of FHF shows long-term survival ranging from 52 percent in infants to 79 percent in older children. Mostly a short interval between symptoms or jaundice and encephalopathy (most of acetaminophen-induced FHF and some of hepatitis A or B etiology) is associated with the high-risk of brain edema and greater possibility of spontaneous recovery, whereas a long interval is associated with less frequency of brain edema, lower survival, and more common non-A-to-E cryptogenic etiology. A study of FHF in the SPLIT (The Studies in Pediatric Liver Transplantation) database suggested that grade 4 encephalopathy, age less than 1

year and dialysis before transplantation were risk factors for poor outcomes.⁴⁰

KEY POINTS

Author's Experience on Liver Transplantation Till October 2011

- Infants and children with FHF should be referred early to centers with expertise in pediatric liver disease, as determination of an accurate etiologic diagnosis before encephalopathy occurs is critical.
- In pediatrics—presence of encephalopathy is not essential for diagnosing acute liver failure.
- Fresh frozen plasma should be avoided as long as no active bleeding is present. It will modify coagulation factors for 24 hours that are important criteria by which to evaluate FHF severity.
- Encephalopathy and coagulation parameter (factor V activity, PT) kinetics are major FHF severity criteria that aid in deciding whether to perform emergency liver transplantation.
- NAC is of beneficial role even in nonacetaminophen acute liver failure, when given early.
- Liver transplantation has drastically changed prognosis of pediatric FHF and end-stage liver disease.

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DEFINITION

Acute diarrhea is the abrupt onset of increased fluid content of the stool above the normal. Normally stool output in infants and toddlers is up to 10 ml/kg/d, while in older children and adults it is up to 200 gm per day. Practically this manifests as loose or liquid stools (decrease in stool consistency) and an increase in stool frequency to ≥ 3 bowel movements per day. The increased frequency of bowel movements can range from 4 to more than 20 times per day. The increased fluid content of the stools is the result of an imbalance in the absorption and secretion of electrolytes, organic substrates, and hence water by the small and large intestine.

In terms of duration acute diarrhea is classically defined as an episode of diarrhea that has an acute onset and lasts no longer than 14 days; while as an episode lasting more than 14 days is called as persistent diarrhea.

EPIDEMIOLOGY

Acute diarrhea most often results from infections of the gastrointestinal tract. It is a major problem for child health worldwide. Diarrheal diseases are one of the leading causes of morbidity and mortality in children worldwide. There are about one billion episodes of illness annually. Although in developed countries the prevalence and severity of acute diarrhea has declined, it remains a common and often a severe problem. In developing countries, children suffer from an average of 3 (up to 6-8 in some areas) episodes of diarrhea per year during first 5 years of life. Childhood mortality associated with diarrhea has constantly but slowly declined during the past two decades, mostly because of the widespread use of oral rehydration solutions (ORSs), but still remains high with 3 to 5 million deaths annually.

Person to person transmission through the fecal-oral route or by ingestion of contaminated food or water is the

major mechanisms of transmission for diarrheal pathogens. Factors that increase susceptibility to infection with enteropathogens include young age, immune deficiency, measles, malnutrition, lack of breast-feeding, exposure to unsanitary conditions, ingestion of contaminated food or water, level of maternal education, and attendance at a childcare center.

ETIOLOGY

Gastrointestinal infections are by far the most common cause of acute diarrhea. However the sudden onset of increased stool fluid output can also be caused by many noninfectious disorders. Causative agent can be identified in >70 percent of cases of acute diarrhea in good laboratories.

Infections of the gastrointestinal tract are caused by a wide variety of enteropathogens, including bacteria, viruses, and parasites.

- *Viruses*
 - Rotavirus
 - Calicivirus
 - Norwalk-like virus
 - Astrovirus
 - Enteric-type adenovirus
- *Bacteria*
 - *Campylobacter jejuni*
 - *Salmonella*
 - *Escherichia coli*
 - (i) Enterotoxigenic (ETEC)
 - (ii) Enteropathogenic (EPEC)
 - (iii) Enteroinvasive (EIEC)
 - (iv) Enterohemorrhagic (EHEC)
 - (v) Enterotoxigenic (EAggEC)
 - (vi) Diffusely adherent (DA-EC)
 - *Shigella*
 - *Yersinia enterocolitica*
 - *Clostridium difficile*

- *Vibrio parahaemolyticus*
- *Vibrio cholerae* 01& 0139
- *Vibrio cholerae* non-01
- *Aeromonas hydrophila*
- *Parasites*
 - *Cryptosporidium*
 - *Giardia lamblia*
- *Non-gastrointestinal infections*
 - Otitis media
 - Urinary tract infections
 - Pneumonia
- *Non-infectious causes*
 - Drugs induced, e.g. antibiotics
 - Food allergy (Cow's milk protein, soy protein)
 - Disaccharidase deficiency (sucrase-isomaltase, hypolactasia)
 - Chemotherapy or radiation-induced enteritis
 - Acute appendicitis
 - Intussusceptions
 - Niacin deficiency
 - Ingestion of heavy metals

In India rotavirus and ETEC account for more than half of cases of acute diarrhea.

PATHOGENESIS

The two basic types of acute infectious diarrhea are non-inflammatory and inflammatory. Enteropathogens elicit noninflammatory diarrhea through enterotoxin production by some bacteria, destruction of villus (surface) cells by viruses, adherence by parasites, and adherence and/or translocation by bacteria. Noninflammatory diarrhea may be caused by enteropathogenic *E. coli*, enterotoxigenic *E. coli*, *Vibrio cholerae*. In contrast, inflammatory diarrhea usually is caused by bacteria that invade the intestine directly or produce cytotoxins. Generally, inflammatory diarrhea is associated with *Aeromonas*, *Campylobacter jejuni*, *Clostridium difficile*, enteroinvasive *E. coli*, Shiga toxin-producing *E. coli* (*E. coli* O157:H7), *Plesiomonas shigelloides*, *Salmonella*, *Shigella*, *Vibrio parahaemolyticus*, and *Yersinia enterocolitica*. Some enteropathogens possess more than one virulence property.

CLINICAL FEATURES

Laboratory Investigations

- Often are not required as most episodes of acute diarrhea are self-limited
- Stool may be examination for mucus, blood, and leukocytes, the presence of which indicates colitis
- Stool leukocyte (>50/hpf) indicates the presence of an invasive or cytotoxin-producing organism such as *Shigella*, *Salmonella*, *C. jejuni*, invasive *E. coli*, *C. difficile*, *Y. enterocolitica*.

- Stool culture – to identify organism is not done routinely. *E. coli* is often reported on stool cultures but it can be a commensal. Serotype and toxin assays are available for further characterization of *E. coli*.
- Proctosigmoidoscopy may be helpful in establishing a diagnosis in patients in whom symptoms of colitis are severe or the cause remains obscure.
- Serum electrolytes, BUN, creatinine and arterial blood gas estimation should be done when clinical indicated.

APPROACH TO CHILDREN WITH ACUTE DIARRHEA

The main objectives in the approach to a child with acute diarrhea are to (1) assess the degree of dehydration and provide fluid and electrolyte replacement, (2) prevent spread of the enteropathogen and (3) in select episodes determine the etiologic agent and provide specific therapy if indicated. Information about oral intake, frequency and volume of stool output, general appearance and activity of the child, and frequency of urination must be obtained. The duration and severity of diarrhea, stool consistency, presence of mucus and blood, and other associated symptomatology, such as fever, vomiting, and seizures, should be determined.

Fever suggests a systemic infection, inflammatory diarrhea but also occurs as a result of dehydration. Although nausea and vomiting are nonspecific symptoms, vomiting suggests upper intestinal involvement, as occurs in enteric viruses, enterotoxin-producing bacteria, *Giardia*, and *Cryptosporidium*. Emesis, absent or low-grade fever, mild crampy periumbilical pain and watery diarrhea indicate upper intestinal tract involvement and hence noninflammatory diarrhea. Fever, lower abdominal pain, tenesmus, blood and mucus in stools indicate large intestinal involvement and hence inflammatory diarrhea.

Assessment of Dehydration

During diarrhea there is a net loss of water and electrolytes from the body and the child develops symptoms and signs of dehydration. Based on these symptoms and signs the dehydration status of child is graded into no dehydration, some dehydration and severe dehydration as per WHO criteria given in Table 1.

Treatment Plan A

If a child has diarrhea but no signs of dehydration, treatment plan A is used (Table 2). The aim of this treatment is to prevent dehydration by replacing ongoing fluid and electrolyte loss in stools. Most fluids (preferably one containing salt) that a child normally drinks can be used. These include ORS solution, salted rice water, salted yoghurt water, soup with salt, coconut water and plain water. Carbonated beverages, commercial fruit juices, sweetened tea and coffee should be avoided as they have

Table 1: Assessment of dehydration in children with diarrhea

		<i>A</i>	<i>B</i>	<i>C</i>
Look at	General Condition ^a	Well, alert	Restless, irritable	Lethargic or unconscious
	Eyes ^b	Normal	Sunken	Very sunken, dry
	Tears	Present	Absent	Absent
	Mouth + tongue ^c	Moist	Dry	Very dry
	Thirst	Drinks normally, not thirsty	Thirsty, drinks eagerly	Drinks poorly or not able to drink
Feel	Skin pinch ^d	Goes back quickly	Goes back slowly	Goes back very slowly
Decide	Degree of dehydration	No dehydration	Some dehydration if ≥ 2 signs in B	Severe dehydration if ≥ 2 signs in C
Treat using		Plan A	Plan B after weighing if possible	Plan C after weighing the child

- a. Being lethargic and sleepy are not same. Lethargic child is not simply asleep: child's mental state is dull, cannot be fully awakened and may appear to be drifting into unconsciousness.
- b. It is helpful to ask mother if the eyes are normal or more sunken than usual as they may appear somewhat sunken normally in some infants and children.
- c. Dryness of mouth and tongue can also be palpated using a clean finger. It may occur in habitual mouth breathers. They may be wet owing to recent vomiting or drinking.
- d. Skin pinch is less useful in marasmus, edematous malnutrition and obese children.

Table 2: Guidelines for treating children with no dehydration – Plan A

<i>Age</i>	<i>Amount of ORS/ORT after each stool</i>	<i>ORS to be provided for home use</i>
<24 months	50-100 ml	500 ml/day
2-10 years	100-200 ml	1000 ml/day
≥ 10 years	As much as wants	2000 ml/day

Demonstrate to mother how to prepare and give ORS and amount to be given after each stool using local measures.

Give a teaspoonful every 1-2 minutes to children < 2 years.

Give frequent sips from a cup to older children.

If child vomits, wait for 10 minutes, then give ORS more slowly.

a high osmolality and can worsen dehydration by causing osmotic diarrhea and diuresis. Generally as much fluid as the child wants should be offered until diarrhea stops. The mother should be instructed to bring the child to health care facility if the child does not improve in three days or any of the following danger signs develops: high purge rate, repeated vomiting, marked thirst, eating or drinking poorly, fever or blood in stools.

Treatment Plan B

Children with some dehydration should be treated using plan B (Table 3) in a health care facility. The aim is to correct the existing deficit, to replace ongoing loss and to provide normal daily requirement of fluid and electrolytes. Give 75 ml/kg of ORS over a period of 4 hours. Use age appropriate guidelines for amount of fluid to be

given if weight is not known. Watch for signs of overhydration or worsening of dehydration. If signs of severe dehydration develop, shift to plan C. After 4 hours the hydration status of child should be reassessed. If signs of some dehydration are corrected, child should be offered ORS to replace ongoing stool losses till diarrhea stops (plan A). If child continues to have signs of some dehydration, initiate another 4 hours treatment with ORS solution and start to offer feeds, milk and breast feeding frequently.

Oral Rehydration Therapy (ORT)

The term ORT encompasses:

- Oral rehydration salt (ORS) solution with composition as recommended by WHO
- Solutions made from sugar and salt.

Table 3: Guidelines for treating children with some dehydration – Plan B

Approximate amount of ORS solution to be given in first 4 hours

Age	<4 months	4-11 months	11-23 months	2-4 years	5-14 years	≥15 years
Weight (kg)	<5	5-8	8-11	11-16	16-30	>30
ORS (ml)	200-400	400-600	600-800	800-1200	1200-2200	2200-4000
Local measure	1-2	2-3	3-4	4-6	6-11	12-24

Note: Approximate amount of ORS can be calculated by multiplying child's weight in kg by 75

- Food based solutions.
- A variety of commonly available, culturally acceptable fluids.

ORS is the most commonly used ORT fluid and refers to the oral rehydration salt solution as recommended by WHO. In 2002 WHO recommended the new low/reduced osmolarity ORS in place of standard WHO ORS 1975. In 2004 Government of India based on recommendations of WHO/UNICEF and IAP adopted the reduced/low osmolarity ORS as the single universal ORS to be used for all ages and all types of diarrhea. Table 4 shows the comparison between reduced/low osmolarity WHO ORS and standard WHO ORS. Reduced osmolarity ORS when compared to WHO standard ORS is associated with reduced need for intravenous fluid infusions, lower stool volume, less vomiting and no increased risk of hyponatremia. These advantages led the WHO to recommend reduced-osmolarity ORS as a global ORS in 2002.

Oral rehydration therapy is effective in correcting dehydration in 95 to 97 percent of children. However in 3-5 percent of children ORT failure occurs and such children need parenteral fluids to correct some dehydration. The ORT failure may be due to:

- High purge rate
- Frequent vomiting
- Incorrect preparation, amount or administration
- Abdominal distention with ileus.

- Glucose malabsorption (rare, increased diarrhea after starting ORS)

Treatment Plan C

The preferred treatment for children with severe dehydration is rapid intravenous rehydration as per plan C (Table 5). Start intravenous fluids immediately. However if IV fluids cannot be started immediately (due to no IV access, non availability, or during transport) one can start rehydration with ORS using nasogastric tube till IV access is established. The best IV fluid is Ringer's lactate solution. Normal saline solution can be used if Ringer's lactate solution is not available. Plain dextrose solutions are not effective.

Feeding

ORT itself has a beneficial effect on nutrition by stimulating the child's appetite as a result of the improved water and potassium balance. Furthermore, rapid re-feeding after adequate ORT has been shown to allow a faster recovery from the abnormally increased intestinal permeability.

It has been clear for many years that, breastfed infants should be continued on breast milk without any need for interruption. Breastfeeding not only has a well-known protective effect against the development of enteritis,

Table 4: Comparison between new (reduced osmolarity) and old (standard) WHO ORS

Ingredient	Concentration (mmol/L)	
	Reduced osmolarity WHO ORS (2002)	Standard WHO ORS (1975)
Sodium	75	90
Potassium	20	20
Chloride	65	80
Citrate/bicarbonate	10/30	10/30
Glucose	75	111
Osmolarity	245	311

Table 5: Guidelines for intravenous fluid therapy in severe dehydration

Age	First give	Then give
<12 months	30 ml/kg in 1 hour*	70 ml/kg over next 5 hours
>12 months	30 ml/kg in ½ hour*	70 ml/kg over next 2 ½ hours

*Repeat if radial pulse is still very weak or not detectable.

Use Ringer's lactate solution or normal saline if former is not available.

it also promotes faster recovery and provides improved nutrition.

Lactose intolerance is not a major problem in children with diarrhea and should not be a reason to delay re-feeding milk-based formulas. Very rarely, if fecal pH decreases and more than 0.5 to 1 percent reducing substances are found in the stools, lactose intolerance should be assumed and a lactose-free formula employed at least temporarily to prevent persistent diarrhea.

In children with no dehydration feeding should be continued with usual foods and breast milk (if breast fed). In children with some dehydration breast feeding should be continued during rehydration. In non breastfed children milk preferably mixed with cereals and other semi-solid foods should be offered soon after correction of deficit. Small frequent meals are better tolerated.

During recovery an intake of 1.25 times the normal RDA should be given in the form of energy dense food till child achieves normal weight for age. This may take several weeks.

ANTIBIOTICS

Majority of cases of acute diarrhea in children are caused by viruses and such bacteria, wherein it is neither necessary nor desirable to use antibiotics. In fact enteric bacterial pathogens show increased resistance to standard therapy, antibiotics are variably effective, and their use may prolong the carrier state.

The recommendation for antimicrobial treatment in immunocompetent children with acute diarrhea are:

- Agents for whom antimicrobial therapy is always indicated; these include *V. cholerae*, *Shigella*, and *Giardia lamblia*, *E. histolytica*
- Agents for whom antimicrobial therapy is indicated only in selected circumstance:
 - infections by enteropathogenic *E. coli*, when running a prolonged course.
 - enteroinvasive *E. coli*, based on the serologic, genetic, and pathogenic similarities with *Shigella*.
 - *Yersinia* infections in subjects with sickle cell disease and
 - *Salmonella* infections in the very young infants, if febrile, or with positive blood culture.

Antibiotics to which enteric pathogens remain sensitive and are generally used include fluoroquinolones (e.g. ciprofloxacin, ofloxacin) and third generation cephalosporins (e.g. cefixime, ceftriaxone). *E. histolytica* and *G. lamblia* are usually treated with metronidazole.

Zinc in Treatment of Acute Diarrhea

Zinc deficiency is widely prevalent in children of developing world. In the past few years, a great deal of interest has been generated in the possible role of zinc supplementation in either the prevention or treatment of acute diarrhea in children of developing countries. Several studies are now available which show that zinc supplementation to children with acute diarrhea results in shorter duration of diarrhea, lesser stool output, better weight gain, improved zinc serum status and reduces the incidence of diarrhea for next 3 months. Zinc supplementation is now part of standard management along with ORS for treatment of acute diarrhea. The dose of elemental zinc in acute diarrhea is 20 mg/day (10 mg/day for infants < 6 months of age) for 10 to 14 days.

IMMUNOGLOBULINS

Several studies have shown efficacy of oral/entral immunoglobulin in the treatment and prevention of rotavirus diarrhea. Although this approach may benefit certain infants with severe, protracted rotavirus diarrhea (e.g. immunocompromised) it is not recommended in routine management of rotavirus diarrhea.

ANTI-DIARRHEAL DRUGS

The anti-diarrheal drugs can be categorized into:

- Anti motility, e.g. loperamide, diphenoxylate.
- Binding, e.g. pectin, kaolin, bismuth.
- Anti secretory, e.g. racecadotril, octreotide.

Racecadotril a potent synthetic enkephalinase inhibitor, promotes absorption and having no effect on intestinal motility has shown safety and effectiveness in treatment of acute diarrhea but requires further large clinical trials.

In general it can be said that no anti-diarrheal drugs can and should presently be recommended in children with acute diarrhea.

PROBIOTICS

Probiotics are live microflora meant to have beneficial effect on host. This is one of the hotly researched areas in treatment and prevention of diarrheal diseases. The use of several strains of lactic acid bacteria to treat human diseases is centuries old and lactobacilli are among the most commonly employed bacterial species used to promote health and counteract intestinal infections. Table 6 lists the common probiotics investigated in medical practice.

Among them *Lactobacillus rhamnosus* strain GG is by far the most widely investigated and has shown beneficial effect in treatment and prevention of acute diarrhea especially viral diarrhea. Probiotics in the form of *Saccharomyces boulardii* and *Lactobacillus* GG have also shown efficacy in prevention of antibiotic associated diarrhea.

PREVENTION

Global efforts to reduce the continuing high morbidity and mortality due to diarrheal diseases are being led by WHO and the targeted areas include education, proper

hygiene and sanitation, promotion of breast feeding, food safety and ORT, probiotics and development of vaccines. Simple hand washing with soap decreases the incidence of diarrhea by more than 50 percent, as does education campaigns focused on proper hygiene and sanitation, promotion of breast feeding, food safety and ORT.

Vaccination is now available against rotavirus and has been shown to prevent severe rotavirus diarrhea and associated hospitalizations. Rotarix (Glaxo SmithKline biological) and RotaTeq (Merck and company), both live attenuated vaccines have been licensed for use in humans. Both are safe and have not been shown to be associated with increased risk of intussusceptions.

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Table 6: Probiotic Microorganisms

Lactic Acid Bacteria

Lactobacilli

Lactobacillus acidophilus

Lactobacillus rhamnosus

Lactobacillus gasseri

Lactobacillus casei

Lactobacillus reuteri

Lactobacillus plantarum

Lactobacillus bulgaricus

Lactobacillus johnsoni

Lactobacillus lactis

Bifidobacteria

Bifidobacterium bifidum

Bifidobacterium longum

Bifidobacterium breve

Bifidobacterium infantis

Bifidobacterium adolescentis

Others Bacteria

Escherichia coli

Enterococcus faecalis

Streptococcus thermophilus

Yeasts

Saccharomyces boulardii

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INTRODUCTION

Diarrheal diseases account globally for almost a fifth of all deaths in children less than 5 years of age with an estimated 2.2 million annual deaths.¹ Most episodes of acute diarrhea settle in less than 7 days; however a small but significant proportion are prolonged or persistent lasting longer than 7 to 14 days. These prolonged or persistent episodes contribute not only to a considerable share of the global burden of diarrheal disease in children less than 5 years of age but are also implicated in undernutrition, micronutrient deficiencies, growth faltering, cognitive impairment and higher morbidity and mortality when associated with other diseases. The reported annual disability adjusted life years lost due to persistent diarrhea is also staggeringly high being around 3 million. Therefore, it is imperative that pediatricians are aware of the epidemiology, etiology, risk factors, pathophysiology and management of persistent diarrhea, a preventable morbid continuum of acute diarrhea which is prevalent in developing countries.

DEFINITIONS

Persistent Diarrhea

WHO defined *persistent diarrhea* (PD) as an illness of presumed infectious etiology with an acute onset lasting for more than 14 days excluding conditions, such as celiac disease or other hereditary disorders.² Since the main disturbing feature of PD is growth faltering or undernutrition which is not included in this definition, it may be preferable to express persistent diarrhea as “with or without weight loss”.

The *14 days cut-off point* between acute diarrhea and persistent diarrhea is arbitrary but in 1989, Bhan et al, in a large prospective study clearly documented the sharp rise

in mortality from 0.7 percent in shorter duration illness to 14 percent in PD supporting the necessity of this “two week cut-off” mark.³ Bhutta et al in 2008 emphasized the issue that since the majority of acute diarrheal episodes resolve within 5 to 7 days, it may be necessary to be alert and more cautious in managing children in the interim period of 7 to 14 days in order to avert the major consequences of PD.⁴ The label *prolonged diarrhea (ProD)* for this exclusive episode of >7 days and <14 days diarrhea utilized by Moore et al was to highlight the point that it may be an indicator for children with a high risk for progression to PD.

There are two other diarrheal diseases which are similar in the duration of illness but are different in pathophysiology and prognosis and therefore should be considered as different entities to have a uniform understanding.

Protracted Diarrhea of Infancy

Protracted diarrhea of infancy (PDI) is defined as diarrhea lasting for more than 2 weeks with failure to thrive and requiring specialized enteral or parenteral nutritional support. Avery Jones described this unique entity as early as 1968 in infants less than 3 months of age; later Guarino in 1995 increased the age limit to children less than 2 years of age.

Chronic Diarrhea

Chronic diarrhea (CD) is defined as a diarrheal illness of insidious onset, usually of noninfectious etiology and lasting for more than 14 days which is associated with malnutrition either due to maldigestion or malabsorption of nutrients. The main difference between PD and CD is the presence of an underlying inherent defect such as celiac disease, intestinal lymphangiectasia, etc. in CD which are not included in the diagnostic criteria for PD.

EPIDEMIOLOGY

The burden of persistent diarrhea varies in different regions and accounts for approximately 3 to 23 percent (average 10%) of all diarrheal illness. In India, five percent of all diarrheal episodes was identified as persistent;³ similar studies from Brazil, Peru and Israel indicated that 5 to 18 percent of diarrheal episodes were persistent. In Brazil, 12 percent of all episodes were prolonged with a 6-fold increase of progression to PD. Diarrheal deaths directly related to PD varies from 36 to 54 percent and is related to the environmental characteristics and utilization of medical facilities. Persistent diarrhea is more common in malnourished children and in those less than two years of age. Sixty percent of PD occurs before 6 months and 90 percent below 1 year of age. Boys seem to be more affected than girls. Twenty percent of acute diarrheal episodes in malnourished children persists beyond two weeks. A community-based study from Bangladesh in 2003 has reported that PD accounts for less than 0.5 percent of diarrheal episodes. There is no definite evidence that the global incidence of PD has declined though it appears to be overall less, probably because the number of publications related to PD has decreased over the last decade. There is a definite need to update data regarding the present prevalence of PD.

ETIOPATHOGENESIS AND PATHOPHYSIOLOGY

The etiopathogenesis of PD is not well understood and is probably multifactorial. There is a definite interplay between persistent mucosal injury due to specific pathogens (*E. coli*, *Shigella*, *Salmonella*, *Campylobacter*), sequential infections with multiple pathogens and host factors such as malnutrition (macro and micro-nutrient deficiency) and compromised immune system resulting in prolonged mucosal injury, poor intestinal repair and villous atrophy. Several other factors worsen the villi injury such as cow's milk protein allergy, carbohydrate and fat malabsorption (Flow chart 1).

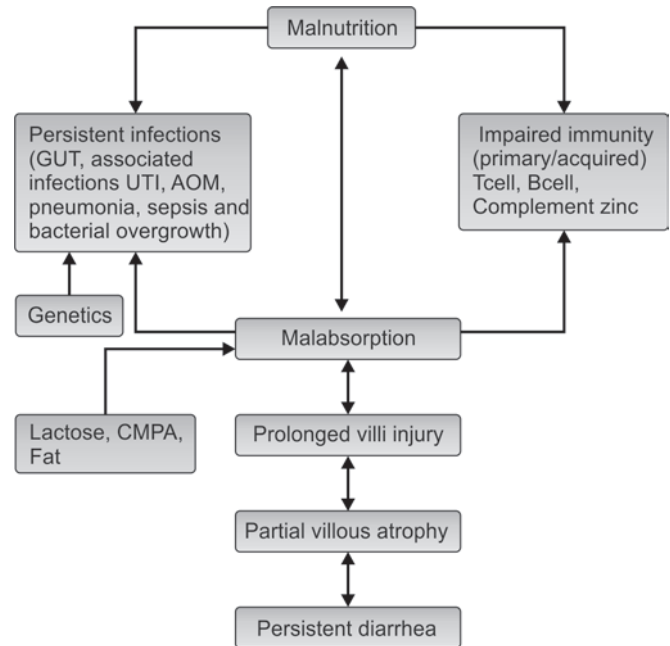
Enteric Infections

Globally, the most important underlying trigger for PD is an enteric infection and its associated sequel. Several pathogens such as bacteria, parasites and viruses have been implicated to cause prolonged or persistent diarrhea.

Bacteria

Shigella infections have been significantly associated with an increased risk of PD (age adjusted relative risk 1.83). Twenty-three percent of children with shigellosis had PD in a study from Bangladesh. Infection by antibiotic resistant *Shigella* isolates and occurrence of shigellosis in infants were observed to be risk factors for *Shigella* persistence.

Flow chart 1: Pathogenesis in persistent diarrhea



Other bacteria that have been associated are enteroaggregative *Escherichia coli*, enteropathogenic *Escherichia coli*, *Campylobacter*, *Salmonella enteritidis*, *Clostridium difficile*, *Aerobacter butzleri* and *Klebsiella* species.

Parasites

Giardia lamblia, *Blastocystis hominis*, *Cryptosporidium parvum*, *Entamoeba histolytica*, Strongyloidiasis, Coccidiosis and *Cyclospora cayetanensis* have been associated with prolonged and persistent diarrhea.

Viruses

Human immune deficiency virus, Human astrovirus 3, enterovirus and Picoberna viruses have all been linked with PD. Children with HIV infection have been reported to have an 11-fold increase in death from PD.

Multiple sequential infections lead to small bowel mucosal injury with blunting of the villi, cellular infiltration of the lamina propria and loss of epithelial barrier and absorptive functions which can persist even into adulthood. There are still major lacunae in the knowledge of the molecular mechanisms relating to the prolonged intestinal injury which is considered the central mechanism in the pathophysiology of PD of infectious etiology. The underlying enteropathy could be either due to a persisting inflammation following infection or due to persistence of the infection itself. In the latter situation, the bacterial effector molecules are translocated into the host cell which in turn downregulates the host immune system resulting in prolonged colonization and inflammation via altered toll-like receptor signaling. Activated macrophages, toll-like

receptor signaling and the microbiota influence the stem cell's response to injury but the potential role in the pathogenesis of PD remains uncertain. Intestinal regeneration is the important component of recovery and understanding this process will benefit in designing therapeutic interventions. Several host factors such as epidermal growth factor, interferon- γ and IL-8 play specific roles in different aspects of intestinal regeneration.

Malnutrition

The underlying nutritional status is an important determinant in the pathogenesis of PD (Fig. 1). Malnutrition causes various changes in small bowel such as partial or subtotal villous atrophy, decreased functional surface area, disrupted mucosal barrier, decrease in brush border enzymes, decreased secretory antibodies and mucins, altered intestinal permeability, decreased crypt cell turn over, decrease in intestinal hormones such as gastrin, CCK-PZ and gastric inhibitory polypeptides, altered motility and intestinal flora which may perpetuate and aggravate the problem. The functions of the pancreas and liver are also disturbed in malnutrition which further worsens the diarrhea. It has been well documented that malnutrition is a risk factor for diarrhea leading to prolongation of diarrheal episode and higher mortality. Children with low height for age Z scores are more prone for prolonged diarrhea which in turn results in further decline of height and weight for age Z scores indicating the vicious cycle of malnutrition- diarrhea-malnutrition. Micronutrient deficiencies such as zinc also share in the causative mechanism of poor intestinal repair. Vitamin A, iron, folate, iodine, selenium deficiencies have also been shown to contribute to the pathogenesis of PD by predisposing to infection, impairing the gut immunity and altering the gut permeability.



Fig. 1: Infant with severe malnutrition and PD
(For color version see plate 13)

Immune Mechanism

The role of immune deficiency in persistent diarrhea is not well understood. Malnutrition can depress the immune functions including cell mediated immunity, humoral immunity and complement function predisposing to recurrent gut infections that contribute to prolonged small bowel mucosal injury. Micronutrient deficiency itself may cause transient immune deficiency which could be an important risk factor for persistent diarrhea.

Genetics

There is considerable interest in the potential role of mannose binding lectin (MBL) in the pathogenesis of enteric inflammation. Monnose binding lectin deficiency is the most common form of immune deficiency and has been implicated in HIV and *Cryptosporidium* infections.

Cow's Milk Protein Allergy (CMPA)

During acute diarrhea there is an increased macromolecular uptake secondary to the mucosal injury. Children who are susceptible and are on animal milk protein feeds present with features of cow's milk protein allergy (CMPA). Acute enteritis, either initiates or magnifies antigen specific T-cell activation within the lamina propria. Continuing milk feeds further worsens the mucosal injury and perpetuates the diarrhea.

Lactose Intolerance

The cells on the tip of the microvillus containing the disaccharidases face the brunt of the attack during prolonged diarrhea. Malnutrition further interferes with the maturation of these absorptive cells as they move upwards from the crypt to the tips. Lactase which is proportionately less in each cell is affected the most, leading to secondary lactose intolerance.

This complex pathophysiology where all the factors have an important role to play needs to be understood for providing the best therapeutic intervention.

CLINICAL FEATURES

Children with persistent diarrhea warranting hospitalization are usually lethargic, apathetic, undernourished, with or without dehydration and generally fall below the 3rd weight percentile with height being less affected (Fig. 2). The skin may show changes of secondary zinc deficiency (acro-oro-genital dermatitis). Very sick children may present with conjunctival xerosis, glossitis, cheilitis, stomatitis and features of hypoproteinemia (edema). Detailed examination of all systems should be done to exclude otitis media, pneumonia and any other source of sepsis. An enlarged liver may indicate fatty infiltration.

Table 1: Investigations in persistent diarrhea

<i>Initial tests</i>	<i>Additional tests</i>	<i>Specialized tests</i>
Full blood count including ESR, CRP, urine microscopy, stool for reducing substance, parasites and occult blood	Tissue transglutaminase antibody	Upper GI endoscopy with duodenal biopsy
Liver function tests, blood urea, serum creatinine, sugar, electrolytes	Immunoglobulin profile, HIV ELISA	Ileocolonoscopy
Urine and blood culture	Cow's milk protein antigen	Duodenal electron microscopy
Mantoux and X-ray chest	Ultrasound abdomen	

CONSEQUENCES OF PERSISTENT DIARRHEA

Unlike the morbidity and mortality in acute diarrhea occurring secondary to dehydration and dyselectrolytemia, a different spectrum of problems are seen in PD. The major and disturbing consequences are growth faltering, worsening of malnutrition, impairment of cognitive functions and increase in mortality and morbidity during the subsequent diarrheal or nondiarrheal diseases.

INVESTIGATIONS

Children with persistent diarrhea need to be extensively investigated for proper and effective management (Table 1). The initial investigations should include complete blood count including ESR, stool microscopy and occult blood, urine routine, urine and blood for culture, blood sugar and urea, serum electrolytes, C-reactive protein, creatinine, liver biochemistry, Mantoux and X-ray chest. The next set of investigations include tissue transglutaminase antibody, HIV and immunoglobulin profile to identify any other probable etiology. Upper GI endoscopy with duodenal biopsy and colonoscopy are done if there is occult blood positivity in stools, protein losing enteropathy and any suggestion of an inflammatory bowel disease. In young infants with a diagnosis of protracted diarrhea electron microscopy of the duodenal mucosa may help in identifying congenital villi disorders.

DIFFERENTIAL DIAGNOSIS

In certain situations, it may be very difficult to exclude conditions listed under chronic diarrhea or protracted diarrhea of infancy since all the three share some similarities. Congenital villi disorders such as autoimmune enteropathy, tufting enteropathy, IgA deficiency, sucrase isomaltase deficiency, acrodermatitis enteropathica and secretory tumors should be considered.

MANAGEMENT OF PERSISTENT DIARRHEA

The cornerstone of management in PD is to provide nutritional support and ensure proper rehabilitation with an objective to restore intestinal function and improve the weight and growth of the child. Therapy is based on a

combination of appropriate fluids to prevent or treat dehydration, nutritious diet that does not aggravate the diarrhea, essential vitamins and minerals and antimicrobials to treat infections. Some children need to be hospitalized specially if they are young infants, dehydrated, severely malnourished or have systemic infections. The treatment of persistent diarrhea can be divided into three phases:

- Phase of resuscitation
- Phase of renourishment
- Phase of rehabilitation.

Phase of Resuscitation

During this phase, the child is assessed regarding hydration status and fluids administered according to the degree of dehydration (no/ some or severe) as plan A, B or C. Associated nonintestinal infections such as pneumonia, sepsis, urinary tract infection, and otitis media should be treated according to standard guidelines. Enteral infections such as amebiasis or giardiasis should be treated with metronidazole. When *Shigella* is isolated it can be treated with ciprofloxacin or ceftriaxone. Children with cholera can be treated with doxycycline or erythromycin. Antifungals may be necessary in the presence of oral candidiasis. Routine treatment with antimicrobials is not effective and should not be given. Blood and blood products need not be administered routinely. If the hemoglobin is less than 4.5 gm/dl packed RBC may be advised.

Phase of Renourishment

The mainstay of therapy of persistent diarrhea is dietary management.

Infants Aged Less than 6 Months

Breast milk should be continued for infants on mother's milk. Since PD is rare in children who are exclusively breastfed, mothers who are not breastfeeding their wards are encouraged to re-establish lactation. The majority of children with PD have some degree of lactose intolerance and infants who are on artificial milk can be offered low (2.5-5 gm/kg/day) lactose feeds such as yogurt. If there is no improvement in 2 days the infant requires a lactose free diet.

Table 2: Diet in persistent diarrhea

<i>Plan A: Low lactose diet</i>	<i>Plan B: Lactose free diet</i>	<i>Plan C: Lactose + sucrose free diet</i>
Sugar: 1½ tsp	Glucose: 1½ tsp	Glucose: 1½ tsp
Oil: 1 tsp	Oil: 1½ tsp	Oil: 1½ tsp
Puffed rice powder: 2 tsp	Puffed rice powder: 3 tsp	
	Egg white: 10 tsp or Moong dhal 1 tsp	Chicken puree: 5 tsp
Water: 100 ml	Water: 120 ml	Water: 150 ml
Calories/100 g: 85 kcal	Calories/100 g: 90 kcal	Calories/100 g: 67 kcal
Proteins/100 g: 2 g	Proteins/100 g: 2.4 g	Proteins/100 g: 3 g
Mix milk, sugar and rice. Add boiled water and mix well. Add oil. Feed the child	Whip egg white well. Add rice, glucose, oil and mix well. Add boiled water and mix rapidly to prevent clumping. If moong dhal is added cook on low fire. Feed the child.	Boil chicken remove the bones and make chicken puree. Mix glucose and oil. Add boiled water and make a smooth paste. Feed the child.

For Infants >6 Months and Young Children

Simple disaccharide intolerances are very common and need minimal dietary intervention. Food prepared with cereals, pulses and curd are best suited for children above six months of age. Breast milk if available is continued and supplemented with standard diets which are prepared from home available ingredients. If breast milk is not available lesser quantity 50 to 60 ml/kg/day of milk to provide 2.5 to 5 gm/kg/day of lactose is offered along with cereals and MCT oil (plan A). Rice is the best cereal and rarely associated with allergy. About 65 to 75 percent of children will improve on this diet. These milk cereal mixtures are highly palatable, provide good quality protein micronutrients and result in good weight gain. In 10 to 15 percent of children who cannot tolerate even low lactose diet, feeds may be substituted by an equally protein energy dense lactose free diets (plan B) as shown in Table 2. Studies have shown that children who have been fed on cereal milk mix in which 35 percent of the calories was provided by milk had significant weight gain than those children on isocaloric milk free cereal based feed. Diets can be designed using one source of carbohydrate (rice, potato, broken wheat, semolina, corn), protein (Bengal gram, casein, green gram, chicken and egg) and fat (any oil preferably coconut oil) besides vegetables and fruits to provide micronutrients. It is ideal to continue low lactose or lactose free diet for at least a couple of weeks before reintroducing milk slowly. A small proportion of children (less than 5%) have to be managed with no lactose, sucrose or maltose diet such as chicken-based diets (plan C) and a very small proportion may require parenteral nutrition.

Principle of Feeding

The energy density of feeds should be around 1 kcal/g with an aim to provide an energy intake of at least 110 kcal/kg/day which is gradually increased to 150 kcal/kg/day with

Table 3: Micronutrient supplementation

Micronutrient supplement: Give for at least 2 weeks

Vitamin A: Oral; <6 months: 50,000 U; 6-12 months: 1 lac unit

Vitamin K: Single dose, 5-10 mg, IM or IV route

Zinc: 2 mg/kg/day

Iron 3 mg / kg/ day is added once child tolerates

Folic acid: 5 mg on day 1 and then 1 mg/day

Copper: 0.3 mg/kg/day

Severe malnutrition: Add Inj magnesium sulfate (50%) 0.2 ml/kg/dose BID × 2 days

a protein intake of between 2 to 3 g/kg/day. Vegetable oil is also added to the diet to provide calories and improve taste and the child is given 6 to 7 feeds per day to provide adequate calories. If the child improves on this diet, it is advisable to continue the same for one more week before switching to regular home available food. Hospitalization is recommended if child does not improve.

Micronutrient Supplementation

It is ideal to provide micronutrients through natural sources but initially it may not be practical and therefore vitamins, iron and zinc may be supplemented through oral medications. The current micro/macronutrient supplement is shown in Table 3. Iron is essential and is given at 3 mg/ kg/ day once child tolerates medications.⁵

Treatment Failure

The criteria for change of diet in the absence of any other predisposing factor such as recent infection are: (1) reappearance of dehydration any time after stabilization (2) Increase in number of stools >6/day (3) No weight gain after 3 days of adequate caloric diet >100 gm/kg/day or

weight loss. A diet from one plan should be given for a minimum period of seven days before changing the plan unless treatment failure occurs earlier.

Successful Treatment

The criteria for classifying success include: (i) Decrease in the frequency of stools (<2 loose stools/ day for 2 consecutive days) (ii) Adequate oral intake (iii) Weight gain (iv) Defervescence of fever.

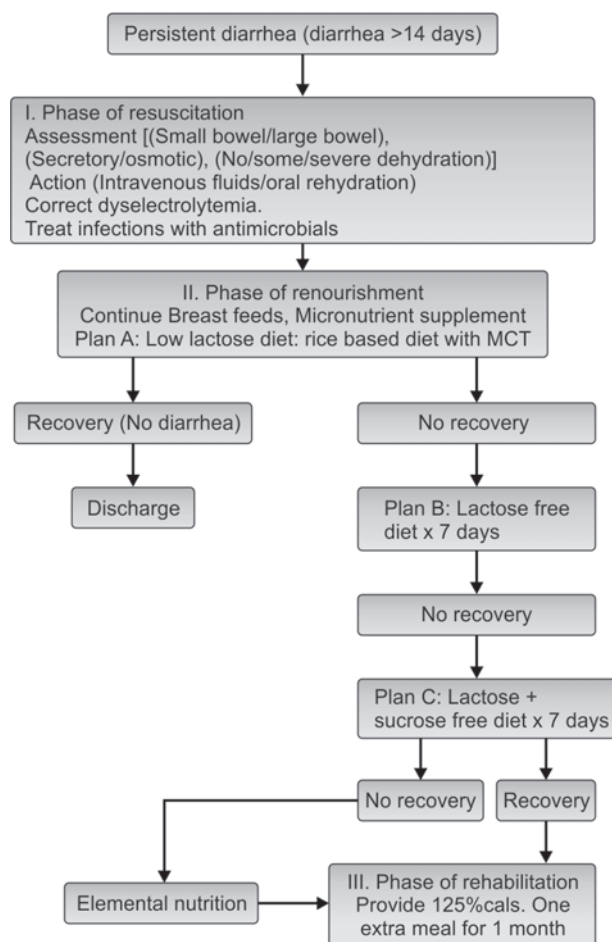
Treatment of Severely Malnourished Child with Persistent Diarrhea

Dietary management is more complicated when the child has PD with severe undernutrition, sepsis and dehydration. These children do not tolerate full enteral feeds and may need judicious balance of enteral and parenteral supply of nutrients till sepsis is cleared and the child's GI tract is ready for full oral alimentation. Albumin infusions may be required if there is significant hypoproteinemia. Simple PPN solutions incorporating additional glucose and amino acid preparations may suffice. Oral alimentation is initiated as early as possible to help villi repair. Nasogastric slow continuous carbohydrate-based feeds with low protein may be given initially and proteins slowly increased till the daily requirement is attained. Medium chain triglycerides are excellent source of energy. Monosaccharides and commercial lactose free are avoided till bowel frequency comes down to <4/day. The treatment protocol for persistent diarrhea is shown in Flow chart 2.

Commercially Available Lactose and Sucrose Free Diets

Many casein or soybean protein-based proprietary preparations with maltose and maltodextrins are available in the Indian market which can be offered to children with PD once the consistency and frequency of stools improve (Table 4). These are recommended when there are practical difficulties and preparations cannot be made at home.

Flow chart 2: Treatment protocol for persistent diarrhea



Children with persistent diarrhea generally do not need specialized elemental formulae. Occasionally partial or extensively hydrolyzed protein diets and elemental diets, are required which may overcome the usage of parenteral nutrition.

Table 4: Commercially available formulas that may be beneficial in persistent diarrhea

Commercially available formula	Composition	Energy (per 100 g)	Protein (per 100 g)
Isomil	Milk free+ lactose free	496 kcal	13 g
Nusobee casein	Lactose free	472 kcal	16 g
Zerolac	Lactose free+ sucrose free	472 kcal	15 g
Nusobee soy	Lactose free+ sucrose free	480 kcal	15.6 g
Prosoyal	Lactose free+ sucrose free	488 kcal	14 g
Simyl MCT	Lactose free+ sucrose free	456 kcal	14 g
Neogain	Hypoallergenic, gluten free, chicken-based formula	372 kcal	10 g
Neocate	Hypoallergenic milk protein free, amino acid formula	475 kcal	13 g

Food Allergies

Cow's milk protein allergy seen in two to three percent of children is the most common food protein allergy which can either cause or perpetuate diarrhea. In India, it has been reported in 13 percent of children less than 2 years of age presenting with chronic diarrhea. Rarely allergens in egg, soy, wheat, peanut, tree nuts, fish and crustaceans may cause diarrhea though their incidence is extremely rare in infantile PD. In some children with CMPA, it is necessary to substitute feeds with hypoallergenic feeds. These costly special commercial formulae are produced through enzymatic hydrolysis of bovine casein or whey, which are further processed by heat treatment and/or ultrafiltration. They are classified as 'extensively' or 'partially' hydrolyzed formulae according to the degree of protein hydrolysis. Partially hydrolyzed milk is more acceptable than extensively hydrolyzed milk since it retains some milk taste. Majority of children with CMPA outgrow it by 3 years of age.

Phase of Rehabilitation

Close supervision of nutrition during the period of convalescence is very important since relapses are common. Catch up growth is as important as cessation of stools and therefore at least 125 percent of calories are provided until the ideal target is reached. This can be achieved by providing one extra meal for 2 weeks after every episode of acute diarrhea and for one month following PD. This practical simple advice will help in the nutritional rehabilitation.

PREVENTION OF PERSISTENT DIARRHEA

Since the pathophysiology of PD is still not clear, it is difficult to either determine the frequency with which PD follows a primary enteric infection or design interventions during the acute diarrheal illness. Certain preventive measures such as appropriate feeding (breast and complementary feeding) and diligent attention to environmental hygiene and sanitation will go a long way in preventing PD in a community. In addition, apart from malnutrition, there are some well recognized risk factors in children, such as diarrhea in infants less than 3 months of age, absence of breast milk, recurrent diarrhea, antibiotic polypharmacy, early introduction of animal milk, lactose intolerance, micronutrient deficiency, associated infections like urinary

tract infections, chronic suppurative otitis media and bronchopneumonia and diarrhea due to enteroaggravative *E. coli*, *giardia* and *cryptosporidium*. These factors if attended to promptly or prevented could decrease the progression of acute diarrhea to PD. Measures such as exclusive breastfeeding till the age of 6 months, avoiding early introduction of animal milk protein and antibiotic over usage, safe complementary feeding strategies, optimal management with improved oral rehydration, zinc supplementation and continued feeding during acute diarrhea are definitely beneficial in preventing PD. The extent to which prevention of infectious diarrhea by vaccine will reduce PD and malnutrition is not known.

Recent additional strategies for preventing, treating and enhancing recovery from diarrhea and PD include the use of probiotics and functional foods. Genetically engineered molecules such as butyrate have been recommended for treatment for shigellosis by the upregulation of cathelicidin an antimicrobial peptide of the innate immune system. Isoleucine and vitamin D also appear to induce these antimicrobial peptides however more work is necessary in this field.

Persistent diarrhea with its associated high morbidity and mortality is therefore still a social and economic burden to the family, community, nation and globally. Though progress has been made in the management in the form of adequate resuscitation and good nutritional support more research is necessary in understanding the pathophysiology and prevention.

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Dietary Management of Celiac Disease

Sarath Gopalan, Neelanjana Singh

Empowering any person diagnosed with celiac disease to lead a normal healthy life on a gluten free diet is the ultimate objective of both the physician and the dietician. In order to achieve this objective, the glutenfree diet (GFD) should provide the recommended dietary allowance (RDA) of both macro- and micronutrients, specific to that age group. In general, the aim is to provide 4 to 8 servings of gluten free cereal, 2 to 3 servings of milk/soy milk/cheese/curd, 2 to 3 servings of legumes/dal, 3 to 5 servings of fresh vegetables, 2 to 4 servings of fruit, 2 to 3 serving of egg/fish/poultry, a handful of nuts (30g), 4 to 6 teaspoon fat.

Once the diagnosis of celiac disease has been made, the real challenge begins. From then on, the patient is expected to interact regularly with the dietician/clinical nutritionist. In the early stages, the clinical nutritionist has the additional very important task of being entrusted with the responsibility of providing emotional support to the family along with diet counseling of the affected individual. This can be a daunting task as the average north Indian family is emotionally shattered when they are told that wheat has to be eliminated from the diet for the rest of their life in order to treat this problem. Lifelong exclusion of wheat, rye, barley and their products is the only form of treatment for celiac disease. *It is extremely important to convey to the patient at the outset that despite the restrictions that are mandatory, such patients can consume a balanced diet with a variety of foodstuffs from all the major food groups.* In almost hundred percent of the cases, by the time the diagnosis is established, the patients are nutritionally challenged due to malabsorption of nutrients that has occurred over a period of time. However, remarkable recovery occurs quite rapidly in most cases (changes in body weight may be demonstrable in 6-8 weeks).

ENSURING COMPLETE ADHERENCE TO A GLUTEN FREE DIET

Lifelong exclusion of gluten is the prescribed treatment of celiac disease. It is extremely important to explain to the family that the GFD needs to be continued even if the patient appears to have been cured and remains asymptomatic. Cereals form the bulk of the diet in all parts of our country. In the northern and the western parts of our country where wheat is the dominant cereal in all meals the switch to a gluten free diet may require major modifications. A few of the cereals that can be safely used in a GFD plan are water chestnut (Singhara), amaranth (Ramdana), arrowroot (Paniphal), buckwheat (Kuttu), corn (Makki), millets (Ragi, Bajra, Jhangora), quinoa, rice, sago, sorghum (Jowar), tapioca (Shimla alu). Besan, soyabean and legumes can also be safely used as flours in combination with the above cereal flours to give the right texture, elasticity and taste to the “rotis” that are safe and acceptable for individuals with celiac disease. The acceptability of these alternate flours is satisfactory only if the ratios of the suggested flours prescribed by the dietician are adhered to. Failing to follow these instructions may have the “rotis” becoming very dry and brittle, which makes it difficult to knead, roll and cook. Moreover such dry “rotis” are disliked and not accepted by most children. The freedom to use fats in the diet of patient with celiac disease comes is very useful in such a situation. Any of the healthy fat sources can be added to the bread to improve palatability and the energy value of the food. Similarly, many of the gluten free flours require addition of warm water and butter/cream during the kneading process to make the “rotis” soft and edible.

The role of oats in celiac disease deserves special mention owing to the controversy surrounding it. The storage protein in oats is avenin which is not toxic to most individuals with celiac disease. However, the commercial

oats available in India is not gluten free. Gluten is a contaminant from other gluten containing grains, i.e. wheat, rye and barley that are usually grown alongside the wheat crop.

PROCESSED FOODS, THE BANE

The real challenge of adhering to a gluten free diet arises when processed packaged food forms an integral part of the diet, as is usually the case in children. A few examples would explain the intricacies that are involved in processed food ingredients. Baker's yeast is a gluten free product but brewer's yeast is not. Therefore, gluten free flour bread that uses brewer's yeast will be contraindicated in any individual with celiac disease. Similarly, there are many varieties of soy sauce, some of which are fermented using a wheat source. Such soy sauces could be one of the ingredients in the making of other sauces such as teriyaki, Pesto or oyster sauce rendering these products unsafe for patients with celiac disease. Rye is a cereal used for making bread in many Western countries in the developed world and many individuals in India mistake *Rai* seeds used extensively in India as seasoning and as a paste for the cereal rye. The cereal rye is on the 'unsafe list' whereas *Rai* seeds are safe. Most pure spices are gluten free, but when processed, changes in the composition, as in the case of *Hing* (Asafoetida), wheat flour is added to "*Hing*" rendering the product unsafe for use by individuals with celiac disease. Yet another example is the case of malt vinegar and synthetic vinegar. While malt vinegar contains gluten, the synthetic version is safe for use. Therefore, it may be possible for a product to be gluten free to begin with, but the method of manufacturing has a lot to do with the safety of the final product. For example, corn is a safe cereal but cornflakes, which are malted, become unsafe. Many medicines and cosmetic products could also contain gluten in the form of wheat germ oil or bulking agents, thus posing risk to affected individuals.

Many patients fail to understand the gravity of the problem when diagnosed with disease. Quite often, not just children but even adult patients comply poorly and ingest gluten containing foods intermittently. Such poor compliance not only retards recovery but also poses other risks such as stunting and neurological problems both in children and in adults. In untreated or partially treated celiac disease, malabsorption of calcium and vitamin D and iron could lead to osteoporosis and anemia. Celiac disease left untreated could also lead to serious problems such as cell mutation and malignancy. Providing intensive and repeated sessions of counseling is the only way of ensuring strict adherence to the diet. It is also extremely helpful if the family is provided complete information regarding availability of glutenfree products in the neighborhood. It is also feasible to make many glutenfree products at home with safe ingredients without straining the

family's financial resources. It is not mandatory to purchase expensive gluten free products in order to provide the appropriate nutritional support to patients with celiac disease. Locally available, inexpensive food items prepared in a safe work area are equally effective.

Reading food labels, understanding the hidden sources of gluten and the possible mechanisms of cross-contamination are issues to be discussed with the family in detail during the counseling sessions. The use of common toasters and roti containers and common oil for deep-frying all kinds of foodstuff are common pitfalls that occur when following a gluten free diet. Being alert to the various other sources of contamination such as chopping boards, knives, dusters is just as important when following a gluten free diet. Family members are made aware of strategies that help cope with events such as birthday parties and when eating out.

Until recently, celiac disease was considered a disease occurring in the Western world. Emerging epidemiological data from India, though scanty show a prevalence of 1 in 96 persons (Makharia et al, *J Gastroenterol Hepatol*, 2011). Celiac disease, initially thought to be exclusively a pediatric entity, is now known to occur at any stage in life beyond 6 months of age to even 90 years of age. The clinical presentation of the disease is varied and could involve 'atypical' presentations which are not restricted to symptoms suggestive of celiac disease associated with predominant gastrointestinal symptoms. The atypical presentation may involve skin manifestations in the form of a rash. In the 'silent' form of presentation the symptoms could be as nonspecific as feeling of fatigue or peripheral neuropathy with or without growth failure. Some of the recent research seems to suggest that dental enamel defect which is yet another manifestation of celiac disease could help identify with this problem and send them to a specialist for treatment. The varied clinical presentation of this disease is one of the reasons why diagnosis is delayed in many cases. The clinical suspicion of celiac disease should prompt the treating physician/clinical nutritionist to screen for the disorder using serological methods IgA tissue transglutaminase (tTG) antibody or IgA Endomysial antibody (EMA). The confirmation of the diagnosis is through an endoscopically obtained duodenal mucosal biopsy which shows histological features characteristic of celiac disease.

It is true that currently the only treatment option available for a celiac patient is to avoid all products derived from wheat, rye and barley. However, some of the experimental treatment options are showing promise. One such modality that is being tested is the use of enzyme combinations that can detoxify gluten before it enters the small intestine. Yet another method is scavenging the gliadin by using an appropriate binder. This would prevent the digestion of gliadin in the gastrointestinal tract. Other 'adjunctive' therapies such as the use of hookworm (*Necator*

americanus) are some of the nondietary approaches being tested for celiac disease. It seems possible that some of this experimentation and research will bear fruit and make a difference to the patient.

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Neelam Mohan, Vikram Kumar

INTRODUCTION

The role of microbes in the health of human gut has been well documented. Their presence in the gut protects the body from pathogenic organisms. Efforts to optimize the intestinal microbial milieu have increased the interest in adding probiotics and prebiotics to nutritional products. The use of probiotics and prebiotics should be backed by evidence based medicine.

DEFINITION

Probiotic: An oral supplement or a food product that contains a sufficient number of viable microorganisms to alter the microflora of the host and has the potential for beneficial health effects.

Prebiotic: A nondigestible food ingredient that benefits the host by selectively stimulating the favorable growth and/or activity of 1 or more indigenous probiotic bacteria.

Synbiotic: A product that contains both probiotics and prebiotics. Evidence for synergy of a specific prebiotic for a probiotic in the product is not essential. Synbiotics may be separate supplements or may exist in functional foods as food additives.

Postbiotic: A metabolic byproduct generated by a probiotic microorganism that influences the host's biological functions.

Functional food: Any modified food or food ingredient that provides a health benefit beyond that ascribed to any specific nutrient/nutrients it contains. Any food that contains probiotics or prebiotics is a functional food, e.g. yogurt and human milk.

PROBIOTICS

These bacteria are fermentative, obligatory, or facultative anaerobic organisms and are typically nonmotile and

produce lactic acid. These include members of the genera *Lactobacillus*, *Bifidobacterium*, and *Streptococcus*. In the human digestive tract, these organisms predominate in number and do not allow potential pathogenic microorganisms to inhabit and grow. It is currently hypothesized that these microbes generate small molecular metabolic byproducts which may function biologically as immune modulators. *Lactobacillus rhamnosus* GG (LGG), *Bifidobacterium lactis*, *Saccharomyces boulardii* and *Streptococcus thermophilus* are the most studied probiotic bacteria. Recently, some yeasts and their byproducts have also been studied and have been frequently used as probiotics.

PREBIOTICS

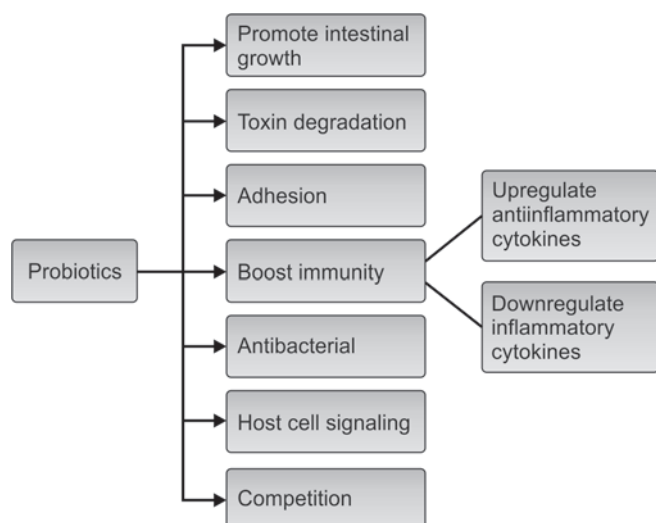
Prebiotics usually are naturally occurring indigestible oligosaccharides which may be added as dietary supplements to foods, beverages, and infant formula. In the presence of these prebiotics there is enhanced proliferation of probiotic bacteria. Examples of prebiotic oligosaccharides include fructo-oligosaccharides (FOSs), inulin, galacto-oligosaccharides (GOSs), and soybean oligosaccharides. The dietary fiber and dietary nucleotides although do not fit the exact definition of a prebiotic but have shown to have immunomodulating and direct intestinal biological properties.

MECHANISM OF ACTION OF PROBIOTICS (FLOW CHART 1)

An infant at the time of birth has a sterile gastrointestinal tract, but bacterial colonization occurs rapidly. The intestinal bacterial colonization is affected by gestational age, mode of delivery and diet. There is delay in those born by cesarian delivery, born preterm, and/or exposed to perinatal or postnatal antibiotics.

The composition of intestinal microflora does not change significantly after infancy. The intestinal microflora is important to the host for several reasons:

Flow chart 1: Mechanism of action of probiotics



- Microflora benefits the host by increasing colonization resistance (preventing overgrowth of potentially pathogenic organisms).
- Intestinal flora has a metabolic activity similar to that of the liver.

Probiotics and prebiotics are believed to exert positive effects on the development of the mucosal immune system. It is also believed that exposure to pathogenic microorganisms, lifestyle, illness and antimicrobial agents in the childhood may result in immune dysregulation in susceptible individuals and may lead to some chronic disease states.

The concept of treatment with probiotics comes from a belief that modern humans do not consume or replenish the beneficial microbes in their bodies and that they can do so by consuming probiotics.

Historically, ingested probiotic strains were believed to:

- Adhere to the gut wall,
- Block pathogen adhesion and growth and
- Give a nonspecific boost to immunity

It has been suggested that probiotics have other functions like producing anti-infectives, such as hydrogen peroxide and bacteriocins. They are also assumed to stimulate the cell signals that strengthen host-cell mucus barriers against pathogen invasion; and other signals that prevent virulent factors, such as toxins, from being released and maintaining balance of the TH1/ TH2 system.

USE OF PROBIOTICS IN CURRENT CLINICAL PRACTICE (TABLE 1)

Acute Infectious Diarrhea

Published randomized controlled trials (RCTs) in preventing acute gastrointestinal tract infections with the use of probiotics in healthy infants and children have

Table 1: Recommendations for probiotic use

Clinical condition	Effectiveness
Diarrhea	
Infectious childhood—treatment	A
Prevention of infection	B
Prevention of AAD	A
Prevention of CDAD	B
IBD	
Pouchitis—Preventing and maintaining remission	A
Ulcerative colitis, Crohn's	C
IBS	
	B
Allergy	
Atopic eczema associated with cow's milk allergy	A
NEC	
	C
<i>H. pylori</i> eradication	No efficacy

shown modest benefit. The results of a meta-analysis of probiotic prevention of acute rotavirus gastroenteritis in child care centers indicated that approximately 7 children would need to have been given LGG to prevent 1 child from developing nosocomial rotavirus gastroenteritis. To date, the available data do not support routine use of probiotics to prevent nosocomial rotavirus diarrhea in child care centers. However, there may be special circumstances in which probiotic use in children in long-term health care facilities or in child care centers is beneficial.

In a randomized, double-blind, placebo-controlled trial, administration of LGG significantly shortened the duration of acute rotavirus diarrhea by a mean of 40 hours, but duration of diarrhea of any other etiology was not affected. Probiotic administration also shortened the time necessary for intravenous rehydration by a mean of 18 hours. Results of several other meta-analyses and a Cochrane review 1 indicate that probiotics reduce the number of diarrheal stools and the duration of the diarrhea by approximately 1 day. The best results were observed with *Lactobacillus* GG. No obvious adverse effects of the probiotics were reported. Clinical and statistical heterogeneity of the prophylactic interventions precluded drawing clear conclusions about the efficacy of probiotics in prevention of acute infectious gastroenteritis.

Clostridium Difficile Associated Antibiotic Associated Diarrhea

Several open studies have suggested that *Saccharomyces boulardii*, *Lactobacillus* GG and *Lactobacillus plantarum* LP 299v could be beneficial in CDAD. However, larger controlled studies have not been performed in children. A randomized placebo controlled trial of *S. boulardii* plus standard antimicrobial therapy in adult patients with

recurrent CDI showed a risk reduction of recurrence down to 34.6 percent as compared to 64.7 percent in placebo group. In a recent study, Szajewska et al, gave the first demonstration of the efficacy of *Saccharomyces boulardii* in a double-blind, placebo-controlled trial in infants. Patients receiving *Saccharomyces boulardii* had a lower prevalence of AAD (AAD decreased by 81%) compared with patients receiving the placebo.

In an open study 19 infants and children presenting with a clinical picture of chronic diarrhea and in whom toxigenic *C. difficile* was the only enteropathogen identified by stool culture and stereotyping were evaluated. Most of the patients have been given one or more courses of antibiotics for intestinal infections in the weeks or months proceeding admission. Treatment with *Saccharomyces boulardii* at a dosage of 500 to 1000 mg/day (depending on age) for 15 days led to a rapid regression of the symptoms in 18 of the children, and clearance of toxin B and *C. difficile* in 16 of them.

Antibiotic-Associated Diarrhea

The antibiotics with which AAD is commonly associated are; Penicillin G and V (3%), Penicillin A and M, amoxycylav, cephalosporins, macrolides, trimethoprim-sulphamethoxazole and erythromycin.

There are 3 meta-analyses involving only children: The first review (December 2005) identified 6 RCTs involving 766 children. The review found that the treatment with probiotics compared with placebo reduced the risk of AAD from 28.5 to 11.9 percent. The second (August 2006 and the third meta-analysis or Cochrane review were by the same authors. They included 10 RCTs, (6 of them were included in the first review) involving 1986 children comparing treatment with lactobacilli species, bifidobacterium species, *Streptococcus* species or *Saccharomyces boulardii* alone or in combination.

The summary of the Cochrane review is as follows:

- Probiotics seem to have a positive effect on the incidence of diarrhea that is their use prevented AAD.
- However, once the AAD was set in the mean duration of diarrhea and stool frequency was no different with the use of probiotics versus controls.
- 5 of the 10 trials reported adverse events and there was no increase in adverse events with the use of probiotics.
- The probiotic strains that were found to be most effective were *Lactobacillus* GG and *Saccharomyces boulardii*.
- The studies were divided into 2 groups, namely ≥ 5 billion CFU of probiotics/day, and <5 billion CFU probiotics/day.
- It was seen that the probiotic dose of >5 billion CFU/day had a significant impact in preventing the incidence of AAD as compared to the dose of <5 billion CFU/day.

Traveller's Diarrhea

The use of probiotics for this disease remains controversial. The main advantage of probiotic therapy in TD that is mediated through changes in intestinal microflora in response to exposures incurred during travel is that they are therapeutically effective without disrupting the re-establishment of the normal protective intestinal microbial flora.

The conclusion drawn from an important meta-analysis was that several probiotics (*Saccharomyces boulardii* and a mixture of *Lactobacillus acidophilus* and *Bifidobacterium bifidum*) are safe and effective for the prevention of TD. No serious adverse reactions were reported. Probiotics may offer a safe and effective method to prevent TD.

Efficacy was also observed to be influenced by travel destination in several trials—the rate of TD observed in tourists from developed countries administered *Saccharomyces boulardii* who travelled to Africa was reduced by 50 percent whereas in those who travelled to India, there was no protection.

ATOPIC DISEASES

Probiotics have been shown to reduce inflammatory cytokines and intestinal permeability *in vitro*. Such an effect would be beneficial in allergic disorders. Therefore, several studies have looked at the efficacy of probiotics in allergic conditions, such as eczema, allergic rhinitis and food allergies. The results of these studies are promising, but a definitive role is yet to be confirmed. When *Lactobacillus* GG or placebo was given to pregnant mothers with a strong family history of eczema, allergic rhinitis or asthma and to their infants for the first 6 months after delivery, the frequency of developing atopic dermatitis in the offspring was significantly reduced at 2 and 4 years. Another placebo-controlled study showed significant improvement in children with atopic dermatitis after a 6-week administration of *L. rhamnosus* 19070-2 and *L. reuteri* DSM 122460. Children with high immunoglobulin E levels and 1 or more positive skin tests were more responsive to probiotic therapy. Infants with atopic eczema and cow's milk allergy responded more effectively to hydrolyzed whey formula when *Lactobacillus* GG was added in a large controlled study. When *L. paracasei* was given for 30 days to 80 children with perennial rhinoconjunctivitis, the quality of life questionnaire scores significantly improved relative to placebo. However, *L. rhamnosus* supplementation failed to show any benefit in birch-pollen allergic children in placebo-controlled trial. In a 2008 Cochrane review, probiotics have not yet been proven to be effective in the treatment of eczema.

CHRONIC INFLAMMATORY BOWEL DISEASE

In theory, probiotics may be beneficial in the treatment of IBD. It has been proposed that in individuals with

genetic susceptibility to IBD, chronic inflammation occurs in response to commensal digestive microflora because of various inherited defects of innate inflammatory-response pathways. Hence, modulating the commensal intestinal bacterial environment with probiotic supplements may reduce the inflammatory response in patients with IBD.

CHRONIC ULCERATIVE COLITIS

Evidence-based research suggests that probiotic therapy, either alone or along with an adjuvant, may be an effective alternative for some UC patients. The research does not definitively state that probiotic therapy is beneficial for either active disease or maintaining remission. Clinical trials suffer from small sample sizes, a noticeable lack of controls, and inconsistent results. The first pediatric RCT on the use of VSL#3 with standard IBD therapy showed promising results both in indication and maintenance of remission. However, the numbers were small. Future studies could examine the appropriate dosing, the effect of different formulations on probiotic efficacy, and a formalized safety testing strategy to assess novel bacterial strains for probiotic therapy.

Pouchitis is the most frequent long-term complication following pouch surgery for ulcerative colitis. The etiology is unknown, but an increased gut bacterial concentration is one of the main risk factors. The rationale for using probiotics in pouchitis is based on evidence implicating intestinal bacteria in the pathogenesis of this condition.

VSL#3, a highly concentrated mixture of probiotics, has been shown to be effective in the prevention of pouchitis onset and relapses and may be helpful in patients with mildly active pouchitis. It should be noted that the beneficial effect of one probiotic preparation does not imply efficacy of other preparations containing different bacterial strains, because each individual probiotic strain may well have unique biological properties.

CROHN'S DISEASE

Recent RCTs in which probiotics were used in pediatric as well as adult patients with Crohn's disease resulted in no significant benefit. A recent Cochrane review indicated that there is, as yet, no proven benefit for maintaining remission by administering probiotics to adults with Crohn disease.

IRRITABLE BOWEL SYNDROME AND CONSTIPATION

A number of studies have evaluated the response of irritable bowel syndrome to probiotic preparations. Although results between studies are difficult to compare because of differences in study design, probiotic dose, strain and duration of therapy, some studies suggest symptom

improvement. There are 9 randomized and 2 open studies in adults, whereas there is only 1 randomized pediatric study. Ten of the 12 studies report amelioration of symptoms such as bloating, abdominal pain or colonic transit. Many of the studies were fairly short and do not reflect improvement in the quality of life.

NECROTIZING ENTEROCOLITIS

Necrotizing enterocolitis (NEC) may result from an absent intestinal microbial colonization. Recently, a systematic review with meta-analysis or randomized controlled clinical trials has been published. The authors aimed to review all randomized controlled trials, evaluating efficacy as well as safety of any probiotic supplementation, in preventing stage 2 or greater NEC in preterm neonates (gestation <33 weeks) with very low birth weight (<1500 g), started within the first ten days, with a duration of at least seven days. Only 12 were randomized well-controlled clinical trials in preterm infants and five studies were excluded from the meta-analysis data regarding the NEC due to sepsis mortality and feeding practices. The results of the analysis are quite promising. A higher proportion of neonates in the control group developed definite NEC (38 of 690, 6%), compared to the probiotic group (15 of 730, 2%). Meta-analysis of data reduced risk of NEC in the probiotic group.

PROBIOTICS IN *H. PYLORI*/INFECTION

Role of probiotics in preventing the acquisition of *H. pylori* infection in uninfected subjects has not been investigated formally. A recent study indicates that the effectiveness of an eradication therapy regimen can be enhanced by using probiotics. A recent open, prospective trial undertaken in Italy showed that a mixture of nine probiotics and bovine derived lactoferrin and inulin, as a prebiotic, increased the success rate of eradication to 89 percent compared to just 72 percent compared to those treated with triple therapy alone for 7 days. One prospective, randomized, and controlled study assessed the success of triple therapy given for 7 days together with unfermented pasteurized milk, compared with the same triple therapy regimen and 1010 colony-forming units of *L. casei* DN-114 001 given once daily, in 100 mL of fermented milk, for 14 days. Triple therapy alone (57.5%) was less successful than triple therapy and probiotic (84.6%) in eradicating *H. pylori* infection. By contrast, another study evaluating *H. pylori*-infected children living in Argentina reported no benefit of adding yoghurt.

USE OF PREBIOTICS IN PREVENTION AND TREATMENT OF CLINICAL DISEASES

Few RCTs have evaluated the use of prebiotics in preventing or treating specific childhood diseases.

Prevention and Treatment of Allergy

A 2007 Cochrane review concluded that there was inconclusive evidence for giving prebiotics to prevent allergic disorders in infants. In a recently conducted RCT a reduced incidence of atopic disease was noted. Infants were fed a partially hydrolyzed formula with either an added mixture of FOS and GOS or maltodextrin placebo in the first 6 months of life. Confirmatory studies of the benefits of prebiotics are needed before any recommendations can be made for the use of prebiotics in infants and toddlers to prevent infection or atopic disease.

Other Disorders

It has been shown that the addition of dietary fiber has ameliorated diarrheal stools when added to infant formula. There have been controlled animal research studies that have shown that prebiotics may prevent or lessen carcinogenic processes, but there have been no RCTs in humans.

Combined Prebiotics and Probiotics to Prevent Allergy

Clinical benefit in preventing allergic diseases by co-therapy with probiotics and prebiotics in pregnant women and their infants was demonstrated in an RCT in Finland. Probiotic/prebiotic treatment showed no effect on the cumulative occurrence of allergic diseases but tended to reduce immunoglobulin E-associated (atopic) diseases. Probiotic and prebiotic treatment reduced the occurrence of eczema and atopic eczema but confirmatory studies are necessary prior to recommendations for their use.

PREBIOTICS AND PROBIOTICS IN INFANT FORMULA

Prebiotics

The European Commission's Scientific Committee on food concluded that they had no major concerns regarding the addition of oligosaccharides to infant formulas, including follow-up infant formulas (formulas modified especially for 6 to 12-month-old infants), up to a total concentration of 0.8 g/dl in ready-to feed formula products. A large multicenter trial to evaluate the safety of FOS supplemented infant formula demonstrated that infant growth was maintained during the 12-week study period for the FOS supplemented infant-formula group without any adverse effects. However, more information, including data from RCTs, is needed before the efficacy of adding prebiotics to infant formulas can be determined.

Probiotics

The overall health benefit efficacy of adding probiotics to infant formula remains to be demonstrated in large RCTs.

SAFETY OF PROBIOTICS AND PREBIOTICS IN INFANTS AND CHILDREN

Most of the probiotics in the market are nonpathogenic assigned generally regarded as safe (GRAS)—US standards or qualified presumption of safety (QPS)—EU standards. Extensive clinical trial literature is available with very few reports of significant complications (bacteremia, fungemia, endocarditis, caries) with the use of probiotics. Mild abdominal discomfort and flatulence are the only adverse effects reported regularly in most of the trials.

Theoretically, probiotics may be responsible for 4 types of side-effects in susceptible individuals.

Infections

There are case reports of probiotics being assumed to have caused infection due to accidental contamination of lines with lyophilized powder opened in the ICU in immune incompetent patient or after tooth extraction. However, organisms that are used as probiotics are easily identifiable and antibiotic susceptibility patterns are known. So infections with these organisms are easy to treat.

Transfer of Antibiotic Resistance

The danger of transfer of antibiotic resistance from probiotics to pathogenic organism is field of major concern. *Enterococcus faecium* could carry resistance factors like vancomycin resistance factor and hence organisms with pathogenic potential like *Streptococcus* and *Enterococcus* are not suitable candidates for use due to safety concerns.

Deleterious Metabolic Activities

Lactobacilli have been associated with dental caries. Other possible adverse effects related to deleterious metabolic activities of probiotics could be deconjugation of bile salts, degradation of intestinal mucus, lactic acidosis, toxic effects due to enzymatic activity and generation of biogenic amines.

Excessive Immune Stimulation

The cell wall components of the probiotics, especially bacterial species can induce cytokines and cause fever, arthritis and even induce autoimmunity.

In the *American Journal of Clinical Nutrition*, Boyle et al have identified potential risk factors for probiotic sepsis and created a scoring system for the same.

Major factors: Immunocompromised state

Minor factors: Central venous catheter, impaired intestinal epithelial barrier (intestinal inflammation, concomitant administration of broadspectrum antibiotics to which probiotic is resistant) and valvular heart disease

1 Major Factor or >1 Minor Factor Caution Against Use of Probiotics

In immunocompromised states like in a newborn or in pregnancy period, probiotics have been used extensively without any adverse events. Ingested bacteria only transiently colonize the gut and do not become permanent residents of the host.

DOSING

Probiotic supplement activity is measured in CFU. A daily dose of 5 to 10 billion CFU's is recommended for most conditions. The CFU's in these preparations can vary tremendously between brands. They should be protected from light, refrigerated and not be taken with food and antibiotics (gap of at least 2 hours between the two). Dry powders in bottles which have to be reconstituted should be stored in

Grade Evidence

"A" Strong, positive, well-conducted, controlled studies in the primary literature, not abstract form.

"B" Positive, controlled studies but the presence of some negative studies.

"C" Some positive studies but clearly inadequate amount of work to establish the certainty of "A" or "B".

dark or amber-colored bottles and reconstituted with cool water but the stability (probiotic viability) tends to go down with time. The dose needed for probiotics varies greatly with the strain and product, e.g. *B. infantis* is effective in alleviating the symptoms of IBS at 100 million CFU/day, whereas studies with VSL#3 use sachets with 300 to 450 billion CFU thrice a day for the same. It is not possible to state a general dose that is needed for probiotics; the dosage has to be based on human studies showing health benefit.

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Pediatric Inflammatory Bowel Disease

RK Gupta

INTRODUCTION

Inflammatory bowel disease (IBD) is the umbrella term used to describe chronic intestinal diseases including Crohn's disease (CD), ulcerative colitis (UC) and indeterminate colitis (IC).

In a large prospective study from UK and Ireland CD accounted for 60 percent and UC for 29 percent of childhood IBD. Remaining 11 percent accounted for IC, where a clear distinction between CD and UC was not possible.¹ Incidence of IBD, in particular CD has increased over last 10 to 20 years.²

IBD appears to be more common in countries in the northern hemisphere and in industrialized countries. Highest incidence is seen in Scandinavian countries (5.2 to 10 per 100000 children). Though incidence of IBD is considered less in developing countries, some studies suggest incidences almost similar to west. Incidence of IBD in south Asian population residing in western countries appear to be higher than the native population both in children and adults.¹

The most common time of onset of IBD is during pre-adolescent/adolescent era and young adulthood. A bimodal distribution has been shown with an early onset at 10 to 20 years and a smaller peak at 50 to 80 years of age. About 25 to 30 percent of patients present before 20 years of age.²

CD is a transmural inflammatory disease of gut with episodic progression. It can affect every part of the GI tract from the mouth to anus. UC is a nontransmural inflammatory disease with episodic progression that is restricted to colon.³

ETIOLOGY

The etiology of IBD is multifactorial, resulting from complex genetic, environmental, and immunological interactions.

The risk of IBD in family members of an affected person has been reported in the range of 7 to 30 percent; a child whose both parents have IBD has a >35 percent chance of acquiring the disorder. The gene contributing to CD susceptibility within IBD1 susceptibility locus at chromosome 16 is NOD2 or CARD15 gene. This gene has been identified as a cytoplasmic molecule involved in the sensing of unique microbial cell wall components. Despite the strong association with CD, alterations of NOD2/CARD15 gene are neither sufficient nor necessary for the development of CD. Patients with NOD2/CARD15 genotype have demonstrated fibrostenosing disease, usually in the ileum and earlier disease onset. Other genes studied are IBD5 locus on chromosome 5 and DLG5 locus on chromosome 10.⁴

Environmental factors including breastfeeding, smoking, education, occupation, climate and stress, etc. have been implicated in causation of IBD. Cigarette smoking is a risk factor for CD but paradoxically protects for UC. An infectious etiology has been considered and essentially all patients with IBD have high titers against various bacteria and viruses. Measles virus, *E. coli* especially adherent-invasive type and *M. paratuberculosis* have been considered but no association has been proven.¹ An abnormality in intestinal immunoregulation may be of primary importance in the pathogenesis of IBD.

In summary, IBD results from an inappropriate innate and acquired immune response to commensal microorganisms in genetically susceptible individuals.³

CLINICAL FEATURES (TABLE 1)

Traditionally diarrhea, abdominal pain and weight loss are considered as classical triad of IBD, but only 25 percent of children present with this triad. Clinical suspicion of IBD is raised in children with persistent (>4 weeks)

or recurrent (>2 episodes in 6 months) symptoms such as abdominal pain, diarrhea, rectal bleeding and weight loss. Other symptoms may be fever, growth retardation, malnutrition, nausea, vomiting, psychiatric symptoms, arthropathy, erythema nodosum, secondary amenorrhea, retardation of pubertal development or perianal disease. Growth failure is present at diagnosis in 10 to 40 percent of affected children.²

At the time of presentation about 45 percent children with UC have rectosigmoid disease, 40 percent have left sided disease and 15 percent have pancolitis. In children with CD, 50 to 70 percent present with terminal ileum involvement with more than half also involving colon specially ascending colon. Ten to twenty percent children of CD have isolated colonic disease and 10 to 15 percent has diffuse small bowel disease.⁵

UC commonly present with diarrhea, rectal bleeding and pain abdomen while CD presents as pain abdomen and weight loss which may lead to delay in diagnosis. A mass in the right lower quadrant may be indicative of CD. A rectal examination is important to check for fecal blood, to evaluate for fissures or hemorrhoids and to evaluate fistulas or other perianal disease.⁵

Extraintestinal manifestations are common and are found in about 25 to 35 percent children. These may precede the onset of GI symptoms by months and even years. Common extraintestinal manifestations are:³

- *Musculoskeletal*: Peripheral arthritis, axial arthropathies
- *Dermatological*: Pyoderma gangrenosum, erythema nodosum
- *Ocular*: Uveitis, episcleritis

- *Hepatobiliary*: Primary sclerosing cholangitis, hepatitis
- *General*: Fever, weight loss, malaise
- *Other*: Pancreatitis, nephrolithiasis, amyloidosis
- *Associated autoimmune diseases*: Addison's disease, hemolytic anemia, thyroiditis, etc.

To diagnose growth failure, height and weight must be recorded at diagnosis and all subsequent visits.

MONTREAL CLASSIFICATION OF IBD³

Ulcerative Colitis

E1-proctitis, E2-left colitis, E3-pancolitis

Crohn's Disease

Age at onset: A1-<16 years, A2-17 to 40 years, A3->40 years.

Area involved: L1-terminal ileum, L2-colon, L3-ileocolon, L4-upper GIT, L4+-lower GIT and distal disease.

Depth involved: B1-nonpenetrating, without stricture formation, B2-with stricture formation, B3-internally penetrating, B3p-perianally penetrating.

In 2010, few modifications have been done (Paris modifications) in montreal classification for convenience in pediatric IBD and to denote presence or absence of growth failure.⁶

DIFFERENTIAL DIAGNOSIS

Differential diagnosis for IBD includes common causes of pain abdomen like amebiasis, tuberculosis of gut, constipation, peptic ulcer disease, gastroesophageal reflux disease, urinary tract infection, mesenteric adenitis, etc. Rectal bleeding can be seen in infective colitis, polypoidosis, hemorrhoids, anal fissures, Meckel's diverticulum and intussusceptions. It is important to remember that whenever symptoms of diarrhea, rectal bleeding and pain abdomen occur with weight loss, anorexia, growth failure or extraintestinal manifestations, the diagnosis of IBD must be considered and ruled out.⁶

DIAGNOSTIC WORK-UP

In a child with suspicion of IBD following laboratory studies are suggested:⁵

- CBC, ESR, CRP, anemia studies
- LFTs, serum protein and A/G ratio
- RFTs-urea, creatinine, electrolytes

Stool studies: microscopic examination, culture, for ova and cyst and for calprotectin. Stool culture is must to rule out infectious causes of enteritis or colitis especially *C. difficile*, *Salmonella*, *Shigella*, *E. coli* (O157:H7) and *Campylobacter*. *Giardia lamblia* and *E. histolytica* should also be ruled out by good microscopic examination.²

Table 1: Differences in clinical features of UC and CD³

	UC	CD
Hematochezia	Common	Rare
Diarrhea and mucus	Common	Rare
Small bowel involvement	Rare	Common
Upper GI involvement	Rare	Common
Abdominal mass	Not present	Sometimes
Growth failure	Uncommon	Common
Perianal disease	Rare	Common
Rectal involvement	Universal	Rare
Colonic disease	100%	50–60%
Small bowel ileus	Rare	Common
Colonic obstruction	Rare	Sometimes
Strictures	Rare	Common
Perianal fistulae	Rare	Common
Risk for cancers	Greatly increased	Increased
p-ANCA positive	Common	Rare
ASCA positive	Rare	Common

Fecal calprotectin is a major protein found in the cytosol of inflammatory cells. This protein is stable in stool samples for few days in room temperature and a sample of about 5 g is sufficient to measure its level. It has been suggested by many researchers as a screening test of IBD as well as a test to denote mucosal healing.⁷

Serum ASCA and P-ANCA-ASCA antibodies against *Saccharomyces cerevisiae* and p-ANCA antibodies against the cytoplasm of neutrophils are found in serum of CD and UC patients respectively. P-ANCA is found in about 70 percent of UC while ASCA is found in about 55 percent patients with CD. If IgG and IgA ASCA are both detected, this is 100 percent sensitive for CD. High ASCA titers are associated with onset at young age and with fibrostenosing disease.⁸ When both ASCA and p-ANCA are considered together, they have a specificity of 95 percent and positive predictive value of 96 percent for IBD.⁵

Antibody to *Escherichia coli* outer membrane protein (anti-OmpC), anti-flagellin (anti-CBir-1) antibodies.

Celiac serology: As clinical features overlap, celiac serology should be done.

Imaging

X-ray abdomen plain—if sick child to look for complications as obstruction, toxic mega-colon or perforation.

USG Abdomen—Useful Noninvasive Test

Barium meal with follow through can identify mucosal lesions, strictures, fistulas. It is very important when upper GI endoscopy and colonoscopy are normal in a suspected case.

Barium enema can identify strictures and abnormal mucosa. It is useful to evaluate colon and distal ileum.

CT scan abdomen can identify intestinal abnormality and extraluminal abnormalities as abscess. UC is

associated with mural thickening <1.5 cm, no thickening of small bowel, increased perirectal and presacral fat and target appearance of rectum. Findings consistent with CD include mural thickening >2 cm, small bowel involvement, perianal disease, abscesses and fistulas.

- MRI abdomen and MR enteroclysis has great value nowadays.
- Bone density studies to evaluate bone mineralization.

ENDOSCOPIC EVALUATION (TABLE 2)

Upper GI endoscopy and biopsy- looks at esophagus, stomach and duodenum and is advocated in all cases.

Colonoscopy and biopsy: Colonoscopy including intubation of the terminal ileum and multiple biopsies for histology obtained from all segments of lower intestinal tract is essential. It is the most important investigation to differentiate between CD and UC and identifies localization and extent of inflammatory disease. Intubation of terminal ileum with terminal ileum biopsies should always be attempted as isolated ileal disease may occur in 9 percent of CD cases. Rectosigmoidoscopy alone is insufficient. Upper endoscopy is advocated in all cases irrespective of presence or absence of upper GI symptoms.

Capsule endoscopy is increasing being used in detection of obscure small bowel lesions. It is indicated when CD is strongly suspected but cannot be documented by barium study and upper GI endoscopy. The drawback is high cost and risk of capsule impaction in strictured area of small bowel.

MANAGEMENT

The main goal of medical management of IBD is to achieve clinical and histological remission by suppression of inflammation with the least amount of side effects. Good control of the inflammatory process will decrease chances

Table 2: Endoscopic and histological findings in CD and UC²

	CD	UC
Endoscopy	Ulcers (aphthous, linear, stellate) Cobblestoning Skip lesions Strictures Fistulas Abnormalities in oral or perianal area Segmental distribution	Ulcers Erythema Loss of vascular pattern Friability Spontaneous bleeding Pseudopolyps Continuous distribution with variable proximal extension from rectum
Histopathology	Submucosal or transmural involvement Ulcers, crypt formation Crypt abscess Granulomas (noncaseating, nonmucin) Focal changes Patchy distribution	Mucosal involvement Crypt distortion Goblet cell depletion Crypt abscess Mucin granulomas (rare) Continuous distribution

of surgical intervention. In addition successful treatment should provide adequate nutritional support to promote normal growth and should attempt to minimize alteration in the physical and social functioning of the child.⁵

ASSESSMENT OF SEVERITY (ECCO CONSENSUS)³

Ulcerative Colitis

- *Mild (S1)*: Up to 4 stools per day, normal ESR, pulse rate, Hb, temperature.
- *Moderate (S2)*: Four to six stools per day with no evidence of systemic involvement
- *Severe (S3)*: >6 bloody stools per day, ESR >30, Hb <10.5, HR >90/min, fever
- *Remission (S0)*: <3 stools per day without blood.

CROHN'S DISEASE

- *Mild*: patient is able to walk, can tolerate oral nutrition, no ileus, no abdominal mass, no systemic involvement. CRP may be elevated.
- *Moderate*: weight loss >10 percent, intermittent vomiting, painful abdominal mass but no ileus, lack of response to drug therapy in mild CD.
- *Severe*: cachectic patient or has ileus, an abscess, or persistent symptoms despite intensive treatment.

MEDICAL MANAGEMENT (TABLE 3)

Following drugs may be used in management of IBD:

- *Aminosalicylates*: Mesalamine, Sulfasalazine, Olsalazine
- *Corticosteroids*: Prednisolone, Budesonide, methylprednisolone
- *Immunomodulators*: Azathioprine, 6-Mercaptopurine (6-MP), Methotrexate (MTX), Cyclosporine, Tacrolimus

Table 3: Medical management of IBD

	CD	UC
Mild	Aminosalicylates Antibiotics	Aminosalicylates
Moderate	Corticosteroids Aminosalicylates or AZA or 6-MP or Methotrexate	Corticosteroids Aminosalicylates or AZA or 6-MP or Methotrexate
Severe	Corticosteroids AZA or 6-MP or Methotrexate or Infliximab	Corticosteroids AZA or 6-MP or Methotrexate or Cyclosporine
All cases	Nutritional support Monitor growth closely	Nutritional support Monitor growth closely

- *Biologic agents*: Infliximab Adalimumab
- *Others*: antibiotics and probiotics.

Mild-to-moderate CD is treated initially with 5-aminosalicylic agents or antibiotic therapy with metronidazole and ciprofloxacin. For moderate to severe CD corticosteroids are effective in inducing remission. In patients who have achieved remission with steroids, immunomodulators like azathioprine and 6-MP are helpful in maintaining remission. Steroids are not used for maintenance therapy. Methotrexate may be used for induction of remission in patients who do not respond to steroids for remission. Infliximab, a monoclonal antibody directed against tumor necrosis factor-alpha is being used more commonly to treat moderate to severe CD in patients who do not respond to steroids and immunomodulators. It can be used as first line therapy in CD with severe, perianal, fistulising disease. About 30 percent children may not respond to infliximab. Adalimumab is another biological agent which may be used in severe CD.

In mild-to-moderate UC, 5-aminosalicylic agents are used. In UC topical treatment with enemas is also very effective. In moderate to severe disease steroids are used to induce remission. In severe UC who fail to respond to steroids, cyclosporine is an option. Azathioprine, 5-MP, MTX may be used in refractory cases of UC for maintenance of remission. Biological agents are usually not needed in UC.

Aggressive nutritional support can improve growth parameters in IBD children.⁹ All children with IBD need appropriate nutritional assessment and support to minimize growth retardation due to malnutrition. Special attention should be paid to calorie intake and vitamin and mineral supplementation. Calcium and vitamin D are needed to prevent bone disease.

SURGICAL MANAGEMENT

Surgical management of IBD is typically required for complications of the disease. Indications include perforation/abscess, obstruction, strictures, fistula, toxic mega-colon and malignancy.^{3,6} Ultimately more than 50 percent of patients of CD may require resection. In severe nonresponding UC total proctocolectomy may be needed.¹⁰

INDETERMINATE COLITIS

The term "indeterminate colitis" has been used to delineate a group of patients with IBD limited to colon the diagnosis of CD or UC is not certain. Diagnosis of IC may be kept if in a child with colitis, rectum is normal endoscopically or histologically, or mild ileitis is present. IC is the diagnosis in a child with pancolitis along with anal tags or fissures.¹¹

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Nonalcoholic Fatty Liver Disease in Children

Prashant Mathur, Narendra K Arora

INTRODUCTION

Globally overweight and obesity have emerged as an epidemic in children and adults with a spectrum of psychosocial and medical consequences manifesting across the lifespan.¹ Adiposity affects almost all organs of body, but some systems like cardiovascular and endocrine are affected to a greater extent than others. Obese children are at higher risk for hypertension, hyperlipidemia, arteriosclerosis, and diabetes mellitus type-2. Chronic liver disease associated with obesity has been identified in adults as a distinct identity since 1970's, and after almost a decade the condition was reported in children and adolescents. Moran et al provided the first report on severe hepatitis and fibrosis associated with obesity in 3 children aged 10 to 13 years.²

Nonalcoholic fatty liver disease (NAFLD) describes a spectrum of liver disease in persons who have not consumed alcohol in significant amounts so as to cause liver damage, and in whom no other etiology for fatty liver is present. The pathological spectrum ranges from simple hepatic steatosis, to infiltration by inflammatory cells and mild to moderate fibrosis (Nonalcoholic steatohepatitis) leading to cirrhosis.³ With advancing fibrosis, the steatotic component diminishes so that in cirrhotic livers the fat may no longer be seen. Pathologically, NAFLD is a result of complex hepatocellular metabolic dysfunction in which insulin action is deranged, leading to deranged metabolism of fat and free fatty acids and subsequent oxidant mediated damage to the hepatocytes. Several factors sustain and amplify this cytotoxic mechanism. Usually the abnormality of liver is discovered incidentally while evaluating a child for pain abdomen or some other unrelated ailment. In the absence of significant consumption of alcohol in childhood, the nomenclature may not deem fit, as it describes the entity best in adults.

Childhood presents a unique period of growth and development where the causes of fatty liver are enumerable as compared to adults. Broadly, they can be divided into:

HEPATIC CAUSES

- Overweight and obesity related
- Metabolic liver diseases (Wilson disease, galactosemia, hereditary fructose intolerance, glycogen storage disorders, sialidosis, mannosidosis, fucosidosis, hereditary tyrosinemia, alpha anti-trypsin deficiency, homocystinuria, abetalipoproteinemia, wolman disease, tangiers disease)
- Syndromes (Schwachman-Diamond syndrome, Bardet-Biedel syndrome, Alstrom syndrome, Lipodystrophy syndromes, Turners syndrome, Cohen syndrome, Prader-Willi syndrome, Kabuki-Niikawa-Kuroki syndrome, Dorfman-Chanarin syndrome, Poly Cystic Ovarian syndrome)
- Chronic viral hepatitis C (HCV)
- Autoimmune hepatitis, sclerosing cholangitis and others.

Nonhepatic Causes

- Nutritional: prolonged protein calorie malnutrition, total parenteral nutrition, starvation, intestinal bypass surgery, rapid weight loss
- Infections: HIV
- Drugs (glucocorticoids, hypervitaminosis-A, methotrexate, L-asparaginase, zidovudine, amiodarone, didanosine, diltiazem), and toxins (mushrooms - Amanita phalloides)
- Diabetes mellitus
- Inflammatory bowel disease, cystic fibrosis, celiac disease, nephritic syndrome and others.

Thus, one has to consider and rule out several conditions associated with a fatty liver in children before labeling a patient as nonalcoholic fatty liver disease (NAFLD).

This article describes idiopathic childhood obesity/metabolic syndrome associated liver involvement.

PREVALENCE OF NAFLD IN CHILDREN

The exact prevalence of NASH/NAFLD is not well established. Based on the biopsies of potential donors for transplant, autopsy studies of accident victims and hospital based studies, about 2 to 3 percent of lean and 15 to 20 percent of obese adult individuals have steatohepatitis.⁴ Among children the information on its prevalence is scanty. Pooling data from studies performed mainly in tertiary medical centers, the prevalence of NAFLD in obese children has been reported to range from 20 to 77 percent.⁴

Worldwide studies conducted amongst overweight and obese children and adolescents have shown liver involvement in a significant proportion using various diagnostic modalities in isolation or combination. In Canadian children (n=36; 4-16 years) from multiethnic origin with body weight ranged from 114 to 192 percent of ideal weight-for-height, liver biopsy (done in 24 children) had features of some fibrosis in 71 percent and cirrhosis in one. About 30 percent of the cohort had acanthosis nigricans, a known association with insulin resistance.⁵

DIAGNOSIS OF NAFLD IN CHILDHOOD

A pediatrician is likely to encounter NAFLD in three settings:

1. As an incidental finding of raised aminotransferases (more than 2 times the upper normal value of the laboratory) while testing for some other condition in the absence of overt liver disease.
2. During the work-up of an obese child for management.
3. On investigating a child for liver disease.

NAFLD often coexists with other obesity comorbidities and therefore the pediatrician should also be on the lookout for other common *red flags* which may include acanthosis nigricans (insulin resistance), xanthelasma (hyperlipidemias), biliary colic (gall stones), obstructive sleep apnea symptoms, and elevated blood pressure (left ventricular hypertrophy). This association between NASH and components of the metabolic syndrome (MS) has been investigated in children by the United States national institutes of health (NIH) funded NASH Clinical Research Network (NASH-CRN) that found the risk of concurrent MS, as compared to histologic severity of NAFLD, was the greatest in those with severe steatosis (grade 3 as compared to grade 1).⁶ The investigations in a child suspected of NAFLD are guided by two areas of interest.

1. To assess extent and severity of liver involvement: This involves using imaging techniques (ultrasound,

Table 1: Scheme for investigating a child with suspected NAFLD

Initial Laboratory Work-up

Metabolic evaluation

- Fasting lipid profile
- Fasting glucose
- Fasting insulin
- Hemoglobin A1C
- Thyroid stimulating hormone

Chronic Hepatitis Screening Laboratories

- Autoantibody profile
- Alpha 1 antitrypsin phenotype and level
- Serum ceruloplasmin
- Serum iron, total iron binding capacity, ferritin
- Hepatitis C antibody
- Hepatitis B_sAg and Hepatitis B_sAb
- Prothrombin Time

magnetic resonance imaging), studying liver histology for histopathological changes of NASH and its progression.

2. Assessment of comorbidities which determine the setting of its occurrence and outcome. The suggested scheme is as given in Table 1.

ASSESSMENT OF LIVER INVOLVEMENT IN NAFLD

Investigators have used various methods (either singly or in combination) to determine NAFLD in childhood. The presence, degree and pattern of aminotransferase elevation are nonspecific and do not provide etiological differentiation when used in isolation. Ultrasound of the liver has been found to be a good screening tool for assessment of the degree of fat in the liver, but it does not correlate well with the degree of fibrosis. Joseph et al⁷ reported a sensitivity of 89 percent and specificity of 93 percent in detecting steatosis in the liver, and a sensitivity of 77 percent and specificity of 89 percent in detecting increased fibrosis in the liver. The sensitivity of CT scans varied from 54 to 93 percent and specificity between 87 and 97 percent depending on the protocol which was followed.⁸ Ultrasound screening for presence of fatty liver in high risk individuals seems to be a reasonable tool, while CT scans and MRI are very costly and not feasible at the moment for use in routine work-up of suspected NAFLD. Liver biopsy remains the gold standard for diagnosis of steatosis and various degrees of fibrosis, and for comparison of various other diagnostic modalities.

ELEVATED SERUM AMINOTRANSFERASES

Studies have estimated alanine aminotransferases (ALT) and aspartate aminotransferases (AST), either in isolation or in combination to estimate the prevalence of fatty liver in childhood. In NAFLD the ALT and AST levels are elevated to up to 5 times the upper limit of normal. The ratio of ALT:AST in obese individuals is reported to be greater than 1.

The largest community based pediatric data on NAFLD from US was provided by Strauss et al⁹ in 2000, where they estimated obesity and overweight in 2450 children aged 12 to 18 years of age who were surveyed during the NHANES III (1988-1994), and estimated serum aminotransferases in 86 percent of the sample. The overall prevalence of overweight and obese children was 16 percent (BMI between 85th and 95th percentile) and 10 percent (> 95th percentile) respectively. Serum ALT was raised above 30 IU/L in 75 children, and of these 61 percent were obese. The prevalence of raised ALT levels was significantly higher in overweight (5%) and obese children (9.5%) respectively, as compared to normal weight children (1.5%). The odds of raised ALT levels in overweight and obese children as compared to normal weight children was 3.4 (95% CI 1.7-6.8) and 6.7 (95% CI 3.5-12.8). In this study GGTP levels were also significantly raised in overweight (1.3%) and obese (3.9%) children.

FATTY LIVER ON IMAGING

Ultrasonography, CT and MRI scanning are reliable for detecting moderate to severe fatty changes in the liver. Hepatic fat gives hyperechogenic feature on ultrasound compared to spleen, while it gives hypodense shadows on CT scan. Sonologically accurate diagnosis can be made when there is moderate or severe (>33%) fatty infiltration of liver and radiological modalities may not be able to detect or characterize NASH and differentiate it from steatosis alone.¹⁰ MRI is the only noninvasive modality with ability to quantify the fat content of liver.

No imaging method is able to distinguish between simple steatosis and NASH and/or indicate the stage of fibrosis. Though fibrosis and inflammation may result in a typical ultrasonographic pattern, this finding does not reliably distinguish fat from fibrosis or reliably diagnose cirrhosis. Hepatic inflammation, fibrosis and cirrhosis are most accurately diagnosed by liver biopsy results. Routine CT scanning does not add more information on fatty liver disease that what is known from ultrasonography.

Studies have shown that ultrasonography has a low sensitivity (80% and 88.6%) in measuring the degree of steatosis in the liver and that this is confirmed by its inability to discriminate hepatic fibrosis from steatosis. In the largest epidemiological study on fatty liver in obese children using USG, Tominaga et al¹¹ found the prevalence of

fatty liver in 2.6 percent amongst 810 children aged 4 to 12 years old attending a public kindergarten and elementary school in Northern Japan. The study found a direct relationship between the degree of obesity and the prevalence of fatty liver, subcutaneous fat estimation by USG as a better predictor of fatty liver than Rohrer's index, BMI and JSI.

LIVER HISTOLOGICAL EVIDENCE OF NAFLD

No single microscopic finding is diagnostic of NASH. At present liver histopathology is the gold standard for NAFLD clinic-pathologic correlation and exclusion of other causes. In adults, histological features of NAFLD have been well-described and include microvesicular steatosis, perisinusoidal, or pericellular fibrosis, foci of lobular inflammation, lipid granulomas, Mallory hyaline and megamitochondria.¹² The entire histopathological spectrum of NAFLD has been described in children as well. Thus, NAFLD in childhood can present as steatosis, steatohepatitis, fibrosis, and cirrhosis. The major pitfall in the available literature is the smaller sample size and/or non uniform reporting of histopathology reports.

MANAGEMENT OF NAFLD

At present there is no consensus for the treatment of NASH, especially in childhood. Additionally there is no approved pharmacological therapy for childhood NAFLD. But effort needs to be made to prevent development and progression of fibrosis. As the pathogenesis is unclear, management has been largely empirical. Drugs have been targeted at the NAFLD associated conditions like obesity, insulin resistance and diabetes, hyperlipidemia. Prognosis of NAFLD is dependent on the histologic severity and associated risk factors.

The key principles of NASH management are weight reduction and hepatocyte protection. Studies have shown normalization of serum aminotransferases and steatosis with weight reduction. For adults, a 5 to 10 percent weight loss is thought to be adequate for noticeable improvement, but similar figure for children is not known. Dietary modification, changes in lifestyle with increasing physical activity are the key for this effort. Family based interventions are most effective for its sustenance in long run. Ursodeoxycholic acid used are N-acetylcystine, Betaine have also been used with some positive outcomes. Metformin, has been shown to reverse fatty liver in obese adults, adolescents with type-2 diabetes mellitus.¹³

A strong association exists between the presence of steatosis in a donor liver and poor graft function, and as a result cadaveric donor livers with macrovesicular steatosis >40 percent are not used routinely.¹³ Transplantation in the patients of NASH may be complicated by associated comorbidities like obesity, diabetes and hyperlipidemia.

At present transplantation for overt NASH is rare, but it is possible that its contribution may have been underestimated in past and will most likely rise in view of the increasing obesity prevalence. After development of cirrhosis from NASH, the histological features of steatosis and various necroinflammatory changes may become less evident or disappear.

OUTCOME OF NAFLD

There is lack of information on the natural history of the disease in children and most knowledge is extrapolated from adult data. The long term studies indicate that cardiovascular diseases, cancer and liver diseases related mortality are the major outcomes of NAFLD progression. Simple steatosis is considered as a benign condition with little evidence of progression to more severe liver disease, while those with features of steatohepatitis or more advanced fibrosis have the worst prognosis. Children with NAFLD may be at increased risk for cirrhosis if obesity is not reversed and other factors, such as alcohol consumption are not avoided. Weight loss will reverse elevations in aminotransferases and reduce hepatic steatosis, and it may decrease fibrosis. When liver biopsies were performed in adults after weight loss, all had reduced steatosis, but only 50 percent had a reduction in fibrosis. Rapid weight loss may actually increase fibrosis because of an increase of free fatty acids to the liver and increased lipid peroxidation with resultant increased oxidative stress. This led to the conclusion that rapid weight loss should be avoided in these patients. Patients with NASH who develop cirrhosis may require liver transplantation. But, several case reports have shown recurrence of steatosis, steatohepatitis and cirrhosis in post-transplant patients.¹⁴

The progression and natural history of NAFLD has been shown to vary according to the histological type. Identification of cirrhosis in obese children suggests progression of NAFLD to cirrhosis. Probably it also depends on the associated body fat related comorbidities.

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Section 8

Endocrinology

Editors

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Childhood Obesity

Archana D Arya

DEFINITION

Childhood obesity is a complex problem of global concern having assumed epidemic proportions in developed countries. In particular a significant increase has also been observed in India, a developing nation where obesity is primarily restricted to the affluent urban society, whereas in the developed countries it is rampant amongst the lower socioeconomic population as well.

EXCESS OF BODY FAT

The term Overweight denotes excess of fat or other tissues. Ideally, the diagnosis of obesity should be based on direct demonstration of increased amount of body fat, but this is not practical and requires expensive equipment.

The measures commonly used to define obesity are body weight, weight for height, body mass index, skin fold thickness and waist to hip ratio. Each method has its advantages and disadvantages.

Body Weight

Body weight for age is easy to obtain and hence is frequently used as an index for obesity. This measurement is inadequate since it does not take into account the stature of the child.

Weight for Height

It is a better index for assessing obesity. Weight for height more than the 90th percentile, or body weight more than 120 percent of the ideal body weight (mean weight for height) has been defined as obesity. Body weight more than 130 percent of the ideal body weight is considered as severe obesity. Growth charts have been developed for this purpose.

Body Mass Index

The WHO has recommended using body mass index (BMI) as an index of being overweight or obese. Body mass index is calculated by dividing the weight in kilograms by height in meters squared (kg/m^2).

Normal BMI value for adults is 19-22 kg/m^2 with BMI 25 to 29.9 being termed as overweight and >30 as obese.¹

The adult BMI values cannot be applied to children since the BMI does not remain static in children and changes as they grow. A BMI of 22 kg/m^2 in an 8-year-old male child will fall above the 97th percentile for his age (obese) whereas it would be normal for an adult.

Hence, it is important to use age related standards in children. Age and sex related percentile charts are available for BMI for boys and girls from CDC (USA), KN Agarwal et al and recently from Khadiolkar et al.² The CDC charts are depicted in Figures 1 and 2.

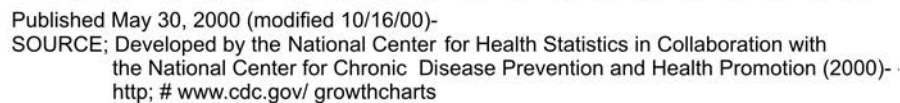
Obesity is defined as BMI >95 th percentile for age and sex.

Body mass index (BMI) between 85th to 95th percentile for age and sex is considered as overweight or at risk for obesity.

Body mass index (BMI) is the most practical method for assessing obesity in a clinical practice and correlates well with the risk of obesity related medical complications.

Skin-fold Thickness

Measurement of skin fold thickness from the trunk and extremities provides a reliable estimate of obesity and regional fat distribution. The correlation of multiple skin folder thickness (SFT) measurements with total body adiposity is 0.7 to 0.8. An experienced person should do the measurements. This method is useful for community pediatrics or large studies but is not used often for routine assessment of obesity. Skin fold thickness centiles for Indian children are available for reference.³



There is limited data from our country but an increase in the prevalence of obesity has been observed in the urban areas and in children of obese parents. A study of 4700 school children aged 13 to 18 years in an urban area of Chennai revealed that the prevalence of overweight children based on the BMI was 17.8 percent for boys and 15.8 percent for girls.⁹

Kapil et al from Delhi have reported a prevalence of 16.2 percent in 2002 while Misra et al reported a prevalence of 29 percent from Delhi in 2008¹⁰⁻¹³ reflecting a marked increase in prevalence of overweight and obesity in urban children in Delhi.^{13,14}

Khadilkar et al in a multicentric study (2009) from 5 geographical zones of India, have reported that compared to Indian data recorded in 1989, the 97th percentile for boys and girls weight at 18 and 17 years respectively was 14.7 kg and 8 kg higher.¹⁵

PATHOPHYSIOLOGY

Increase in the adipose mass is a result of increased storage of triglycerides, the primary stored fuel in humans. This energy surplus occurs when more calories are ingested as food than are expended. Therefore obesity results from either excess consumption of calories or lack of activity, or both.

In normal circumstances the amount of body fat is regulated by a control of appetite and satiety by the hypothalamus. Recent research has identified the feedback hormone, Leptin, which is secreted from the adipose tissue and has a role in the hypothalamic control of appetite. The *ob* gene responsible for the secretion of Leptin has also been identified. Further research in this area will give us a better idea of the mechanisms of obesity and may result in useful new therapies.

ETIOLOGY

The clinical evolution of obesity in children is often multifactorial. The most common cause of obesity in childhood is environmentally determined (simple obesity) with no demonstrable disease. Genetic factors also play a major role followed by endocrine disorders, central nervous system (CNS) and chromosomal disorders, psychosocial factors and drugs. The causes are listed in Table 1.

Genetic Factors

Several monogenic obesity syndromes have been identified. The known genes involved include leptin, the leptin receptor proopiomelanocortin (POMC), prohormone convertase 1, melanocortin receptors 3 and 4, and the transcription factor single-minded.¹

MC4R mutations are the most frequent known cause of monogenic human obesity, occurring in up to 4 percent of early-onset and severe childhood obesity.¹⁶

It is highly probable that childhood obesity is polygenic with susceptibility conferred via complex genetic factors. It is estimated that 30 to 50 percent of the tendency toward excess adiposity can be explained by genetic variations.¹⁷

It has also been demonstrated that the BMI of adopted children correlated more closely to their biologic parents than the adoptive parents¹⁸. Furthermore BMI of identical

twins appears to be similar whether they are reared together or apart confirming the role of genetic factors in obesity.

Environmental Factors

Environmental factors that influence eating behaviors and physical activity influence the development of obesity. Today's children live in an obesogenic food environment that readily provides calorie dense foods. They are consuming diets that are too high in fats and sugar and very few helpings of fruits, vegetables, grains and dairy.

Failure to lose weight despite low caloric intake is often due to misreporting of food intake and physical activity.

Physical activity in children has declined over the last few years and the life style has become sedentary. Indoor entertainment such as television viewing, computers, etc. have become very popular. Relationship between television viewing and obesity may be due to increased food consumption during viewing, influence of food advertisements on eating patterns and decreased energy expenditure. It has recently been shown that television viewing may contribute to obesity by lowering the basal metabolic rate in obese as well as lean individuals. Academic pressure contributes further to the sedentary lifestyle.

Pathological Factors

Organic pathological causes may underlie obesity in a smaller number of children. However, these are important because these are diagnosable and treatable conditions. The physician and parents are also looking for a cause other than simple obesity and may not be satisfied unless endocrine and other causes are ruled out. Pathological causes of obesity are listed in Table 1.

If the child is above average in stature and has overweight family members, organic pathology is unlikely. If the child is below average in stature, especially with slow growth, pathologic cause must be ruled out. Since, appetite and satiety are controlled by the hypothalamus, tumors, malformations and damage to this region can cause obesity. Dysmorphic features should arouse the suspicion of genetic syndromes associated with obesity (Table 1).

CLINICAL MANIFESTATIONS

Children with simple obesity are usually tall for their age and may have slightly advanced bone ages. Puberty starts a little earlier than the lean peers. Psychological disturbances may be present, but it is sometimes difficult to determine if they are the cause or result of obesity.

Endocrine causes of obesity usually result in short stature. In hypothyroidism obesity is due to decreased energy expenditure. Gross obesity is seldom due to hypothyroidism. Bone age is usually delayed in these children. Weight loss may occur once treatment is started but is due to decrease in fat-free mass.

Table 1: Causes of obesity

- Genetic
- Simple obesity (environmentally determined)
- Pathologic
 1. Endocrine
 - Hypothyroidism
 - Steroid excess
 - Growth hormone deficiency
 - Pseudohypoparathyroidism
 2. CNS
 - Hypothalamic tumors
 - Malformations
 - CNS damage
 3. Syndromes
 - Prader-Willi
 - Laurence-Moon-Biedl
 - Beckwith-Wiedmann
 - Carpenter
 - Turner
 - Klinefelter
 4. Leptin deficiency
 5. Psychiatric disturbances
 6. Drugs: Corticosteroids, valproate, etc.

Steroid excess may be due to medications, production from a tumor or Cushing's disease, which is characterized by central distribution of fat, striae, decreased growth rate and hypertension. Since, cortisol production and clearance are increased in obesity, 24-hour urine free cortisol is one of the most sensitive tests. Dexamethasone suppression test may be done to differentiate simple obesity from Cushing's disease.

Growth hormone (GH) deficiency may also manifest as obesity that is truncal and is associated with slow growth.

Central nervous system (CNS) disorders lead to sudden rapid weight gain, insatiable appetite and other neurological symptoms.

Children with genetic syndromes usually have dysmorphic features, hypotonia, hypogonadism and other specific associated features.

CONSEQUENCES OF OBESITY

Adult Obesity

Forty percent of overweight children become obese adolescents and 75 to 80 percent obese adolescents become obese adults.¹⁹

Endocrine Consequences

Alterations in endocrine functions are present in obese children and are a result and not cause of obesity, since they normalize with weight loss. These changes have been summarized in Table 2.

Table 2: Effects of obesity on endocrine hormones

Growth hormone	↓ basal levels		
	↓ response to pharmacological stimuli		
IGF1	Normal		
Thyroid hormones	↑ T ₃ level		
	Normal T ₄ and TSH		
Cortisol	Normal S. cortisol level		
	(↑ production and clearance)		
ACTH	Increased		
DHEA	Increased		
Sex steroids	Females		Males
	↑ LH	↑ LH:FSH	N testosterone
	↓ FSH		
			↑ estrogens
Insulin	Increased		
Calcium and Phosphorus	Normal		
Parathormone	Increased		

Acanthosis Nigricans Metabolic Consequences

1. Insulin Resistance: Obesity leads to insulin resistance. A higher amount of insulin is produced to maintain normal glucose levels, leading to hyperinsulinemia and an increase in the insulin:glucose ratio.
2. Acanthosis Nigricans (AN): These are hyperpigmented, velvety folds of skin, usually present behind the neck, and in the axilla and groin. It is a manifestation of high insulin level. Acanthosis nigricans (AN) are associated with both T2DM and insulin resistance (IR), but the strongest correlation is with obesity.²⁰
3. Type 2 Diabetes Mellitus: Insulin resistance (IR) leads to decrease in insulin mediated glucose uptake and may manifest as abnormalities in the glucose tolerance test and Type 2 diabetes mellitus (T2DM), especially in adolescents with a family history of diabetes mellitus.

The greater prevalence of childhood obesity has resulted in greater prevalence of T2DM in children and adolescents.²¹ Type 2 diabetes mellitus (T2DM) now accounts for 20 percent of diabetes in children aged 10 to 19 years.²²
4. Polycystic Ovarian Disease: Insulin regulates the ovarian androgens through LH. Hence in females, hyperinsulinemia may be associated with benign premature adrenarche followed by functional ovarian hyperandrogenism which leads to hirsutism and menstrual irregularities. Some girls may develop high LH levels and cysts in the ovaries.

Although not a co-morbidity per se, an earlier onset of pubarche and thelarche is associated with an elevated BMI.^{23,24} Whether it is also associated with an earlier onset of menarche is controversial, a question that has been extensively reviewed.²⁵

5. Dyslipidemia: Obesity leads to increase elevation of plasma triglycerides and VLDL. Total body cholesterol synthesis may also increase. Lipid abnormalities have been found in 12 to 17 percent of overweight and obese children.²⁶ Weight reduction normalizes levels of triglycerides and cholesterol and increases levels of HDL.
6. Metabolic Syndrome: Is a constellation of cardiovascular risk factors, comprising abdominal obesity and two or more of the following: elevated triglycerides, low HDL cholesterol, high blood pressure, increased plasma glucose.^{27–29} Prevalence among 12 to 19 years olds in the United States is about 4.2 percent.³⁰ The risk of the metabolic syndrome is nearly 50 percent in severely obese (BMI >40.6 kg/m²) adolescents.³¹
7. Hypertension: Systolic blood pressure correlates with BMI, skin fold thickness, and waist-to-hip ratio in children and adolescents. The relative risk for hypertension in obese children (BMI >95th percentile) was 3.26 after three consecutive blood pressure screenings.³²
8. Nonalcoholic Fatty Liver Disease: The prevalence is unclear and depends on the detection method. Ten to twenty-five percent of obese children have elevated transaminases, primarily alanine aminotransferase (ALT) with levels increasing with the degree of obesity. Weight reduction is an effective treatment for nonalcoholic fatty liver disease (NAFLD).³³ Although, a benign clinical course is typical of NAFLD, it may be associated with increasing fibrosis and, rarely, progression to cirrhosis.³⁴

Medical Consequences

These manifest as hypertension heart disease, hypoventilation and hypercapnia (pickwickian syndrome). Obesity can also result in gall stones³⁵ blounts disease, genu valgum and slipped capital femoral epiphysis.³⁶ Obese children are up to six times more likely than lean children to have obstructive sleep apnea.³⁷ Obstructive sleep apnea is independently related to the development of hypertension, cardiovascular diseases, behavioral disorders, poor school performance in children, and poor quality of life in adults.³⁸

Psychosocial Problems

It may become an issue for many over-weight and obese children and adolescents.³⁹

APPROACH TO DIAGNOSIS

Obesity is a symptom rather than a disease and may be a precursor for other diseases. A detailed history must be obtained in every child regarding.

- Rate of weight gain
- Pattern of linear growth
- Milestones
- Appetite and Lifestyle: Record a rough daily dietary intake. Ask about the time spent exercising or outdoors and time

spent watching TV and on other indoor activities such as reading, computer, etc.

- Headaches
- Visual disturbances
- Menstrual disturbances in postmenarchal girls.
- Family history of obesity, thyroid disorders, diabetes mellitus, hypertension and heart disease
- Cultural and social history regarding eating patterns and psychological.

Physical Examination

- Measure the height and weight to determine if the child's height is appropriate for age
- Plot the weight for height and BMI
- Check vital signs including blood pressure
- Look for acanthosis nigricans
- Identify abnormalities of the hands, feet and other syndrome associated features
- Complete physical examination of the thyroid and other systems should be done
- Assess pubertal status and check for gynecomastia in boys.

In prepubertal obese boys the penis often looks small and is a cause of great worry to parents. This is usually due to the penis being embedded in the suprapubic pad of fat. In such cases a stretched penile length should be measured. The penis should be stretched between the thumb and the forefinger. The suprapubic pad of fat should be depressed with a ruler and the penis should be measured along the dorsum till the tip of the glans penis. The foreskin should not be included in the measurement.

INVESTIGATIONS

Who Should be Evaluated?

All children with a BMI above the 85th percentile should be evaluated. Diagnostic investigations are aimed at identifying the cause and to look for consequences of obesity. These should preferably be done under the guidance of a pediatric endocrinologist. Guidelines for evaluation have been summarized in Table 3.

MANAGEMENT OF OBESITY

Management of obesity is a very tough task for the physician since most pediatric interventions may result in only small changes in weight, and are often associated with relapses in weight gain.

In cases of pathologic obesity, the underlying cause should be treated wherever possible.

Management of simple obesity includes alteration in lifestyle and dietary management. Pharmacological interventions have a limited role in the management of childhood obesity.

Table 3: *Diagnostic evaluation*

Disease suspected	Test
Hypothyroidism	FT4, TSH
Cushing disease	urine free cortisol or Morning and evening S. cortisol
GH deficiency	GH stimulation test, IGF1, IGFBP-3
Genetic syndromes	Karyotyping: Deletion of Chromosome 15
CNS disorder	MRI of the brain
Consequences of obesity	
BMI	
85-94th percentile	Fasting lipid profile, Bone age
> 95th percentile	Fasting lipid profile, blood glucose and insulin HbA _{1c} / Glucose tolerance test with insulin levels, Bone age

ALTERATIONS IN LIFESTYLE

Diet Management

Diet restriction in children has to be done very carefully and under strict supervision since it can affect the growth of the child and cause nutritional deficiencies. The aim should be restriction of calories without affecting the nutrition or growth.

Dietary management will depend on the age and presence/absence of complications.

Less than three years of age: strict calorie restriction is not recommended, but the practice of overfeeding can be avoided.

Three to seven years with no associated co-morbidities: Weight maintenance is required. Try to prevent weight gain rather than advising weight loss so that as they gain height, their BMI reduces gradually.

Three to seven years with co-morbidities: Weight loss is recommended.

>7 years: Weight loss is recommended.

Weight maintenance: Changes in diet should be permanent, rather than short term. Since fast foods soft drinks, etc. are the major culprits, they should be restricted. Restrict calories from saturated fat. Simple changes like taking skimmed milk instead of whole milk, stop applying ghee/butter to chapattis, which is a very common Indian practice, can reduce calories without affecting nutrition. Increase the consumption of whole grain, fruits and vegetables. Intake of fiber rich foods is important since they improve satiety. Restrict eating out and encourage the whole family to eat the same food as the child.

Weight loss should be slow and not rapid. However in older and grossly obese children who have developed complications related to obesity and have achieved their final height, more severe calorie restriction may be undertaken. This can be done as a balanced hypocaloric diet in

which the intake is reduced by 2400-2900 kJ per day. This induces a weight loss of 0.5 kg per week.

Another intensive regime which has been tried is the Protein-sparing modified fast (PSMF). This supplies a daily intake of 2500-3500 kJ and 1.5-2.5 g of high quality protein per kg of ideal body weight. Carbohydrate intake is restricted to 20-40 g daily. Daily intake of vitamins and 1500 ml of water is also recommended. This results in rapid weight loss and should be done under strict medical supervision. It should not be continued for more than 1-3 months. Side effects such as cholelithiasis, hyperuricemia, etc. have been observed. Long-term studies comparing the 2 diets showed similar mean weights. This suggests that the PSMF diet has no long lasting benefit compared with a balanced hypocaloric diet.

EXERCISE

Exercise should be encouraged since sedentary lifestyle has a major contribution to obesity. In the absence of caloric restriction, moderate exercise does not generally cause weight loss. However, in combination with decreased caloric intake, exercise can achieve significant weight loss.

Physical fitness, even without weight loss, may offer some health benefits. Improvement in cardiovascular fitness is associated, in young adults, with improvement in cardiovascular disease risk factors over a 7 years period.⁴⁰

Physical activity should be a part of the daily curriculum in schools. Encourage them to participate in sports that they enjoy such as tennis, football, walking, dancing, swimming, etc. Reduce TV viewing and encourage them to do chores at home too. Studies have shown that supervised resistance training programs are safe for preadolescents. The intensity and duration of a resistance exercise set must be appropriate to the level of maturity of the growing bones and muscles.

BEHAVIOR MODIFICATION

Modification of the child's behavior should be done in conjunction with the diet and exercise management. This should be done as a team with a therapist. Gain insight into the child's problems and the family environment. Educate the family about the importance of healthy foods and exercise and give rewards for achieving goals. Build the child's self-confidence and esteem and help him deal with the peer pressure. Behavior modification helps in achievement of long-term goals.

PHARMACOTHERAPY

Most of the medications used for obesity in adults, have not been used in children frequently or for a prolonged duration and are not recommended routinely because of the high risk of side effects.

The pharmacotherapeutic agents orlistat, and metformin (not FDA approved for the treatment of obesity) are most commonly used at present.

Orlistat specifically inhibits intestinal lipase and can reduce fat and cholesterol absorption by approximately 30 percent.⁴³ It is approved by FDA for use in children >12 yr of age. Studies showed that use of orlistat was associated with a significant fall in BMI of 0.7 kg/m², but treatment was associated with increased rates of gastrointestinal side effects including abdominal discomfort, pain, and steatorrhea. Side effects are usually mild to moderate and generally decrease in frequency with continued treatment. It prevents the absorption of fat soluble vitamins, hence vitamin supplements must be given during treatment.

There have been reports of serious liver injury including liver failure in patients taking Orlistat between 1999 and 2008. Hence, US FDA is studying the drug for its side effects currently.

Metformin reduces hepatic glucose production and plasma insulin, inhibits lipogenesis, increases peripheral insulin sensitivity, and may reduce appetite by increasing levels of glucagon-like peptide, but its mechanism of action on weight is unresolved, hence it is not used or approved for weight loss.

Sibutramine, a nonselective reuptake inhibitor appetite suppressant that is most potent for serotonin and norepinephrine, but also blocks dopamine reuptake^{41,42} was approved for children >16 years of age by the US FDA for treatment of obesity. It has now been withdrawn from the market because of increased risk of cardiovascular events such as heart attack and stroke.

It has been suggested that overweight children should not be treated with pharmacotherapeutic agents unless significant, severe comorbidities persist despite intensive lifestyle modification. In these children, a strong family history of T2DM or cardiovascular risk factors strengthens the case for pharmacotherapy.⁴⁴

It is also suggested that pharmacotherapy be offered only by clinicians who are experienced in the use of anti-obesity agents and are aware of the potential for adverse reactions.⁴⁴

BARIATRIC SURGERY

Surgery is seldom performed in children unless there is a life threatening complication. Roux-en-Y gastric bypass has been done in older adolescents and adults. It is a last resort for adolescent who have a high risk of mortality due to obesity.

MANAGEMENT OF CONSEQUENCES

Dietary restriction, exercise and lifestyle management manages most of the consequences of obesity. Specific medical treatment may be required in obese children with

Table 4: Guidelines for preventing obesity

Infancy

- Encourage sustained breastfeeding (>3-6 months)
- Discourage early introduction of solid foods (emphasize vegetables)
- Goal: Moderate rates of weight gain, including in low-birth weight infants (throughout childhood). Rapid catch-up growth may be detrimental.

Older children

- Encourage intake of vegetables and fruits
- Minimize intake of juice, cold drinks, chocolates, etc.
- Discourage eating out too often
- Encourage physical activity (outdoors and at home)
- Discourage TV viewing (<1 hour daily)
- Behavioral
- Emphasize family-based meals, avoid cooking special meals for kids
- Do not use food as a reward or punishment
- Provide parental modeling of healthy diet, physical activity, and minimal television viewing
- Offer positive reinforcement for healthy choices, avoid criticism
- Support healthy body image, emphasizing strength and health rather than weight and appearance

complications such as diabetes mellitus, hypertension, grossly abnormal lipid profiles, hirsutism, and menstrual abnormalities.

PREVENTION OF OBESITY

Long term follow up of children treated with diet, exercise and behavior modification has shown significantly lower weights 5 to 10 years later than for children treated in other ways. However not all obese children treated successfully initially were able to maintain their reduced relative body weight.

Children should develop healthy eating habits right from infancy. They should have an exercise pattern that prevents excess weight gain. This is especially important for children in high-risk groups, e.g. those with obese parents or family history of diabetes, heart disease, etc. Health professionals should inform parents of the potential risks and provide instructions on preventive measures at an early age. Guidelines for preventing obesity are summarized in Table 4.

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Growth Monitoring and Short Stature

Vaman Khadilkar

INTRODUCTION

Growth monitoring is a screening tool to diagnose nutritional, chronic systemic and endocrine disease at an early stage. Growth monitoring has the potential for significant impact on mortality and morbidity even in the absence of nutrition supplementation or education.¹ Monitoring the growth of a child requires taking the same measurements at regular intervals and seeing how they change. Growth monitoring practices differ greatly among pediatricians and often are not based on evidence. Indian Academy of Pediatrics therefore wrote consensus guidelines for growth monitoring as per IAP Action Plan 2006.²

AIMS AND RATIONALE OF GROWTH MONITORING

Primary aim of growth monitoring is to identify children with growth deviation i.e. under-nutrition and over nutrition and to identify diseases and conditions that manifest through abnormal growth. Secondary aims are to discuss health promotion related to feeding, hygiene, immunization and other aspects of the child's health and behavior; education of parents to allay their anxiety about their child's growth. Growth monitoring also helps to sensitize health care workers to use growth charts in their day to day practice.

GROWTH CHARTS

Although the world's children appear to follow a similar growth pattern, still there are variations due to ethnic, geographical, and regional factors giving different rates of maturation and adult stature. The final height of different ethnic groups is different, even accounting for secular trends. Thus for assessment, an up-to-date national representative sample of population data are ideal as growth standards. The Indian Council for Medical Research (ICMR) undertook a nationwide cross sectional

study during 1956 and 1965 to establish Indian reference charts. The measurements were made on children of the lower socio-economic class and hence cannot be used as a reference standard at the present time. The growth charts compiled by Agarwal et al were based on affluent urban children from all major zones of India measured between 1989 and 1991. The data is now 20 years old and does not reflect the growth of modern Indian children.^{3,4} In 2010-2011 Khadilkar et al have published growth charts on affluent children from 5 to 18 years and have also compared the growth of 2 to 5-year-old affluent Indian children with the new WHO growth charts. Based on these two papers growth charts for affluent Indian children from 2 to 18-year-old are now compiled by the author and are ready for clinical use.^{6,7} These are the most modern national growth references curves available at present in India. WHO published new growth standards for children under the age of 5 years in 2006 which are being adopted in many countries including India as a global single standard of childhood growth for the under five children.

BASICS OF GROWTH CHARTS

Growth chart consists of an x axis which is usually age in years or months and a y axis that changes according to the reference e.g. it can be height in cm or inches, weight in kg or body mass index in kg/m². The x axis is usually divided into 12 equal parts (months) for each year. Standard growth chart has 7 percentile lines and include 3rd, 10th, 25th, 50th, 75th and 97th percentiles. Any individual who is below 3rd and above 97th percentile is considered out of normal range. For the BMI charts however there are 85th and 95th percentile lines which indicate overweight and obesity cut offs. Proportion charts use Z score lines instead of percentile lines and discrepancy of more than 2 Z scores in the upper and lower segment is considered abnormal. On the growth velocity chart 25th

percentile is the cut off line for defining low height velocity. The correlation between Z scores and percentiles can be confusing and in the recent WHO MGRS 2006 study, these correlations have been spelt out by the WHO and are given in the table (Table 1) below for clarity of understanding.

Doctors and health care workers find it difficult to interpret various cut offs for diagnosis of underweight, overweight, stunting, wasting, etc. which have also been clearly spelt out in the new WHO MGRS study and are given below (Table 2). These make it easy for the practicing pediatrician and health care worker to follow as a guideline for management and referral.⁵

IMPORTANCE OF ANTHROPOMETRY OVER TESTS

Anthropometry scores over all the available endocrine tests in the assessment of growth failure. Hence it is of paramount importance that appropriate growth charts are used. Plotting a child's growth must always be the starting point in the investigations of growth failure. Longitudinal data plotted over a period of time is far more useful than a single record of height and weight. Observation of growth pattern usually over a period of minimum one year is necessary before a child is subjected to rigorous endocrine evaluation.

GROWTH STANDARD VS REFERENCE

Growth charts mainly belong to two types: growth standards and growth references. Growth standards are prescriptive and define how a population of children should grow given the optimal nutrition and optimal health. Growth reference on the other hand are descriptive and are prepared from a population which is thought to be growing in the best possible state of nutrition and health in a given community. These describe the growth of children at that time. They represent how children are growing rather than how they should be growing.

WHO 2006 growth charts for children under 5 years is an example of growth standards. They delineate how children of the world under the age of 5 years should grow if most of the controllable variables are kept optimal. (IOTF classification) as opposed to this 1989 K N Agarwal data (3) and 2007 Indian growth charts by Khadilkar et al⁶

Table 2: Growth parameters and their interpretation for the WHO charts

Z-Score (Percentile)	Length/Height for age	Weight for age	BMI for age
>3 (99)	May be abnormal	May be abnormal	Obese
>2 (97)	Normal	(Use BMI)	Overweight
>1 (85)	Normal	Use BMI	Risk of overweight
0 (50)	Normal	Use BMI	Normal
<-1 (15)	Normal	Use BMI	Normal
<-2 (3)	Stunted	Normal	Normal
<-3 (1)	Severely stunted	Underweight	Wasted
		Severely underweight	Severe wasted

for affluent children are an example of growth references which describe how children in India were growing at the given time and are references and not standards.

Advantage of having a growth standard such as WHO 2006 charts is that children of all countries, races, ethnicity can be compared against a single standard thus assessment becomes more objective and easy to compare. The disadvantage of using charts such as these are likely to over diagnose underweight and stunting in a large number of apparently normal children⁷ in the developing countries such as India.

Advantage of a reference is that they are true representative of the existing growth pattern of children and allow us to study the secular trend in terms of height, weight and obesity. The downside of reference curves is that they need to be updated at least once in a decade and in modern times as obesity is on the rise they are likely to define overweight children as normal.

WHO 2006 GROWTH STANDARDS

In 2006 WHO produced growth standards for children under the age of 5 years. The standards are derived from children who were raised in environments that minimized constraints to growth such as poor diets and infection. In addition, their mothers followed healthy practices such as breastfeeding, and not smoking during and after pregnancy. Because the standards depict physiological human growth under optimal environmental conditions, they provide an improved tool for assessing growth. These charts thus are prescriptive standards and not descriptive references.

These standards provide an opportunity to redefine and revitalize actions to promote optimal child growth, foster the adoption of "best practices", such as incorporating height and BMI to assess the dual burden of under and over-nutrition (stunting and overweight); provide coherence between national and international infant feeding guidelines that recommend breastfeeding as the optimal source of nutrition during infancy and the charts are

Table 1: Correlation between percentiles and Z-scores for WHO 2006 charts

Z-Score	Exact percentile	Rounded percentile
0	50	50
-1	15.9	15
-2	2.3	3
-3	0.1	1
1	84.1	85
2	97.7	97
3	99.9	99

recommended for assessing the pattern of infant growth; and harmonize growth assessment systems within and between countries.⁸

WHO recommends using -2Z (3rd percentile) scores for diagnosis of stunting and underweight and -3Z (1st percentile) for the diagnosis of severe stunting and severe underweight.

HOW INDIA AND OTHER COUNTRIES PERFORM ON THESE CHARTS²

In developing countries use of WHO 2006 growth charts will likely over diagnose stunting or underweight or both. In a recent multicentric study done on 1493 affluent pre-school Indian children (selected from all zones of India) published by the author the Mean Z scores for height, weight, body mass index and weight for height [-0.75(1.1), -0.59(1.1), -0.19(1.22) and -0.26(1.18), respectively] were below the WHO 2006 standards. The overall incidence of stunting was 13.6 percent and underweight was 8.5 percent amongst affluent Indian children under the age of five years. This percentage is likely to be higher in rural areas and in under privileged urban areas although at the present time no such data is available from India.

Concerns regarding adoption of new WHO 2006 is also expressed by many authors from many parts of the world such as Indonesia, Czechoslovakia, Malawi, etc. as these standards are likely to over diagnose stunting and underweight. Many authors have expressed caution regarding changing infant feeding policies based on WHO standards for the present time.

NEW 2007 AFFLUENT INDIAN GROWTH CHARTS (FIGS 1 TO 4)

The Need for New Charts

The previously available growth reference curves in India were based on the data collected by Agarwal et al in 1989 which were published in 1992 and 1994 and are almost 2 decades old. WHO recommends that each country should update its growth references every decade and hence new growth references were produced in 2009.

Data Collection

The Indian Academy of Pediatrics divides India into 5 zones i.e. North, South, East, West, and Central. The nutritionally well off areas were identified based on per capita income of cities (from IAP zones). Data collection lasted from June 2007 to January 2008. Of the 19834 children measured, measurements for 18666 were analyzed (10496 boys and 8170 girls) where 5184 (3218 boys, 1966 girls) 3000 (1678 boys, 1322 girls), 698 (696 boys, 1002 girls) 6920 (3837 boys, 3083 girls) and 1864 (1067 boys, 797 girls) children were from the North, South, East, West and Central zones, respectively. The differences between

zones were not significant. Standard percentiles were generated for height, weight and body mass index (BMI) using the universally accepted LMS method, which constructs growth reference percentiles adjusted for skew.⁹

OBSERVATIONS

Secular Trends in Height

The 50th percentile for boy's height was greater than that of the 1989 data at all ages. The 97th percentile at 18 years was 1.7 cm greater than in 1989. The 50th percentile for girls' height was greater than in 1989 at most ages, the greatest difference being 3.1 cm at 12 years. The median final height for girls was similar to 1989, but the 97th percentile was 2.4 cm greater, indicating increased variability.

Alarming Rise in Obesity

The 50th percentile for boys' weight was greater than in 1989 at all ages except 5 years, maximum 6.5 kg at 14 years reducing to 2.9 kg at 18 years. At 18 years the 97th percentile was 14.7 kg, higher than in 1989. The 50th percentile for girls weight was lower than the 1989 up to the age of 6.5 years and higher afterwards, maximum 8.0 kg at 17 years. Unlike in boys, there was no reduction in difference in weight approaching adulthood. Compared with the 1989 data, average difference in the 97th percentile was similar to the 50th percentile (6.8 kg and 4.7 kg, respectively) in girls which was in stark contrast to the data on boys, where the difference was much greater (12.8 kg and 4.1 kg, respectively). In boys, the median BMI values were higher at almost all ages compared with the 1989 data. The difference in the 95th percentile in the two datasets was 2.3 at 18 years. In girls the median BMI values were higher at almost all ages, the maximum difference being 1.1 kg/m² at 18 years.⁶

This dataset was examined for the prevalence of overweight and obesity by international standards. The overall prevalence of overweight and obesity was 18.2 percent by the IOTF classification and 23.9 percent by WHO standards. The prevalence of overweight and obesity was higher in boys than girls. Mean BMI values were significantly higher than those reported in the 1989 data from 5 to 17 years at all ages and for both sexes. The rising trend of BMI in Indian children and adolescents observed in this multicentric study, rings alarm bells in terms of associated adverse health consequences in adulthood.¹⁰

COMPARISON OF 2007 AFFLUENT INDIAN CHARTS WITH CDC AND UK CHARTS

On comparison with the US (NCHS 2000) and UK (1990) data, the height percentiles for both boys and girls are similar until the age of puberty but thereafter Indian affluent children remain shorter and do not show the pronounced pubertal spurt. This is seen in both sexes and

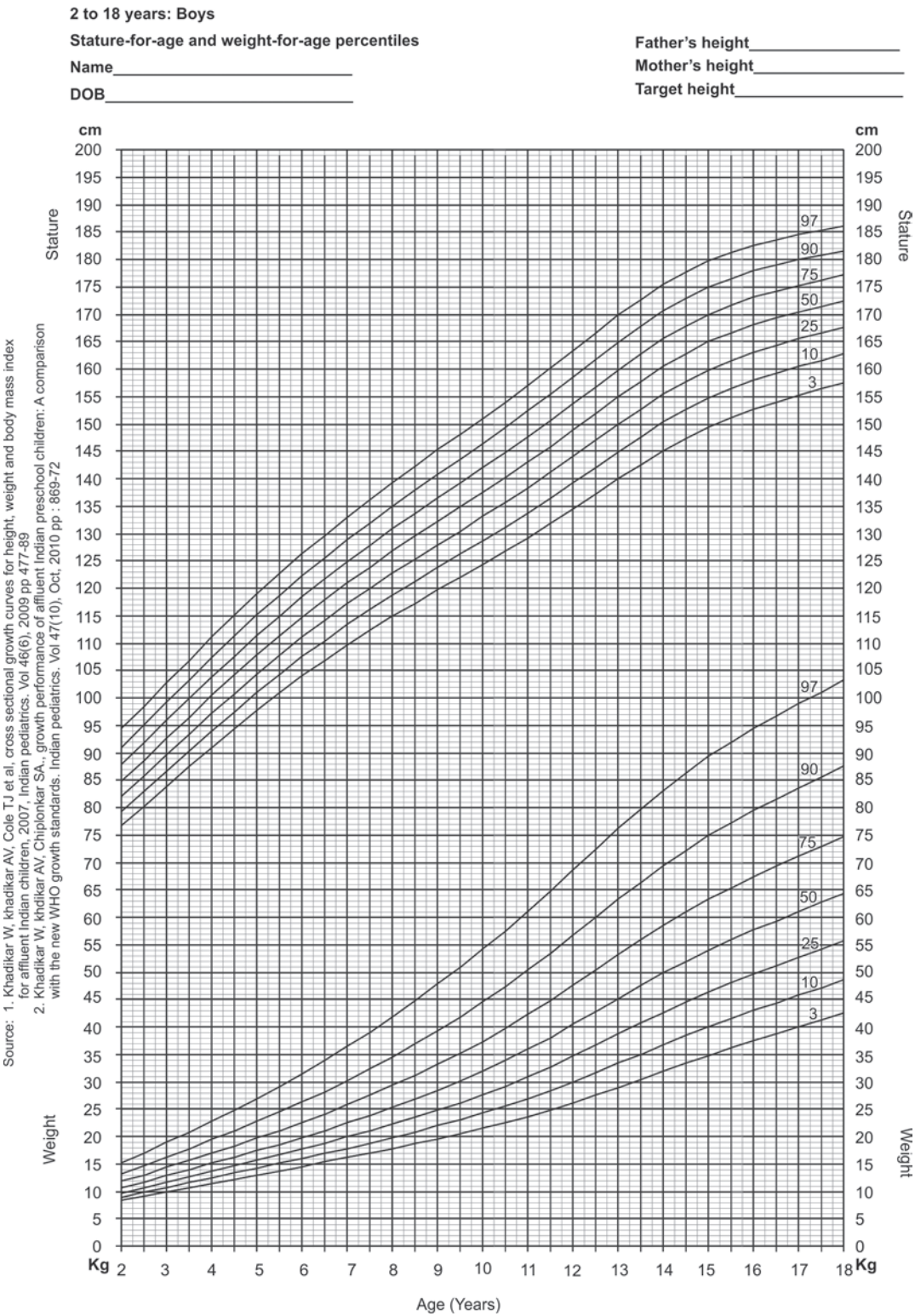


Fig. 1: Height and weight charts for affluent Indian boys 2-18 years
(Modified with permission from Indian Journal of Endocrinology and Metabolism)

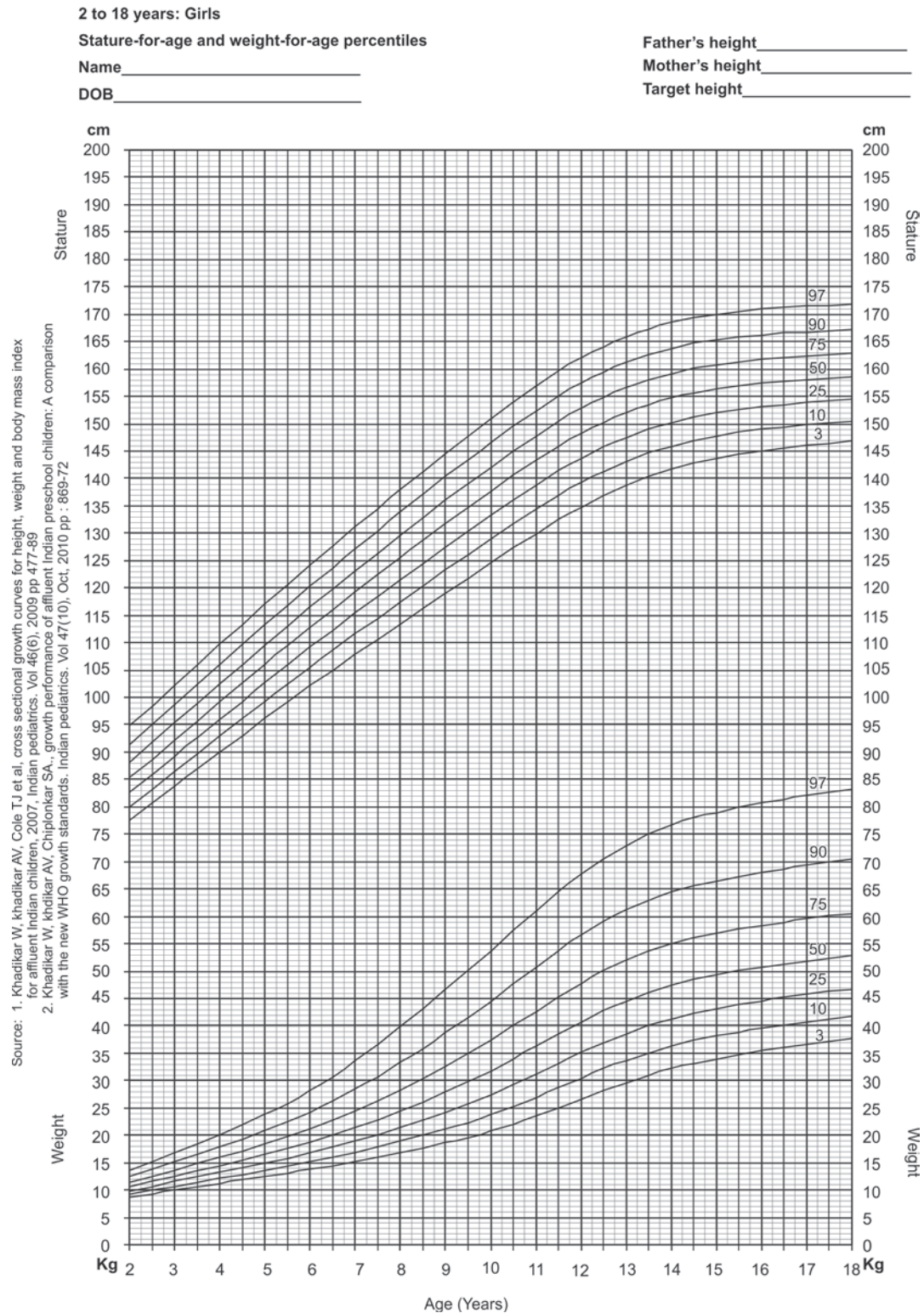


Fig. 2: Height and weight charts for affluent Indian girls 2-18 years
 (Modified with permission from Indian Journal of Endocrinology and Metabolism)

2 to 18 years: Boys

Body mass index (BMI) percentiles

Name _____

DOB _____

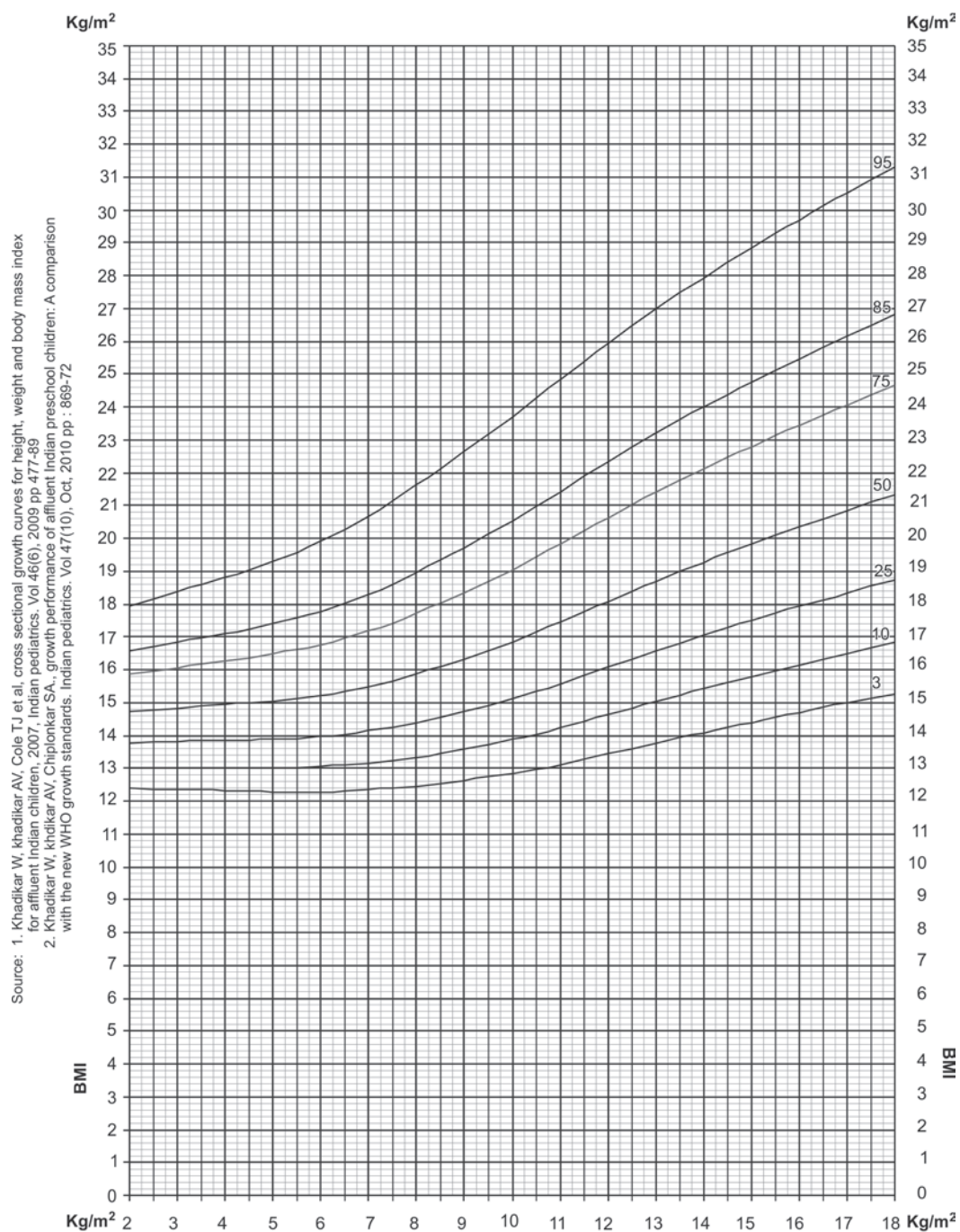


Fig. 3: BMI charts for affluent Indian boys 2-18 years
(Modified with permission from Indian Journal of Endocrinology and Metabolism)

2 to 18 years: Girls

Body mass index (BMI) percentiles

Name _____

DOB _____

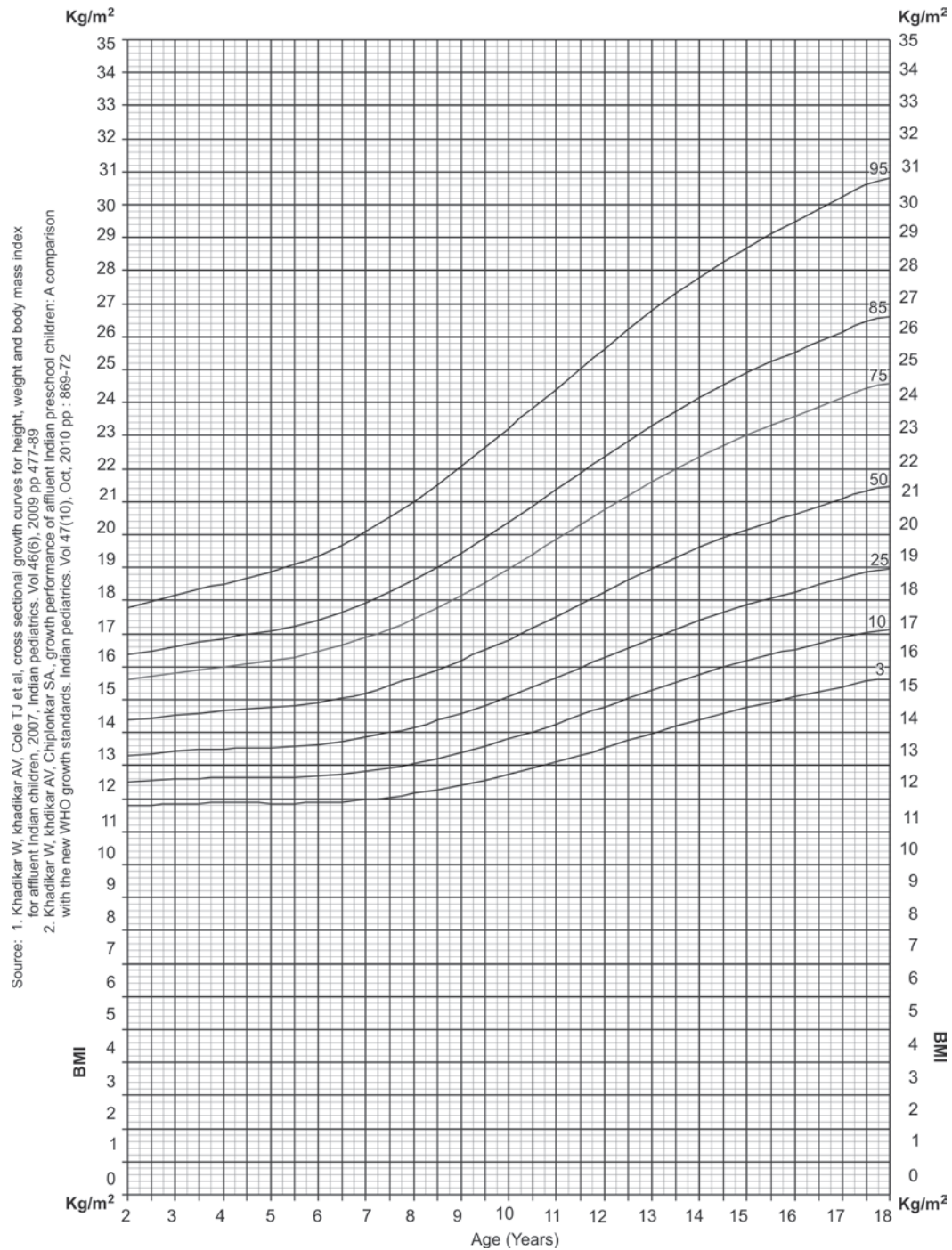


Fig. 4: BMI charts for affluent Indian girls 2-18 years
(Modified with permission from Indian Journal of Endocrinology and Metabolism)

may be related to genetic difference in the populations. On the BMI charts the 75th percentile for the current data was very close to the US and UK 85th percentile on BMI charts, especially after 7 years in boys and 9 years in girls. Boys on the 75th percentile in our study had a mean BMI of 24.2 and girls had a mean BMI of 24 at 18 years, this value is just under the adult cut-off (25) for overweight.¹¹ Seventy-fifth percentile values on the current BMI curves may therefore be used as a cutoff for screening for overweight boys and girls.

BMI CHARTS

As obesity in childhood is increasing around the world, using descriptive growth charts for weight may under diagnose obesity in children as these charts tend to “normalize” obese children as the whole population from where the data is collected is on the higher side of the weight scale. It is therefore suggested that we use prescriptive growth standards for BMI in children. Such charts are made available by WHO. These charts tend to construct percentiles in such a way that they meet the adult cut off for overweight and obese at 25 and 30 BMI at 18 years respectively. These charts are thus most appropriate for non Asian children of the world.

WHO however recommends that for adult Asian Indians the BMI cut off value for overweight should be 23 and for obesity 28. It is thus important that based on the models such as IOTF, cut off standards for BMI at 23 and 28 adult equivalent are produced to screen Indian children for overweight and obesity from 5 year onwards (Below 5 years WHO MGRS has defined the cut offs already). We therefore constructed BMI charts with adult 23 and 28 equivalent cut offs for Indian boys and girls. These were validated against a total of 250 children from schools and a tertiary care pediatric clinic. The children were distributed over the whole range of BMI categories (adult equivalent BMI of <23, 23-25, 25-28, 28-30 and >30) (mean age 11.4 ± 2.9 years). Forty-three percent children in the adult equivalent BMI category of 23-25 had one or more than one risk factor for development of the metabolic syndrome (MS). Similarly, 73 percent children in the BMI category of adult equivalent of 28-30 had one or more than one risk factor for developing the MS and would be classified as overweight rather than obese if an adult equivalent cut-off of 30 were to be used. This validation suggests that Indian children above the adult 23 cut off are already showing risk factors for development of metabolic syndrome and hence it is appropriate to use these cut offs for screening children who are at increased risk of later development of metabolic syndrome.¹²

Thus with these two recent studies contemporary cross sectional reference percentile curves for height, weight and body mass index (adjusted for the Asian adult BMI equivalent cut offs) for the assessment of physical growth

of present day Indian children are thus made available for clinical use and for research purpose.

SHORT STATURE

Introduction

Short stature is one of the common problems in Pediatric practice for which an endocrinologist's opinion is sought. Short stature is not a diagnosis by itself but a presenting symptom of a variety of systemic, genetic and hormonal disorders. Short stature can sometimes be the only symptom of systemic or endocrine disease and a high index of suspicion and good diagnostic acumen are needed to reach the etiological diagnosis. A systematic approach is often the key to reduce the need for a whole battery of tests, which are often expensive and unnecessary.

Definition

A child is considered to be short in stature when his/her height is below the third percentile on a distance growth chart for the specific population. It is important to use country specific growth charts so that appropriate population standards are applied and over diagnosis of short stature is avoided. While using growth charts parents' heights should be considered and mid parental height plotted.

Use of Growth Charts

Distance height charts, height velocity and proportion charts are essential tools in the diagnosis of short stature. When height velocity observed over a period of 6 months or more falls below 25th percentile on the velocity chart, it is considered abnormal and more significant than a single height reading below the 3rd percentile on a distance chart. Growth velocity is a very sensitive and reliable way to decide whom to investigate. Proportion charts consist of sitting height and subischial (SIL) leg length. These are expressed as standard deviation scores and not as percentiles. When the disproportion between SIL and sitting height is more than 2 z scores, the child is considered to be disproportionate. As a primary screening tool distance charts are useful and when a short child is detected, velocity charts are used to follow his/her progress over a period of time.

Target Height and Familial Short Stature

Parents' height should be taken into consideration so that height of the child can be properly interpreted for the family's genetic potential. The formula used for calculation of target height (TH) is (Mother's height + Father's height divided by 2) + 6.5 cms for a boy and - 6.5 cms for a girl. This value is then plotted as adult height at 18 years and the spread is 6 cms on either side of the TH. This then is the target range and if the child's height is within these percentiles it is taken as normal. Auxological data

mainly TH, child's current height, height velocity and body proportions are some of the most important tools for proper evaluation and management of short stature. Proper use of these techniques will reduce the cost of subsequent tests.

ETIOLOGY

Common causes of short stature seen in India are as follows:

- Chronic malnutrition
- Chronic systemic disease
 - Chronic infections such as tuberculosis
 - Chronic renal failure
 - Cardiac disease
 - Respiratory disease such as asthma
 - Collagen vascular disease, JRA, etc.
 - Inflammatory bowel disease
- Familial short stature
- Chromosomal abnormalities and syndromes
- Endocrine disease
 - Hypothyroidism
 - Growth hormone deficiency and GH resistance syndromes
 - Cushing syndrome
 - Delayed puberty

The proportion of etiologies for short stature in Indian referral centers is familial short stature (20%), systemic disease (10-20%), syndromes and skeletal dysplasia (10-19%), Turner syndrome (7-10%), growth hormone deficiency (15%), hypothyroidism (5-10%) and constitutional delay of growth and puberty in 10-15 percent.¹³

Clinical Clues

ICP model of growth: The infancy childhood puberty model of growth suggest that during infancy the main determinant of growth is nutrition, during childhood years it is thyroxine and growth hormone and during puberty it is sex steroids. Based on this model if the growth failure starts for the first time in infancy nutritional deficiency is the likely cause, where as if it starts in childhood hypothyroidism or GH deficiency are more likely. Growth failure first time at the time of adolescence is usually due to disorders of puberty and commonest being constitutional delay of growth and puberty¹⁴ (Fig. 2).

Certain clinical clues are useful to reach the diagnosis and are summarized in the Table 3.

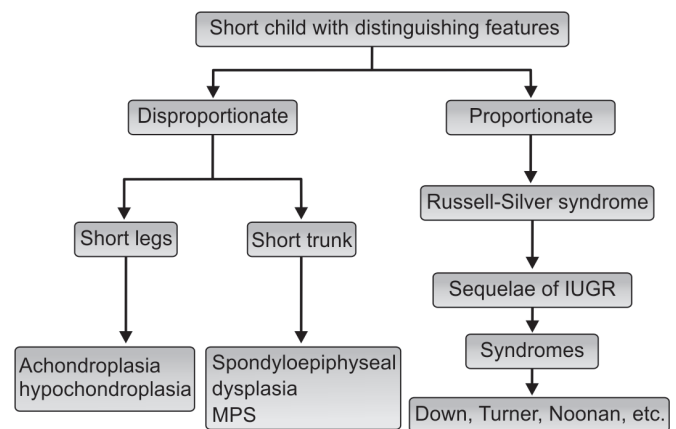
Besides the above mentioned features pathognomonic clinical signs can be seen in syndromes such as Russell Silver, Down or Turner.

In a disproportionately short child, short limbs usually suggest skeletal dysplasia such as Achondroplasia or hypochondroplasia where as short spine suggests a metabolic defect such as Mucopolysaccharidosis (Flow chart 1).

Table 3: Clinical clues to etiology

Clue	Etiology
Disproportion	Dysplasia, rickets
Dysmorphology	Syndromes, hypopituitarism
Frontal bossing, micropenis	GHD
Goiter, coarse skin	Hypothyroidism
Obesity, buffalo hump	Cushing syndrome
Short metacarpals	Turner, SHOX, pseudohypoparathyroidism
Ophthalmic problems	Pituitary tumor, craniopharyngioma, Septo-optic-dysplasia

Flow chart 1: A short child with distinguishing features



Height age and weight age: In a short child who is also thin, height age higher than weight age suggests chronic malnutrition or chronic systemic disease where as weight age higher than height age (short and fat) suggests a hormonal disease such as GHD or hypothyroidism.

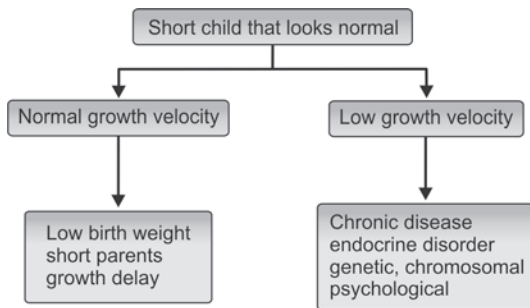
Tanner sexual maturity rating (SMR): Growth disorders that manifest around puberty are often caused by delayed puberty. One of the most important clinical clues to reach the diagnosis of puberty disorders or endocrine disorder is sexual maturity rating. As a routine, Tanner SMR staging should be done in all children who manifest with short stature.

INVESTIGATION

The algorithm given above (Flow chart 2) helps in deciding which investigations are necessary. Following is a brief interpretation of these tests.

Commonly done investigations are as follows:

1. Hemogram, ESR
2. S. creatinine, urea
3. Liver function tests
4. Bone age, skull X-ray
5. Tissue transglutaminase
6. Thyroid function tests

Flow chart 2: A short child that looks normal

values below 7 ng/dl on a stimulated sample are considered to be low suggesting GH deficiency.

Newer tests for diagnosis of GH deficiency are insulin like growth factor 1 (IGF-I) and insulin like growth factor binding protein 3 (IGF BP3). IGF-I is influenced significantly by nutritional status and but BP3 is not and two together are a better guide for the diagnosis of GH deficiency.¹⁵

In a recent review of all the available methods for diagnosis of GH deficiency, it is suggested that IGF-I, BP3 and neuroimaging as a combination is a more reliable way of diagnosis GHD particularly when combined with genetic studies.¹⁶

Neuroimaging

A plain X-ray of the skull may show a wide sella and calcification suggesting a space occupying lesion but does not give much information about the anatomy of the pituitary gland. MRI remains the best neuroimaging modality to diagnose pathology of the pituitary gland and hypothalamic area.

TREATMENT OF SELECT CONDITIONS

Chronic Disease and Malnutrition

Chronic malnutrition is treated by nutritional supplements and chronic disease such as chronic renal failure or ulcerative colitis will need appropriate management of the condition. As the condition improves the child will gain height and no specific treatment for the short stature is necessary except in chronic renal failure where growth hormone will improve the final height.

Hypothyroidism

Thyroxine is needed for physical growth and juvenile hypothyroidism may only manifest with short stature. The treatment consists of replacement therapy with levothyroxine in a dose of 100 mcg per meter square per day. Children show good catch up growth with treatment but often fail to achieve their genetic potential due to the time lost from development of disease to starting of therapy. The treatment of juvenile hypothyroidism is usually for life and regular monitoring is necessary.

Growth Hormone Deficiency

GH deficiency can be due to variety genetic defects. It can be isolated or in combination with other hormonal deficiency. Acquired causes are usually due to intracranial space occupying lesions or it's treatment in the form of surgery, radiation and chemotherapy. The dose of GH used for treating classical GHD is 20-30 $\mu\text{g/kg/day}$ for several years. It is possible to achieve a normal height after years of GH replacement therapy. GH remains a very expensive medication and the cost of therapy is often the limiting factor in continuation of therapy in India.

7. GH stimulation tests
8. IGF-1, IGF – BP3
9. Neuroimaging – MRI
10. Karyotype and DNA studies

Bone Age

The methods used for calculation of bone age are Tanner Whitehouse and Grulich and Pyle. The bone age is a very useful, cheap and reliable tool for the assessment of short stature. When the bone age is retarded or advanced by 2 years or more it is abnormal and usually suggests an endocrine disease such as hypothyroidism, growth hormone deficiency or Cushing disease. In children who have chronic systemic disease or delayed puberty, bone age is delayed but not as much as in endocrine deficiency.

Karyotype/DNA Analysis

Turner syndrome does not always manifest with characteristic features but may only present as short stature. It is therefore important to check Karyotype in a girl with unexplained short stature. Recently a heritable form of genetic defect, the SHOX gene defect has been described in short children, which leads to a heritable form of short stature, short 4, 5 metacarpals, bowing of forearm bones and exostosis. This condition has been shown to respond to GH therapy. Similarly conditions such as Down syndrome, Prader Willi syndrome can be detected by chromosomal/DNA analysis.

Test for Growth Hormone

One of the most difficult tests in terms of interpretation and reproducibility is the GH stimulation test. A non-stimulated fasting GH does not give much information and should be avoided. GH should be checked after stimulation with either Clonidine, l-dopa, Glucagon, arginine or insulin induced hypoglycemia. The last test can be dangerous and should be avoided in young children. Even stimulated GH is not always reliable and hence newer tests are being invented. Some experts recommend priming the patient with sex steroids before GH stimulation test especially in peripubertal children. Growth hormone

Other uses of Growth Hormone

In 1985 recombinant GH became available and since then its use has been expanding with newer and newer indications being added to the list of conditions for which it is already licensed. At the present time growth hormone is approved for use in growth hormone deficiency, Turner syndrome, chronic renal failure, SGA who fail to catch up by 2 years and severe familial/idiopathic short stature. It is also being evaluated in conditions like Prader Willi Syndrome, Noonan syndrome, skeletal dysplasia, etc. Growth hormone is generally a well-tolerated medication with a few known side effects viz. headaches and benign intracranial hypertension, water retention, glucose intolerance and rarely slipped capital femoral epiphyses, gynecomastia and local reactions.

In conclusion, the diagnostic ability and treatment avenues for short children are ever expanding. A systematic and analytical approach is the key to the etiological diagnosis and successful management of short children.

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Growth Hormone Therapy

Archana D Arya

INTRODUCTION

Human growth hormone (hGH) was first used in 1950's to stimulate growth in children with hypopituitarism.¹ It was obtained by purifying cadaveric pituitary extract, and hence the availability was limited. In 1985 the first case of Creutzfeld-Jacob disease was reported in a patient who had received growth hormone and subsequently more cases were reported. The preparation was banned and in the same year,² the 192 aminoacid biosynthetic GH was approved by the food and drug administration (FDA), USA. Since then there has been abundant supply of the recombinant rhGH.

Benefits of GH therapy in GH deficient children have been well documented, but since the recombinant GH preparation has been available, its growth promoting effect in children who do not have classical GH deficiency has been investigated in a large number of children. Now it is also being studied for its metabolic effects besides the effect on linear growth. The paradigm has shifted from GH replacement to GH augmentation therapy. The number of FDA approved indications has more than doubled in the last 5 years. This has made the decision about GH use for short stature, more complex. There is a concern about short children developing psychological problems, but data to support that improvement in height would improve psychological health is scarce, except in severe GH deficiency.³

PHYSIOLOGY OF GROWTH HORMONE

Human growth hormone is secreted by the anterior pituitary gland. Growth Hormone Releasing Hormone (GHRH) stimulates the secretion of GH and somatostatin inhibits it. Both GHRH and somatostatin are synthesized by the hypothalamus.

The secretion of GH is cyclical and pulsatile, and it is released in response to sleep, exercise and hypoglycemia. It

is bound to GH binding protein in the circulation and has a short half-life of less than 20 minutes. Due to the pulsatile secretion and short half-life, frequent sampling is required to identify peaks. Hence GH response to pharmacological stimuli is used for judging adequacy of secretion.

Growth hormone mediates its effects through insulin like growth factor I (IGF-1), which is a peptide secreted by the liver in response to stimulation by GH. It is bound in the circulation to IGF binding proteins (IGFBP) the most important one being IGFBP-3.

Insulin like growth factor-1 (IGF-1) levels correlate with the clinical state of GH deficiency, sufficiency or excess but do not exclusively reflect GH production because levels of IGF-1 vary with age. Insulin like growth factor-1 correlates better with bone age and puberty rather than chronological age. Poor nutrition and chronic disease may decrease the IGF-1 levels.

EFFECTS OF GROWTH HORMONE

The most apparent effect of GH is to stimulate linear growth in children before epiphyseal fusion occurs. Besides this it has a number of other metabolic effects:

- Anabolic (Cell proliferation and protein synthesis)
- Lipolytic (Decreases adipose tissue)
- Increases lean tissue
- Increases bone density
- Bolsters cardiac contractility
- Improves mood and motivation
- Increases exercise capacity
- Alters the carbohydrate metabolism

INDICATIONS OF GROWTH HORMONE THERAPY

The FDA, USA has approved the following indications of GH therapy:

GROWTH HORMONE DEFICIENCY

Growth hormone has been used for GH deficiency (GHD) for almost 50 years now. The tests that have been used for diagnosing GHD are not physiological, are expensive, invasive, may be risky and results are not reproducible very often. The cut offs have also been arbitrary and have changed from <7 to <10 ng/ml over the last few years. Provocative tests are fairly accurate for diagnosing complete GH deficiency, but are not good for distinguishing between partial GH deficiency and normal short stature.

The gold standard for diagnosing GHD was to demonstrate inadequate GH stimulation with 2 pharmacological agents. Growth hormone level of <10 ng/ml on provocative stimulation is suggestive of GH inadequacy. As more children were tested for GH insufficiency, it was observed that about 20 percent children with normal stature show stimulated levels of <7 ng/ml and a large number of short children had normal levels of GH on stimulation. It is likely that these children are not able to secrete sufficient amounts of GH to sustain normal growth. Hence auxological parameters are far more important than provocative testing for making a diagnosis of GHD¹¹ and the onus of this lies with the pediatrician, who should monitor height and weight of children regularly. Due to these observations the diagnostic criteria for GH deficiency have changed over the years.

The Growth Hormone Research Society recently recommended measurement of IGF-1 and IGFBP-3 in addition to provocative GH testing to identify children with abnormalities in the GH/IGF axis not detected by standard tests.

Children with GH levels in the high subnormal range and with normal stimulated levels but low spontaneous secretion or low IGF-1 and IGFBP-3 are now considered to have partial GH deficiency.

An MRI of the brain for hypothalamic-pituitary region should be done prior to initiating therapy to rule out an anatomical defect or presence of a mass.

Early initiation of treatment with GH, in cases with growth hormone deficiency results in normal adult height.⁴

Recommended dose of GH in children with GHD is 0.07 to 0.1 IU/kg or 0.21 to 0.3 mg/kg day. Daily dose results in better growth than thrice-weekly injections. The best response is seen during the first year of treatment.

Turner Syndrome

The longest trials of GH therapy, after GHD have been on girls with Turner syndrome. Turner syndrome (TS) occurs because of the complete deletion of an X chromosome or a part of one of the arms. Mosaicism may occur in this condition. 95 to 100 percent of these girls have growth retardation and untreated their height is about 143 cm as reported from the western literature, which is about

20 cm less than their average height. Turner girls also have hypogonadism due to ovarian dysgenesis, which worsens their short stature.

Special growth charts are available for girls with Turner syndrome.

Short stature in Turner girls is due to the combined effect of aneuploidy, primary skeletal dysplasia, mild GH secretory dysfunction and estrogen deficiency. The SHOX (short stature homeobox containing gene) gene is located in the pseudoautosomal region of the short arm of the X chromosome. Haplo-insufficiency of the SHOX gene due to deletion of part of X chromosome results in short stature and skeletal abnormalities in TS.

Turner girls usually fall below the 3rd percentile of the growth chart after the age of 7 years leading to a delay in diagnosis. By the age of 9 years most girls are below the 3rd percentile. Due to hypogonadism there is no pubertal growth spurt, hence there is worsening of short stature by the age of 13 years. These girls are at a higher risk of developing thyroid and celiac disease and presence of any of these would worsen the short stature. Both these conditions should be ruled out prior to initiating therapy. Since these girls are usually not GH deficient once a diagnosis of TS has been made, provocative testing for GHD is not required.

Growth hormone therapy with or without anabolic steroids like oxandrolone accelerates growth in girls with TS.⁵ Studies have shown that the mean final height of girls with TS treated with GH was 150.4 cm, which was about 8.4 cm more than the expected average height and those treated with GH and oxandrolone was 152.1 cm, which was 10.4 cm more than the predicted height without treatment.⁶

At this time initiation of therapy is recommended as soon as females with TS have dropped below the 5th percentile of the normal female growth curve. This could be as early as 2 years of age. Final height improves by about 12 cm if GH therapy is started by 7 years of age. Treatment after 12 years of age improves final height by only about 5 cm. Hence GH should be started at a younger age for a good response.

The recommended starting dose is 0.05 mg/kg/day. Sas et al¹² treated 68 girls with Turner syndrome (mean age 6-7 years) who were randomly assigned to three different regimens of growth hormone. The girls attained normal adult height (mean values 159-162 cm).

Escalating doses over time above the initial 0.05 mg/kg per day resulted in a 2 to 3 cm greater increment in growth, although the safety of this approach is not known. These excellent height results were achieved after average treatment duration of seven years.

In older girls or those >8 years of age if therapy is started when short stature is extreme, concomitant administration of oxandrolone should be considered. Routine use of oxandrolone is not recommended. It should be reserved for those in whom GH therapy is delayed, in very low doses to prevent

virilization. Monitoring of GH therapy should be done as for any other child on GH therapy.

Timing of hormone (estrogen) replacement therapy (HRT) for hypogonadism, in Turner girls is very important, since HRT results in acceleration of bone maturation and epiphyseal fusion. Hormone replacement therapy should be initiated in a manner so that it does not hamper the growth potential and on the other hand does not result in poor bone mineralization.

Chronic Kidney Disease

Growth failure is often the presenting symptom of chronic kidney disease (CKD). The genetic height potential is usually not attained in these children and the mean adult height is 2 standard deviations below the mean.

Poor growth in children with CKD is due to non-endocrine factors like malnutrition, acidosis, and renal osteodystrophy and endocrine factors such as GH resistance suggested by exaggerated response on provocative stimulation, decreased levels of IGF-1 and increased levels of IGFBP-I.

Despite dialysis, growth failure persists in these children and post-transplant, growth rate may normalize, but no catch up growth is seen.

Pharmacological doses of recombinant human GH (rhGH) corrects height deficit in most children with CKD before transplant. Growth hormone reverses the hypercatabolism in CKD and increases circulating IGF bioactivity that may result from the differential action of rhGH on plasma IGFs (significant increase) and inhibitory IGF binding proteins (no major change). The end result is an increase of IGFs in extravascular fluids that interact with the Type 1 IGF receptor for stimulating longitudinal growth.¹⁹

In a study of 38 children with CKD, GH treatment resulted in a final height that was 1.4 SD above standardized height at baseline and the mean final height of 50 non-treated matched control children with CRF was 0.6 SD below standardized height at baseline.⁷

The Cochrane database¹³ reviewed 15 randomized control trials involving 629 children to evaluate the benefits and harms of rhGH treatment in children with CKD. They concluded that 1 year of rhGH treatment at a dose of 28 IU/m²/week in children with CRF resulted in a 3.80 cm/y increase in height velocity above that of untreated patients. Trials were too short to determine if continuing treatment resulted in an increase in final adult height. The frequency of reported side effects of rhGH were similar to that of the control group.

Seikaly et al¹⁴ evaluated the utilization and potential benefits of rhGH in children with CKD and following renal transplantation in a large patient cohort. They queried the chronic renal insufficiency (CRI), dialysis, and transplant

registries of the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) to characterize the frequency of rhGH utilization, factors related to its usage, and the relationship between rhGH usage and catch-up growth.

The analysis revealed that of 6505 children with CKD, 22 percent received rhGH. Recombinant human GH therapy was associated with catch-up growth in 27 percent of treated patients in this group.

Of the 5122 children on dialysis, 33 percent received rhGH, of which 11 percent patients showed catch-up growth.

Of the 4478 children who received a renal transplant, 3 percent received rhGH and catch-up growth was seen in 25 percent of treated patients.

In all groups, the highest catch-up growth was seen in patients in Tanner stage 1 or 2 of puberty.

In another study by Seikaly et al¹⁵ of children with chronic renal insufficiency who were treated conservatively (i.e. not on dialysis and had not received a renal transplantation), 787 children treated with rhGH were matched to 787 control patients who did not receive any GH by age, gender, height, and length of time on the registry. The estimated GFR of the treated group was less than the control group (37.5 versus 42.3 ml/min per 1.73 m²) and the height SDS were similar (-2.29 ± 0.04 and -2.23 ± 0.04). At the end of two years, the height SDS of the rhGH-treated group was 0.56 greater than the control group (-1.46 versus -2.02).

Growth hormone also appears to be effective in infants and growth-retarded pubertal children after renal transplantation. In addition, limited data from patients with CKD suggest that GH therapy may also improve bone metabolism.^{16,17}

A study of 10 prepubertal patients with CKD showed that rhGH therapy for 1 year produced a significant increase in lumbar spine and total body bone mineral content and bone mineral density.¹⁸

Studies on the use of rhGH in CKD suggest that:

- Children with preterminal CRF appear to respond better to rhGH than those on dialysis.
- Recombinant human GH therapy should be initiated at a young age with the goal of restoring the level of growth to a normal genetic percentile well before the need for renal transplant.
- Therapy should be instituted when the patient falls below the 3rd percentile for height and does not show spontaneous catch-up growth after other factors contributing to uremic growth failure have been adequately stabilized.
- The dose of rhGH in children with CKD is 0.045 to 0.05 mg/kg per day.
- Therapy is continued until final height is reached or a well-functioning renal transplant is achieved.

- Aim for a minimal height greater than the third percentile of the general population.
- Treatment of growth retardation after renal transplantation appears promising but is still experimental.
- Current information suggests no adverse effect of GH on the glomerular filtration rate.
- Growth hormone therapy is approved for treatment of children with growth failure associated with CKD, up to the time of renal transplantation and it should be used in conjunction with optimal management of CKD.

Prader-Willi Syndrome

Prader-Willi syndrome (PWS) occurs due to deletion in chromosomal region 15q11-13. The incidence is 1:10,000-25,000 live births. This condition is characterized by hypotonia, hyperphagia leading to gross obesity, short stature that is often due to GH deficiency, hypogonadism and psychomotor retardation. They typically have small hands and feet and almond shaped eyes.

Scoliosis is common in PWS. These patients are also at an increased risk for hip dysplasia and lower limb alignment abnormalities. Unlike other children with obesity, they do not appear to have increased risk for slipped capital femoral epiphysis.²⁰

They are also at a higher risk of developing complications such as gastric distension and rupture, sleep apnea and choking episodes.

Growth hormone therapy is recommended for children with PWS who have associated GH deficiency. Several clinical trials have demonstrated beneficial effects of growth hormone treatment on linear growth.²¹⁻²⁴ Body composition, including fat-free mass and bone density abnormalities, also appears to improve with growth hormone treatment.

Use of growth hormone for children with growth failure and genetically confirmed PWS was approved by the US FDA in 2000, and has been approved for this use in most countries.

Most individuals with PWS will have growth hormone deficiency when formally tested. Criteria for diagnosis of GH deficiency are the same as in other children. Nonetheless, it is generally not always necessary to evaluate formally for growth hormone deficiency before considering growth hormone treatment for patients with PWS and growth failure. IGF-1 and IGFBP-3 may be measured for adjusting doses of GH.

In USA use of GH in PWS indication requires growth failure.²⁵ Many studies have investigated the effect of rhGH on linear growth, body composition and bone density in children with PWS, and virtually all have demonstrated beneficial effects.^{21,22}

The optimal age to begin treatment, dosing, and duration of therapy has not been established.

Eiholzer et al²⁶ assessed the body composition of 11 infants with PWS <2 years of age by using deuterium dilution and investigated the efficacy of early institution of rhGH therapy in increasing lean mass (LM) and preventing massive obesity.

This group was compared before and during 30-month rhGH therapy (GH group) was compared with 6 infants administered only coenzyme Q (10) for 1 year (Q10 group).

They found that initially, LM (Ht) of all patients was below the normal average. They concluded that diminished LM (Ht) found in infants with PWS further declines during the early years. Early institution of GH therapy lifts LM (Ht) into the normal range and delays fat tissue accumulation.

Similar improvements in body composition with rhGH were reported in a randomized, placebo-controlled trial of 29 infants and toddlers with PWS (aged 4-37 months).²⁷ Initiating treatment before the age of 18 months was associated with accelerated acquisition of mobility skills compared with controls of the same age.

The response to GH in children with PWS is greatest during the first 12 months of therapy.²¹ Nevertheless, patients have had continued improvement in linear growth, bone density, and body composition when GH has been administered in sufficient doses for as long as five years.²⁸ Even with long-term growth hormone treatment, body composition is not completely normalized.

It results in growth rate increases similar to those seen in other GH deficient children. Growth hormone has additional positive metabolic effects in these children. It improves the muscle tone, decreases the fat mass, increases the lean body mass and bone mineral density⁸ in these children. Growth failure related to PWS is an approved indication for GH treatment.

Safety of rhGH in PWS: There have been reports of a few fatalities worldwide coinciding with the use of rhGH in children with PWS.²⁹ The deaths were associated with respiratory problems and/or were unexpected, and most occurred within the first three months of rhGH treatment. The patients had one or more of the following risk factors: severe obesity, sleep apnea, or respiratory infection.

It is unknown if the deaths were related to rhGH since children with PWS have an increased risk of sudden unexpected death independent of treatment with growth hormone.^{30,31}

Recombinant human GH may have effects on sleep-disordered breathing

Growth hormone may stimulate adenotonsillar hypertrophy via IGF-1 signaling. This mechanism is supported by case reports that correlate worsening obstructive apnea in some patients with higher IGF-1 levels.³²

On the other hand growth hormone may act directly on the hypothalamus and improve central hypoventilation.

This mechanism is consistent with observations that, in the majority of patients with PWS, growth hormone improves sleep-disordered breathing and/ or pulmonary function.³²⁻³⁴

Growth hormone therapy is contraindicated in patients with Prader-Willi syndrome who are severely obese or have severe respiratory impairment.

Pretreatment evaluation—rhGH therapy should be avoided in severely obese PWS patients. (e.g. >225 percent of ideal body weight).

Polysomnography should be done prior to initiating treatment and if an abnormality is found it should be treated prior to initiating therapy. Monitoring with polysomnography should be done during therapy and if there are signs of upper airway obstruction or sleep apnea, treatment should be discontinued.

Patients should be monitored with glucose tolerance tests prior to and during treatment and for scoliosis if present.³⁵⁻³⁸

The child should be evaluated for upper airway obstruction or apnea before starting growth hormone treatment and GH treatment should be interrupted if patients develop signs of upper respiratory obstruction (including onset of or increased snoring) and/ or new onset of sleep apnea. In addition, patients should be monitored for adverse progression of glucose tolerance and scoliosis.

We suggest that all patients with PWS undergo polysomnography prior to beginning growth hormone treatment. Growth hormone treatment should not proceed until the sleep disordered breathing is effectively treated. Those with abnormal polysomnograms should have follow-up studies approximately one month after beginning GH treatment, and all patients with PWS on GH treatment should be clinically re-evaluated if they develop intercurrent upper respiratory tract infections or increased obstructive symptoms. Particular care should be taken in managing this issue in infants and toddlers, who appear to be at the highest risk for respiratory compromise because of underlying hypotonia. For these children, we suggest monitoring oxygen saturation during sleep for the first one to two months after starting GH treatment, if possible.

Small for Gestation

Small for gestation (SGA) is defined as a birth weight or length, more than 2 SD below the mean (Birth weight <2.5 kg of a baby >37 weeks gestation). Three to ten percent neonates are born small for gestation (SGA). This usually occurs because of intrauterine growth retardation (IUGR). After birth majority of these infants show good catch-up growth and normalize their height and weight. About 10 percent of them continue to remain short (<-2SD) and do not achieve normal adult height, resulting in psychosocial problems.

Small for gestation infants usually have low levels of insulin, IGF-1 and IGFBP-3 at birth. Levels of these

hormones rise in the babies who show catch-up growth. Infants who do not show catch-up growth usually have an alteration in the GH-IGF-1 axis that is poorly understood. An irreversible deficit in cell number, inadequate calorie intake during the first year of life, may contribute to the lack of catch-up growth.

Classic GH deficiency rarely is found in these children, however there may be subtle abnormalities in the GH secretory pattern similar to those documented in adults during prolonged critical illness.³⁹

Initial trials with GH therapy did not show a good response probably because low doses of GH were used and administration of the drug was infrequent. A number of multicenter trials have been carried with GH therapy for SGA babies who do not show catch-up growth, over the last few years. Growth hormone was used irrespective of their GH status. Both high and low dose GH and continuous and discontinuous treatments have been used in these children. These studies conclude that:

- Growth hormone therapy in short SGA children with no catch-up growth normalizes adult stature and results in an adult height that is within the target range.
- Better adult height is achieved if treatment is started at a younger age, although some improvement in adult height is found even if treatment is started during adolescence.
- Both, low dose continuous and high dose discontinuous treatments are almost equally effective.
- Growth hormone therapy is equally beneficial in GH deficient and non-GH-deficient SGA children.⁹
- Long-term GH treatment normalizes adult height (AH) (above -2 SDS) in 85 percent children, and 98 percent achieve an AH within their target height range.

The US FDA has approved GH therapy for the treatment of growth failure in children who are born SGA and do not achieve catch-up growth, i.e. height remains less than 2 SDS below the mean for age and sex at 2 years of age⁴⁰ at dosages up to 0.48 mg/ kg/week.

In Europe, the approved indication is for short SGA children whose height is less than 2.5 SDS below the mean for age and sex at 4 years of age.^{41,42} In addition, the European indications include low growth velocity (i.e. height velocity less than average for age) and predicted height (>1 SD below mid-parental height).

Treatment is reasonably safe with no significant side effects. Short children born SGA are at increased risk for diabetes and cardiovascular disease when compared to children with normal birth weight. Whether treatment with growth hormone either improves or exacerbates these long-term risks has not been established. However, there appear to be no difference in the short-term risks of GH treatment in this population as compared with other children treated with growth hormone. The risk of

developing accelerated bone maturation is minimal with high or low doses of GH.

IDIOPATHIC SHORT STATURE

Short children whose heights are two standard deviations (SD) or more below the mean for age, i.e. 3rd percentile, who have no demonstrable functional abnormality (no endocrine, metabolic, or other diagnosis) and whose parents are normal in height are considered to have idiopathic short stature.^{43,44} It is suspected that these children/adolescents have an abnormality of the GH-IGF axis that cannot be detected by biochemical testing or there may be underlying genetic defects in these individuals that may not have been identified at this time. Mutations in the SHOX gene are responsible for up to 4 percent of cases of apparent "idiopathic" short stature.

A recent study of 80 non-GHD children treated with GH showed a mean increase in SD score for height from -2.7 to -1.4. The mean difference between the predicted adult height before treatment and achieved adult height among boys was 5.0 ± 5.1 cm and 5.9 ± 5.2 cm for girls. Only a few subjects in this study reached their mid-parental height.¹⁰ It seems that long term GH treatment of non-GHD children can lead to statistically significant increases in final height in some children. Several similar studies have demonstrated that growth hormone therapy generally increases height velocity acutely and may increase adult height in children with ISS. Growth hormone therapy for these children was approved by the US FDA in 2003. The indication is for children with current height below -2.25 SD of the mean, in whom the epiphyses are not closed, and whose expected adult height is less than 63 inches (160 cm) for boys and 59 inches (150 cm) for girls.

Growth hormone therapy in children with ISS is still controversial despite being approved. The reasons for controversy are that:

- A majority of children with short stature will experience some catch-up growth during puberty without GH treatment. Despite improvement in final height the adult height was 5 to 6 cm below target height.⁴⁵
- Other studies report a spontaneous increase of between 0.5 and 1.9 SD in untreated children.⁴⁶
- There is little evidence that short stature has a detrimental effect on an individual's psychosocial or physical functioning.
- It is difficult to predict responsiveness to GH treatment, due to the clinical and molecular heterogeneity of the condition and also the inconsistent criteria for ISS and GH treatment doses used in clinical trials.⁴⁶⁻⁵⁰
- The available evidence suggests only modest efficacy for GH treatment in children and adolescents with ISS, which must be weighed against the potential adverse

financial, psychosocial, and physiological effects of the treatment.

Other conditions for which GH is being used often are:

- Skeletal dysplasias esp. hypochondroplasia
- Thalassemia major
- Hypophosphatemic rickets
- Patient's on chronic glucocorticoid therapy (juvenile rheumatoid arthritis, asthma)
- AIDS wasting (FDA approved)
- Adult GH deficiency (FDA approved)
- Slow growth in children on LHRH analogs for precocious puberty

Conditions in which GH therapy has been investigated, but not used routinely:

- Familial short stature
- Constitutional growth delay
- Syndromes (Noonan's, Down's)
- Cystic fibrosis
- Postoperative wound healing
- Burns
- Inflammatory bowel disease
- Aging

DOSAGE AND MONITORING OF GH THERAPY

The dose of growth hormone used varies according to the condition being treated. Pharmacological doses are 0.07 to 0.1 u/kg/day. Higher doses are used in certain conditions such as Turner syndrome and SGA. Higher doses have also been used during puberty to improve adult height. IGF-1 based dose of GH is also being used by some clinicians. GH dose should be adjusted to maintain IGF-1 within a normal range. The GH dose is adjusted to keep the IGF-1 level at approximately 1 SD above the mean for age and gender. If IGF-1 levels are consistently elevated (>2.5 SD), the GH dose should be reduced.⁴⁴ IGF-1 levels should be checked approximately four weeks after beginning therapy or changing the GH dose, and approximately every 6 to 12 months thereafter, similar to the approach used for patients with GH deficiency.

It is given as a daily subcutaneous injection at night to mimic the timing of natural GH secretion. Growth with daily dosing is better than with thrice weekly doses, which were being used earlier. The preparation can be given with a pen device by the parents at home.

Routine monitoring of thyroid functions, blood glucose, IGF-1 and IGFBP-3 during therapy is recommended. Glucose tolerance test should be done in high-risk children. Cost of GH therapy is very high and is approximately Rs 18,000 per month for a child weighing 20 kg. Treatment should be continued till response to therapy is good or satisfactory height is achieved or till epiphyseal fusion occurs.

SIDE EFFECTS OF GROWTH HORMONE THERAPY

Side effects of GH therapy are listed below. They are not encountered very often but monitoring for side effects must be done regularly.

- Hypothyroidism
- Pseudotumor cerebri
- Slipped femoral capital epiphysis
- Possible salt and water retention
- Hyperinsulinemia
- Gynecomastia
- Growth attenuation from antibody formation

In the past there had been a concern about recurrence of malignancy/occurrence of new malignancies in GH treated patients. Prolonged follow-up studies indicate that the rates of new leukemia in patients without pre-existing factors who are treated with GH are not greater than the general population. There is also no risk of developing non-leukemic neoplasms or recurrence of malignancy in GH treated patients.

ETHICAL ISSUES IN GROWTH HORMONE THERAPY

Availability of recombinant Growth Hormone (GH) in abundance has resulted in a marked increase in its usage. Earlier the only indication for GH therapy was severe GH deficiency and the purpose was to normalize adult height of children who had severe growth retardation. In the last few years the diagnostic criteria for GH deficiency have changed and so have the cut off values, which has resulted in more and more children being treated.

Use of GH in non-GH deficient children has also increased with more indications being included and the aim is now to enhance normal stature very often. Although GH therapy is reasonably safe, a small number of children do develop permanent complications like diabetes, slipped capital femoral epiphyses, etc. The cost of GH therapy is also very high worldwide.

Keeping this in mind, GH therapy should be used only if it enhances the adult height in children who would otherwise be abnormally short and should not be used to improve normal stature.

There is no role of short-term GH therapy and it should only be used if the patient can afford treatment for a long enough period to normalize adult height.

Expectations should be realistic and the risks and benefits must be explained to the parents before starting therapy.

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Precocious Puberty

S Srinivasan

Puberty is an important, transitional but critical developmental event in children's life, whereby these children attain physical and sexual maturation with reproductive capability. This orderly process results in the development of secondary sexual features, gonadal functional maturity and completes the final phase of linear physical growth with sex dependent changes in body composition and psychosocial maturation. An intact hypothalamic – pituitary – gonadal (HPG) axis is essential for the initiation and completion of puberty. Any interference in the functioning of this axis can result in temporary or permanent disorders of reproductive endocrine function. The HPG axis, active and functional during second half of fetal development and early infancy, enters a relative quiescent state, often referred to as the juvenile pause. The factors that mediate the juvenile pause and those that lead to increased gonadotropin-releasing hormone (GnRH) secretion at the onset of puberty are the keys to the regulation of pubertal timing.¹

MATURATION OF THE HYPOTHALAMIC-PITUITARY-GONADAL AXIS

In humans, maturation of the reproductive system occurs in a phasic manner in well-defined stages.

The first stage begins during fetal life and lasts until late infancy. In the first trimester of gestation, the presence of hypothalamic gonadotrophin releasing hormone (GnRH) and pituitary luteinizing hormone (LH) and follicular stimulating hormone (FSH) has been demonstrated. The development of the neuroendocrine system, responsible for regulation of the reproductive system, is heralded by the formation of gonadotrophin releasing hormone (GnRH) neurons in the rostral forebrain associated with the olfactory placode. These neurons migrate to an area in the arcuate nucleus of the hypothalamus destined to become the GnRH pulse generator. These neural cells

develop intrinsic and unregulated pulsatile activity by around 11 weeks of gestation. By midgestation the pituitary portal system is completed, thereby allowing transport of hypothalamic peptides to the pituitary. At 20 weeks of gestation, GnRH secretion is maximal and stimulates secretion of LH and FSH. In the male fetus, testosterone increase causes penile enlargement before birth. Later in gestation, this increase in gonadal steroids exerts negative feedback and begins to regulate the pulse generator.

The second stage starts from the time of delivery when the neonate is cut off from the placenta—the dominant source of estrogenic sex steroids. This withdrawal of the negative feedback results in raised levels of gonadotropins (LH and FSH) in episodic pulses until 4 to 6 months of age. This is responsible for a transient secondary gonadal stimulation occurring in the first months following birth. Although occurring in both boys and girls, this is observed most readily in female infants in whom there may be prolonged neonatal breast budding. After 6 months of age, these elevated plasma gonadotrophin and sex steroid levels decrease to low levels until the peripubertal period.

The third stage of maturation, termed the juvenile pause, begins at 6 months of age when gonadotropin and sex steroid concentrations fall to low levels. This stage is the period between infancy and puberty when hypothalamic GnRH is kept restrained in spite of low plasma concentrations of LH, FSH, and sex steroids by an additional inhibitory mechanism, suggested to be present in the central nervous system (CNS)/hypothalamus. Although mean serum concentrations of gonadotropins are low during the prepubertal period, the reproductive system is not totally inhibited as small spontaneous LH pulses occur at a low frequency in normal children.

The fourth stage is characterized by the reactivation of the reproductive axis, reactivation of GnRH secretory activity and activation of the cascade of pituitary-gonadal

maturation resulting in puberty. The mechanisms responsible for the initiation of pubertal events are extremely complex. They involve the integration of numerous different signals including attainment of a certain body mass or composition which is probably linked with levels of leptin, a hormone produced in the adipose cells. The effect of increased leptin levels on the initiation of puberty appears to be secondary to the suppression of the neuropeptide Y by leptin, thus releasing its inhibition of the pituitary gonadotropin axis. Leptin though considered necessary to initiate puberty is not the only factor. There is normal progression of puberty even with small amount of leptin, where as in its complete absence there will be absence of progression to puberty. At the time of puberty, leptin binding sites decrease, allowing small amount to exert greater effect. Neural signals derived from centers within the central nervous system that serve as a biological clock are also likely involved.

GONADARCHÉ

A striking increase in amplitude and frequency of LH pulses, especially at night, heralds the onset of puberty. These increases of LH precede rise of sex steroid concentrations and the development of secondary sex characteristics. As pubertal maturation progresses, similar increase in the amplitude and frequency of gonadotropin pulses occurs during the day until the final stage of sexual maturation is reached. Regular pulses of GnRH establish the mature pattern of gonadal steroid secretion during this period. The mechanism underlying the relative suppression and subsequent pubertal activation of hypothalamic GnRH is still to be elucidated. Pulsatile GnRH stimulates pituitary FSH and LH secretion, which in turn bind to ligand-specific receptors in the gonads, causing gonadal maturation and production of sex steroids, most notably testosterone and estradiol ultimately stimulating gametogenesis in males and females.^{2,3} This process is termed gonadarche.

Testosterone and estradiol, together with inhibin, activin, and follistatin, regulate the subsequent activity of the hypothalamus and pituitary gland. The transition from childhood quiescence to the adolescent pattern of GnRH secretion is a gradual process, and LH and FSH pulsatility has been detected in normal children as young as 4 years of age. In females, this results in the regular cyclical variations of gonadotropins, estrogen, and progesterone characteristic of the menstrual cycle. In the ovary, FSH stimulates follicular maturation and estrogen production through aromatization of androgens, whereas LH stimulates production by theca cells, triggers ovulation, and maintains progesterone production by the corpus luteum. In males, the same regular pulses of GnRH establish a pattern characterized by relatively constant levels of testosterone and gonadotropins, with minimal diurnal

variation. In the testis, FSH acts on Sertoli-Leydig cells to initiate spermatogenesis and LH acts on the Leydig cells to stimulate testosterone production.⁴

ADRENARCHÉ

The physical changes of puberty result from both gonadarche and adrenarche. Adrenarche refers to the maturation of the zona reticularis of the adrenal gland, resulting in increased production of adrenal androgens. This is associated with development of secondary sexual characteristics such as the pubic hair (pubarche), axillary hair, body odor, and acne. Adrenarche begins usually at the age of 8 years, but can occur as early as 6 years.^{5,6} The onset of adrenarche, like gonadarche, is a gradual and progressive maturational process that begins in early childhood and is marked by further increases in the production of adrenal androgens (DHEA, DHEA-S, androstenedione) around the time of puberty.⁷ Adrenarche may precede gonadarche by 1 to 2 years in boys and girls, but the timing of clinical signs can vary. Adrenarche and gonadarche often overlap, but they are separate processes that are regulated independently.^{8,9} The triggers for adrenarche remain unknown; however, the developmental process is likely to be modulated by the alterations in body weight and body mass index (BMI) besides fetal and neonatal physiology.^{10,11}

A variety of other hormones are also modulated with the onset and progression of puberty. As a result of increased sex steroid concentrations, sex hormone-binding globulin is lower during puberty than in childhood. While secretion of LH is inhibited by androgens and estrogens, the secretion of FSH is suppressed by gonadal production of inhibin, a 31-kd gonadal glycopeptide produced by the Sertoli and granulosa cells. Inhibin, consisting of α and β subunits joined by disulfide bonds, shows a progressive increase in mean concentration with advancing puberty in both sexes. The β - β dimer (activin) also occurs, but its biologic effect is to stimulate FSH secretion. The biologic features of these newer hormones are being delineated. In addition to its endocrine effect, activin has paracrine effects in the testis.¹² It facilitates LH-induced testosterone production, indicating a direct effect of Sertoli cells on Leydig cells. Concentrations of the glycoprotein anti-müllerian hormone (AMH) show marked sexual dimorphism. The AMH is produced in Sertoli cells and the levels are relatively high in newborn boys but are undetectable in girls. In contrast, the hormone becomes very low in boys during puberty, at which time AMH concentrations increase in girls.

Growth hormone (GH) spontaneously increases during puberty and the increase is more marked at nights. IGF-1 levels during puberty are higher than those of the adult and it has a role in the pubertal growth. Their levels do not correlate with the pubertal velocity of growth.

The role of genetic and chromosomal mutations in regulating the timing of puberty in healthy adolescents remains unclear. Pubertal timing is correlated highly within ethnic population groups, within families, and between monozygotic twins, with heritability estimates suggesting that 50 to 80 percent of the variation in pubertal timing is determined by genetic factors. Environmental factors also play a definitive role in the initiation of puberty. Diet, obesity and leanness, exercises and sports like athletics, gymnastics and ballet dancing are well-known factors in influencing the pubertal age and attainment of menarche.

There are interesting facts that are emerging with regard to chemical neurotransmitter peptides that regulate, control and initiate the pubertal development. In spite of voluminous information available, it is a fact that even today the exact mechanisms responsible for the initiation of normal puberty are not clearly understood.

PRECOCIOUS PUBERTY

Definition

Precocious puberty is a clinical state in a child, where the physical and hormonal signs of pubertal development appears at an earlier age than is considered normal—8 years in girls and 9 years in boys.¹³⁻¹⁷

The definition of precocious puberty as seen in the standard textbooks has been traditionally “development of secondary sexual characteristics” in girls less than eight years of age. In a cross-sectional study to assess breast and pubic hair development of 17,000 females, aged 3 to 12 years by Herman-Giddens and coworkers in 1997, girls in the United States have been found to undergo pubertal development at younger ages than previously reported.¹⁸ In white girls, the mean age for attainment of Tanner 2 breast development was 10.0 ± 1.8 years, while Tanner 2 pubic hair began at a mean age of 10.5 ± 1.7 years. In African-American girls, onset of puberty occurred even earlier, with a mean of 8.9 ± 1.9 years for Tanner 2 breast development and 8.8 ± 2.0 years for Tanner 2 pubic hair. Additionally, 6.7 percent of white and 27.2 percent of African-American girls had evidence of breast or pubic hair development before the age of 8 years, indicating that application of traditional definitions would result in a high proportion of girls being diagnosed with precocious puberty.

Kaplowitz and colleagues, having analyzed available studies on recent change, i.e. advancing age in the appearance of Tanner stage 2 breast development and stage 2 pubic hair in American girls,¹⁹ especially among blacks, have issued some guidelines for evaluation and treatment of girls with possible precocious puberty. In 1999, the Drug and Therapeutics and Executive Committees of the Lawson Wilkins Pediatric Endocrine Society (LWPES) published new recommendations suggesting the age cut-off for precocious puberty should be

decreased to 7 years in white girls and 6 years in African-American girls. In boys, there has been no such modification in the definition.¹⁴ This report not only suggested a change in the age limit but also recommended that white girls with breast development after age 7 or African-American girls with breast development after age 6 years should undergo evaluation if the tempo of pubertal progression is abnormal resulting in a bone age advanced more than two years and a predicted height that is either less than 150 cm (59 in) or two SD below the genetic target height; headaches, focal neurologic deficits, or an underlying neurologic problem are present; or the child's or family's emotional state is affected adversely by the progression of puberty and potential for early menarche.

The controversy with regard to the recommendations of LWPES of 1999 is that the implementation of the same by lowering the cutoff age would result in failure to identify young girls with underlying pathology. Several retrospective cohort studies have described cases of astrocytomas, gliomas, adenomas, craniopharyngiomas, hamartomas, congenital adrenal hyperplasia, and McCune-Albright syndrome that may have been missed using the new LWPES guidelines.²⁰⁻²² These data have led some to hold to the recommendation that all girls with pubertal onset before age 8 years have a complete evaluation including a head magnetic resonance imaging (MRI).^{23,24} Pending new data regarding normal age of pubertal onset and rates of pathology, most of the pediatric endocrinologists still perform a complete evaluation in all girls with pubertal onset younger than 6 years and in most girls with onset between the ages of 7 and 8.

Classification of Precocious Puberty

1. Central or GnRH dependent precocious puberty (CPP).
2. Peripheral or GnRH independent precocious puberty or precocious pseudopuberty (PPP).
3. Incomplete, unsustained, and intermittent forms of sexual precocity

Premature Adrenarche

Early appearance of pubic hair without breast development (girls) or enlargement of the penis or testes (boys). Although children with premature adrenarche (PA) typically grow at a normal rate, rapid growth was noted often enough, as discussed below, that this finding did not exclude a diagnosis of PA.

Premature Thelarche

Appearance of breast tissue (Tanner stage 2) in a girl under 3 years of age without evidence of rapid progression over time and no evidence of a central nervous system problem.

Table 1: Causes of central precocious puberty – (gonadotrophin –dependent)

<ul style="list-style-type: none"> Idiopathic (constitutional/functional) Central nervous system abnormalities 	
Congenital anomalies	Hypothalamic hamartomas, hydrocephalus, arachnoid cysts, suprasellar cysts, septo-optic dysplasia, meningomyelocele
Acquired	Static encephalopathies (hypoxia, trauma, radiation, etc.) Postencephalitic, Postmeningitic and Postsurgical scars, infective or inflammatory granulomas
Brain tumors	Craniopharyngiomas, pinealomas, gliomas, astrocytomas, ependymomas, adenomas secreting LH, neurofibromatosis
<ul style="list-style-type: none"> Increased intracranial pressure Hypothyroidism (prolonged and untreated) Silver-Russell Syndrome 	
Combined gonadotropin independent and gonadotropin dependent precocious puberty	
<ul style="list-style-type: none"> Congenital adrenal hyperplasia (treated) McCune-Albright syndrome (late) Familial male precocious puberty (late) 	

Central (GnRH dependent) Precocious Puberty (True PP)

Central (GnRH dependent) precocious puberty (CPP), as the name suggests refers to those conditions where there is demonstrable premature activation of hypothalamic GnRH pulse generator- pituitary gonadotropin - gonadal axis resulting in earlier initiation and appearance of pubertal changes in children. Hence, in these conditions grouped under CPP, a pubertal type of pulsatile release of LH is seen with a similar increase in serum LH levels after GnRH administration as seen during normal pubertal development. GnRH dependent precocious puberty is always isosexual. The pace and pattern of advanced pubertal development varies depending on the cause of CPP. In complete CPP, ovulation and spermatogenesis are reported to occur. The causes of CPP are listed in Table 1.

GnRH independent - Peripheral Precocious Pseudopuberty (Table 2)

Here, extrapituitary source of gonadotropin or sex steroids is independent of premature activation of hypothalamic – pituitary - gonadal axis leads to earlier appearance of pubertal features (Table 2).

In gonadotrophin independent – Peripheral precocious pseudopuberty (PPP), sexual maturity may be either isosexual or heterosexual with only some of the features appearing early. The diagnostic criteria for PPP are:

Table 2: Causes of peripheral precocious pseudopuberty

(Gonadotrophin independent)	
Females isosexual (Feminization)	Males isosexual (Masculinization)
1. Ovarian tumors	1. Primary Leydig cell hyperplasia
2. Granulosa-theca cell tumor associated with Ollier disease	2. Sporadic
3. Teratoma, dysgerminomas	3. Male limited AD
4. Chorionepithelioma	4. Tuberous sclerosis
5. Sex-cord tumor with annular tubules (SCTAT) associated with Peutz-Jeghers	5. Leydig cell tumor
6. Autonomous functional cyst of the ovary	6. Congenital adrenal hyperplasia
7. McCune-Albright syndrome	7. Adrenocortical tumor
8. Simple follicular cysts	8. Teratoma
9. Feminizing adrenocortical tumor	9. Exogenous androgens
10. Exogenous steroids	
Heterosexual (Virilization)	Heterosexual (Feminization)
1. Congenital adrenal hyperplasia	1. Adrenocortical tumor
2. Adrenocortical (testosterone secreting) tumor	2. Exogenous estrogen
3. Androblastoma (arrhenoblastoma)	3. Sertoli cell tumor
4. Teratoma (androgen producing)	4. Sex-cord tumor with annular tubules (SCTAT)
5. Exogenous androgens	associated with Peutz-Jeghers

1. Absence of spontaneous gonadotropin pulsatile activity.
2. Weak but variable response to GnRH test.
3. No clinical response to GnRH analog therapy.
4. Cyclical steroidogenesis.

Occasionally, in longstanding and untreated cases, the elevated sex steroids due to adrenal or ovarian pathology may stimulate early maturation of hypothalamic-pituitary axis resulting in GnRH dependent precocious puberty.

Etiology

Central precocious puberty represents four-fifths of the total number of patients with precocious puberty and is much more frequently seen in girls than in boys, the ratio being 10:1 in favor of girls. Central precocious puberty in girls, i.e. activation of the hypothalamus-pituitary-ovary axis, accounts for more than 90 percent of precocious puberty cases in published series. Idiopathic central precocious puberty is diagnosed when early pubertal development (including acceleration of growth and bone maturation) is associated with a pubertal pattern of gonadotropin secretion (increased LH secretion) and when there is no evidence of organic cause provided through history, physical examination, or brain imaging.

Among patients with central precocious puberty, the proportion of idiopathic forms varies between 58 and 96 percent. This proportion is greater in girls than in boys (nearly 80 percent of CPP in girls). Boys show a higher prevalence of recognizable organic forms. With more frequent use of MRI in the work-up of girls with idiopathic central precocious puberty, benign hypothalamic hamartomas are increasingly reported. This difference in sex in the incidence of idiopathic CPP may indicate a lower gonadotrophin threshold to endogenous pulsatile GnRH in girls. In girls, it is now recommended that investigations like ultrasound of the ovaries and a low dose (0.25 mcg/kg IV) GnRH test be undertaken to confirm the mechanism of CPP and to exclude an underlying cause. While neuroradiological investigation is compulsory in boys with CPP, it may be carefully considered in girls with CPP. Gonadotrophin stimulation in boys is indicated by a testicular size of more than 2.5 cm or a testicular volume of more than 4 ml. These boys must be evaluated radiologically and endocrinologically (early morning testosterone, hCG and GnRH test) for organic causes based on history and physical examination. The causes of CPP are indicated in Table 1.

In both types of sexual precocity there is increased height velocity, somatic development and sexual maturation due to increased gonadal sex steroids. The advanced bone development with initial tall stature results in premature epiphyseal fusion and final short stature. Left untreated, most boys will not grow taller than 155 cm (5 feet 2 inches), and girls often do not grow taller than 150 cm (5 feet).

Central Nervous System Disorders in CPP²¹⁻²⁷

Lesions of the CNS are well recognized as causing central precocious puberty. Common causes include static encephalopathy due to infection, hypoxia, trauma, or irradiation during infancy or early childhood.

Hypothalamic Hamartomas

A less common but important cause of central precocious puberty is a CNS tumor. Hypothalamic hamartomas are benign tumors that have been shown to contain measurable GnRH. They probably act as ectopic GnRH pulse generators that have escaped from the normal inhibitory influences exerted in the prepubertal period on the centers that normally secrete GnRH. These small tumors are more frequently diagnosed in boys than in girls and are most easily visualized using MRI, as some may only be 2 or 3 mm in size. These tumors tend to grow slowly, if at all, and uncommonly cause neurologic symptoms. Symptomatic hamartomas are associated with gelastic or laughing seizures. Precocious sexual development is adequately controlled with GnRH agonists in patients with hamartomas. Optic and hypothalamic gliomas, astrocytomas,

ependyomas, or craniopharyngiomas may also cause CPP by possibly impinging on the neural pathways that inhibit the GnRH pulse generator in childhood. Treatment for these tumors is surgical.

The chance of finding CNS pathology in either sex is inversely proportional to the age of the child, with the greatest yield in children younger than 4 years old. In girls whose pubertal development start began after 6 years of age, any CNS pathology will be already known or clinically evident, suggesting that routine MRI in these children will less likely have positive findings.²⁷ In contrast, Pescovitz and coworkers reported that in a series of 4000 children referred to the National Institutes of Health, about one third of the girls and over 90 percent of the boys had an identifiable lesion of the CNS visible on computed tomography or MRI scans.²⁸ This high prevalence of CNS lesions in their series reflects the referral population.

PRECOCIOUS PSEUDOPUBERTY

McCune-Albright Syndrome

(Precocious Puberty with Polyostotic Fibrous Dysplasia and Abnormal Pigmentation)

McCune-Albright syndrome refers to a syndrome of autonomous hyperfunction of single or multiple (pituitary, thyroid, and adrenal) endocrine organs associated with patchy cutaneous pigmentation and fibrous dysplasia of the bones. Sexual precocity in girls has been the commonly noted endocrinopathy. A missense somatic gene mutation encoding the α -subunit of GS, the G protein stimulates cyclic adenosine monophosphate (cAMP) formation, resulting in the formation of the putative gsp oncoprotein. Activation of receptors (e.g. corticotropin [ACTH], TSH, FSH, LH receptors) that operate with a cAMP-dependent mechanism, as well as cell proliferation, ensues. Because the mutation is somatic, rather than genomic, it is expressed differently in different glands or tissues; hence, the variability of clinical expression in different patients.

In girls, the most common presentation is precocious puberty, occurring even as early as 6 months with vaginal bleeding reported at 4 months of age and development of secondary sex characteristics. Estradiol levels vary from normal to markedly elevated; levels of LH and FSH are suppressed with no response to GnRH stimulation. The ovaries are often enlarged asymmetrically and there are multiple functional cysts. In boys, precocious puberty is less common. Unlike ovarian enlargement in girls, testicular enlargement in boys is fairly symmetric. It is followed by the appearance of phallic enlargement and pubic hair, as in normal puberty. Testicular histology has demonstrated large seminiferous tubules and no or minimal Leydig cell hyperplasia; these findings may simply reflect the fact that biopsy specimens were obtained at an early stage

of pubertal development. In girls and boys, when the bone age reaches the usual pubertal age range, gonadotropin secretion begins, and the response to GnRH becomes pubertal. True (gonadotropin-dependent) precocious puberty overrides the antecedent (gonadotropin-independent) precocious pseudopuberty. In girls, menses become more regular, but often not completely, and fertility has been documented.

Multinodular goitrous hyperthyroidism/ bilateral nodular adrenocortical hyperplasia with Cushing syndrome may antedate the sexual precocity. The ACTH levels are low, and adrenal function is not suppressed by large doses of dexamethasone. Bilateral adrenalectomy is the treatment in such instances. Increased secretion of growth hormone may cause gigantism or acromegaly or tall stature with increased rates of growth even in the absence of precocious puberty. Girls and boys are equally affected. Serum levels of prolactin are increased in most patients, but fewer than half of the patients have a demonstrable pituitary tumor.

Pubertal progression is variable in these patients. Functioning ovarian cysts often disappear spontaneously; aspiration or surgical excision of cysts is rarely indicated. For girls with persistent estradiol secretion, agents that interfere with the final step of estrogen biosynthesis, that is, aromatase inhibitors such as testolactone, letrozole or anastrozole, or antiestrogens (such as tamoxifen) may limit, to a variable extent, the estrogen effects on pubertal and osseous maturation. Associated therapy with long-acting analogs of GnRH is indicated only for patients whose puberty has shifted from a gonadotropin-independent to a predominantly gonadotropin-dependent mechanism. Octreotide, a long-acting somatostatin analog, has been used to treat the hypersomatotropism. The prognosis is favorable for longevity, but deformities, repeated fractures, pain, and occasional cranial nerve compression may result from the bony lesions.

Of the extraglandular manifestations, phosphaturia, leading to rickets or osteomalacia, is the most common. Cardiovascular and hepatic involvement (e.g. severe neonatal cholestasis) is rare but may be life-threatening.

Syndrome of Precocious Puberty and Hypothyroidism

Precocious puberty is described in children with long-standing, untreated hypothyroidism. Unlike other children with precocious puberty, the bone age is retarded. Other characteristic features of hypothyroidism are noted along with growth retardation and delayed bone age. Testicular enlargement with modest or no penile enlargement but no pubic hair development is seen in boys. Primarily breast enlargement and menstrual bleeding are the features of advanced sexual development in these girls with hypothyroidism. Large, multicystic ovaries are often

seen by pelvic sonography. Skull film or MRI may show enlargement of the sella. Marked elevation of plasma levels of thyroid-stimulating hormone (TSH) and mild elevation of prolactin are seen. Serum FSH and LH are low.

Precocious puberty associated with hypothyroidism behaves as an incomplete form of gonadotropin-dependent puberty. Highly elevated TSH probably interacts with the FSH receptor ("specificity spillover"), thus inducing FSH-like effects in the absence of LH effects on the gonads. Unlike in true precocious puberty, testicular enlargement occurs without substantial Leydig cell stimulation and testosterone secretion in affected boys. In affected girls, ovarian estrogen production occurs without a concomitant increase in androgens. Treatment of the hypothyroidism results in rapid return to normal of the biochemical and clinical manifestations. Macroorchidism is known to persist in adult life despite adequate thyroxine therapy.

ECTOPIC PRODUCTION OF HUMAN CHORIONIC GONADOTROPHINS

Gonadotropin-Secreting Tumors

Hepatic Tumor

Hepatoblastoma in boys may be associated with isosexual precocious puberty because of tumor cell synthesis and release of human Chorionic Gonadotropins (hCG), which stimulates the LH receptors in the Leydig cells of the testes. Whenever, in a case of isosexual precocious puberty, the physical examination reveals hepatomegaly, this diagnosis must be entertained. The children with early onset of puberty are usually in the age range of 3 to 8 years. Plasma levels of hCG and α -fetoprotein are usually markedly elevated; they serve as useful markers for following the effects of therapy. Plasma levels of testosterone are elevated, and the FSH and LH levels, as measured by specific, immunometric assays, are low. Plasma levels of hCG and α -fetoprotein are usually markedly elevated; they serve as useful markers for following the effects of therapy. Plasma levels of testosterone are elevated, and the FSH and LH levels, as measured by specific immunometric assays are low. Prognosis even after treatment of the tumor is poor.

Other Tumors

Choriocarcinomas, teratocarcinomas, or teratomas (also called ectopic pinealomas or atypical teratomas), located in the CNS, mediastinum, gonads, or even adrenal glands may elaborate chorionic gonadotropin, thereby causing precocious puberty. These are more common in boys than in girls. Affected patients often have marked elevations of hCG and α -fetoprotein. In boys with Klinefelter syndrome, strangely, mediastinal tumors and not gonadal tumors have been responsible for the appearance of precocious puberty.

Medicational Precocity

Premature appearance of secondary sexual characteristics may be caused by medicines, creams, ointments, cosmetics containing estrogens. Breast development in girls and gynecomastia in boys have occurred because of exposure to these agents. Precocious pseudopuberty has occurred in both boys and girls from the accidental ingestion of estrogens (including contraceptive pills) and from the administration of anabolic steroids. The use of estrogens in animal husbandry is believed to be responsible for the high prevalence of premature thelarche and precocious pseudopuberty in Puerto Rico. A careful history focused on exploring the possibility of accidental exposure to or ingestion of sex hormones is important. Exogenous estrogens may produce an intense, dark brown color in the areola of the breasts that is not usually seen in endogenous types of precocity. The precocious changes disappear after cessation of exposure to the hormones.

Incomplete, Unsustained, and Intermittent Forms of Sexual Precocity (Variations of Normal Puberty—Early)

Premature Thelarche

Limited breast development developing prematurely in young girls, sometimes as young as eighteen months of age, without further progression to a mature breast and without any other signs of puberty is termed premature thelarche. The growth rate is normal as in other prepubertal girls, with a bone age appropriate for chronologic age. Levels of gonadotropins and estradiol are normal, and ultrasound images of the ovaries are unremarkable. This benign condition usually resolves spontaneously and requires no treatment. A biopsy of the breast tissue, being an anatomic equivalent of a partial mastectomy, is not warranted as it alters the subsequent breast development.

Some children who present with breast development later than 2 years are more likely to have some degree of continued breast development, representing an early stage of precocious puberty. Once breast development is stimulated much beyond the breast-bud stage and reaches early adolescent proportions, breast contour generally does not regress. Approximately 10 to 15 percent of these girls develop CPP, but in the majority of patients the breast bud is a transient event that warrants only close follow-up for the appearance of other pubertal signs.

Premature Pubarche

Precocious pubarche is most often a benign condition secondary to early adrenarche. Mild errors of steroidogenesis have been reported with ACTH stimulation tests in 12 percent of children with precocious pubarche. In the majority of those basal 17-OH progesterone levels were higher than in pubertal norms and were felt to be

a good screening test to determine which patients should undergo ACTH stimulation testing. In some patients premature pubarche may predict the future development of chronic anovulation and androgen excess associated with polycystic ovarian syndrome.

Symptoms, Signs, and Diagnosis of Precocious Puberty

In both true precocious and pseudoprecocious puberty, boys may exhibit facial, axillary, and pubic hair; penile growth and increased masculinity. Girls develop breasts and pubic and axillary hair. Girls begin to menstruate more commonly with true precocious puberty, but menstruation may also occur with pseudoprecocious puberty (such as in McCune-Albright syndrome). Body odor and acne, as well as behavior changes, may be present in both sexes. Linear growth is initially rapid in both sexes, but the adult height is shortened by premature closure of the epiphyses. Testicular or ovarian enlargement, which occurs in true precocious puberty, is usually absent in pseudoprecocious puberty. However, ovarian cysts may occur in some cases of McCune-Albright syndrome or in association with sporadic menstruation.

Evaluation of Children with Precocious Puberty (Flow charts 1 and 2)

The evaluation starts with history and physical examination and they contribute immensely to the diagnostic possibility and give a lead to the type of laboratory evaluation. A detailed medical history is essential and must be obtained with special focus on the occurrence of prior CNS injury at birth or later, infections, radiation, seizure activity, headache, visual disturbance, and polydipsia, exposure to exogenous sex steroids in cosmetics or food, or a positive family history – age of puberty and the height of parents and siblings and occurrence of PP in other family members.

The clinical examination must be carried out in the presence of a chaperone and will pay attention to record

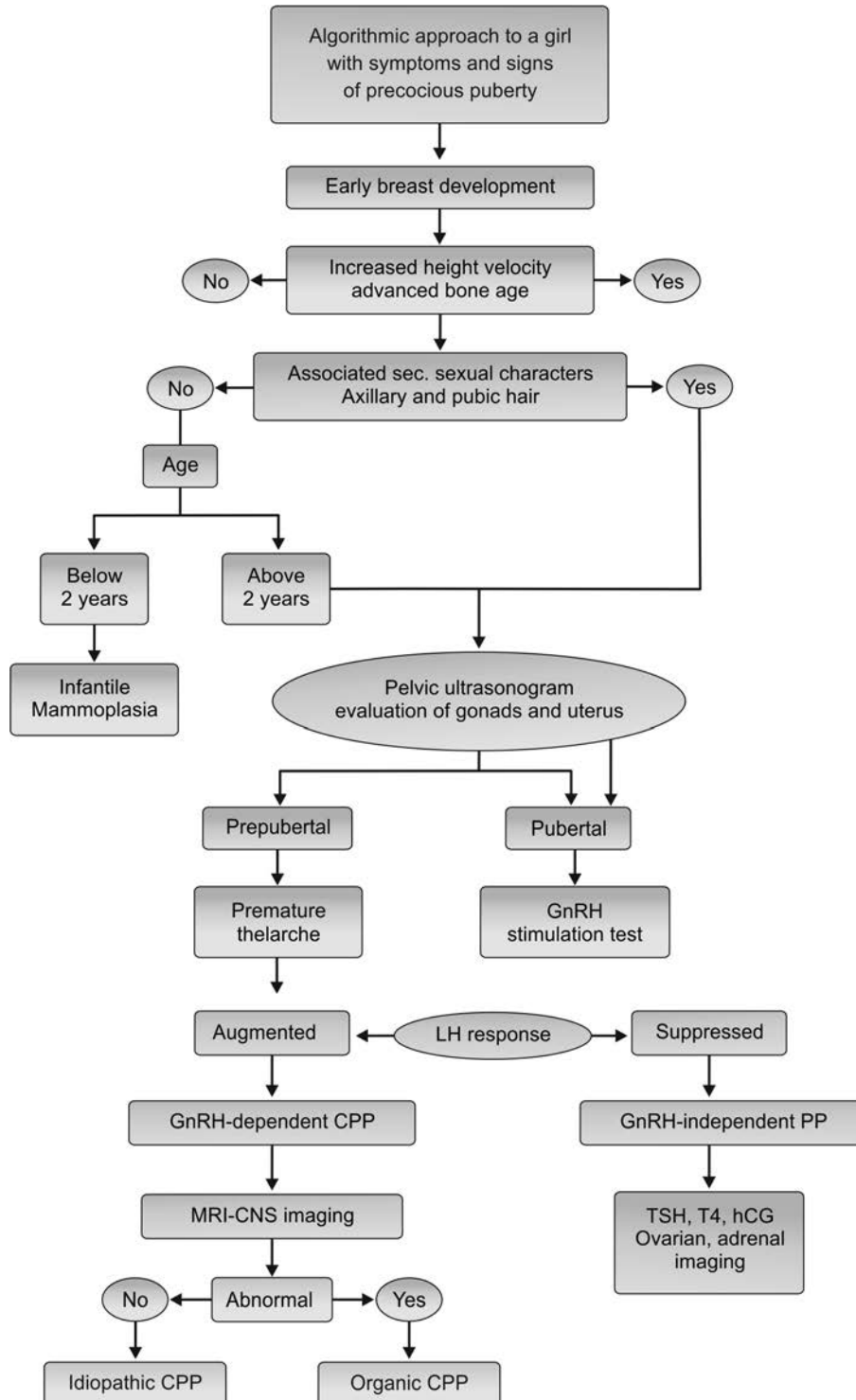
- The presence of various signs of pubertal development - acne, comedones, skin oiliness, facial hair, axillary hair and odor, voice change and muscular development.
- The stage of advancement of gonadal and pubic hair development with attention to details like size, shape and volume of the testes and penile length in boys and the stage of breast and pubic hair development in girls.

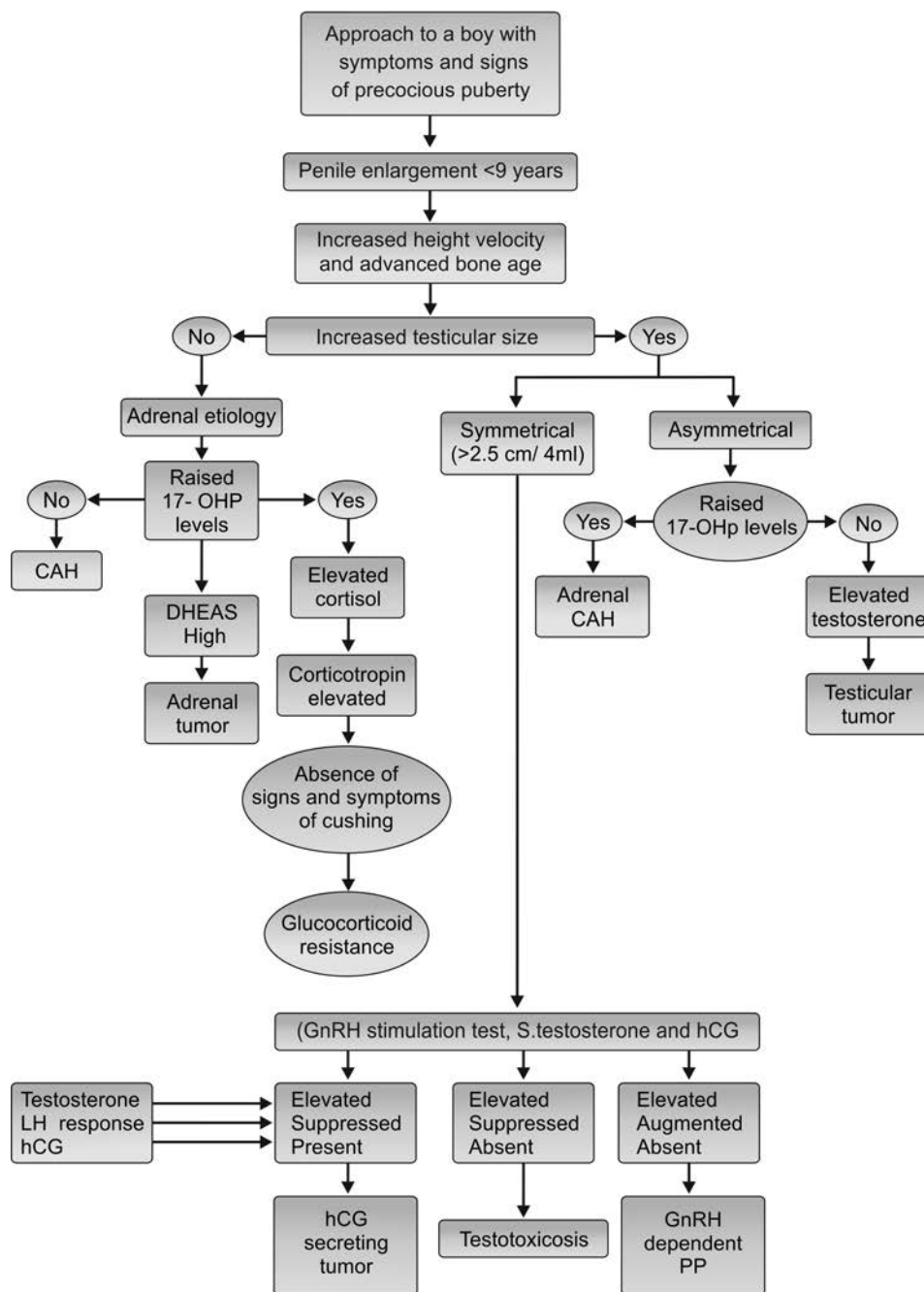
In girls, physical examination should focus on determining whether the development reflects androgen action, estrogen action, or both. In boys with true precocious puberty, the testes will start enlarging symmetrically, whereas in boys with Leydig cell tumors or adrenal rests, the testes show asymmetrical, nodular enlargement.

Examination of the skin may identify presence of café au lait spots of neurofibromatosis or McCune-Albright syndrome, neurofibromas, dry and thick skin of hypothyroidism. A detailed neurological examination must evaluate

the optic disks, visual fields and identify signs of increased intracranial pressure. Acanthosis nigricans has been noted with significant endocrinal conditions in 58 percent (15 of 26) of 6 to 8 year girls referred for early puberty.

Flow chart 1: Approach to a girl with early development of breast and/or other secondary sexual characters



Flow chart 2: Approach to a boy with early development of penile enlargement

Examination of the skin may identify presence of café au lait spots of neurofibromatosis or McCune-Albright syndrome, neurofibromas, dry and thick skin of hypothyroidism. A detailed neurological examination must evaluate the optic disks, visual fields and identify signs of increased intracranial pressure. Acanthosis nigricans has been noted with significant endocrinal conditions in 58 percent (15 of 26) of 6 to 8 year girls referred for early puberty.

Diagnostic Evaluation (Tables 3 to 5)

Radiological Evaluation

Radiological assessment of bone age (hand and wrist X-ray) as a marker for sex steroid hormone is an essential step to determine the need for specific therapy. In general when skeletal age is concordant with chronological age continued close observation may be elected. An advanced bone age by 2 years or more associated with secondary sexual

Table 3: *Evaluation of precocious puberty*

Common initial screening tests

- Careful history, physical examination, and assessment of growth velocity
- Bone age
- LH, FSH
- Estradiol, testosterone
- DHEA-S
- 17-hydroxyprogesterone
- TSH, T4

Secondary tests to consider

- Pelvic ultrasound
- MRI of head
- β -hCG
- GnRH or leuprolide stimulation test
- ACTH stimulation test

characteristics indicate the likely duration of the presence of precocious puberty for a year or more or the rapidity of advancement of puberty. This warrants estimation of levels of estradiol, testosterone, and thyroid hormone. Advanced bone age by only one year needs observation for early development of pubertal features. Skull lateral radiographs may rarely show widening of pituitary fossa or craniopharyngiomas; they are not useful in indicating the presence and type of intracranial tumors or lesions that are often responsible for the development of precocious puberty.

Pelvic ultrasound is an essential investigation for precocious pseudopuberty. Pelvic ultrasound examinations must be performed by competent radiographers trained in pediatric pelvic ultrasound assessments by the full bladder technique obtained by voluntary urine retention following oral administration of fluids. The criteria for assigning appearances as pubertal as opposed to prepubertal were dependent on the appearance of the uterus, including the presence or absence of an endometrial echo. In girls with a definitive diagnosis of Central Precocious Puberty It does not give additional information, except that it may show bilaterally enlarged ovaries, often with multiple small follicular cysts, and an enlarged uterus with an endometrial stripe. Abdominal ultrasound may reveal the presence of gonadal or adrenal tumors or cysts.

Neuroimaging Studies²³⁻²⁶

In most cases, the diagnosis of gonadotropin-dependent precocious puberty (CPP) based on prior endocrinological evaluation warrants a high resolution MRI or

Table 4: *Serum testosterone levels*

Stage	Levels
Generally prepubertal *	<30 ng/dl
Early pubertal	30-100 ng/dl
Midlate pubertal	100-300 ng/dl
Adult	>300 ng/dl

* Depending on the laboratory, testosterone levels of 11-30 ng/dL may represent early puberty.

computerized tomography (CT) head scan with special attention to hypothalamic-pituitary region. The younger the child with CPP (children below 6 years of age), the greater the chance of finding a CNS lesion. Magnetic resonance imaging is now recognized as superior to CT in neuroimaging. For boys, the incidence of CNS findings is much higher than in girls, and MRI should be part of the routine evaluation. Increasing use of MRI in girls with central precocious puberty has been shown to increase the detection rate of abnormalities in the hypothalamo-pituitary region which might have been missed by previous techniques and hence a few investigators feel that neuroimaging with MRI must be routinely included in the work up of girls with CPP.²⁴⁻²⁶

Histopathology

Histopathology of the brain tumor in the hypothalamic-pituitary area is important in prognostication and treatment plan. Gliomas tend to grow more rapidly than astrocytomas, while hamartomas generally are benign.

Endocrinological Evaluation

The endocrinological evaluation includes determination of serum concentrations of gonadotrophins, testosterone and possibly dehydroepiandrosterone (DHEAS) and estradiol measurements

Gonadotropins

Random LH and FSH levels have limited value in the work-up for possible precocious puberty, since standard radioimmunoassays provide ample overlap between levels seen in prepubertal and early pubertal subjects. If random LH and FSH levels exceed 5 IU/L, a diagnosis of precocious puberty is almost certain. Suppressed levels (i.e. <0.1 IU/L) of LH and FSH accompanied by highly elevated testosterone or estradiol levels point to precocious pseudopuberty rather than CPP. The use of newer, more ultrasensitive assays such as chemiluminescence assays for LH and FSH now appear to have greater accuracy for distinguishing levels in prepubertal versus pubertal children and is proposed to indicate the onset of gonadarche even in the absence of a dynamic GnRH test.

Table 5: *Evaluation and diagnosis of central true precocious puberty*

Clinical condition	True precocious puberty (pituitary gonadotrophin dependent states)			
Gonad size	Pubertal - testicular enlargement or ovarian and uterine enlargement			
Plasma gonadotropin levels - assay by 3rd generation	Prominent LH pulses, initially during sleep			
GnRH test - LH response	Pubertal			
Serum sex steroid levels	Pubertal levels of testosterone or estradiol			
Others – clinical and imaging	Skin and skeletal examination and survey: McCune-Albright syndrome Brain MRI/ CT: for CNS/ Hypothalamic tumors or other disorders			
Clinical condition	Chorionic GT secreting tumors	Virilizing CAH (Untreated)	Virilizing adrenal tumor	Leydig cell tumor
Gonad size	Symmetrical, >2.5 cm; but smaller in relation to pubertal development	Prepubertal testes; but enlarged phallus and advanced pubic hair development		Irregular, asymmetrical enlargement
Plasma gonadotropin levels - assay by 3rd generation	High hCG or + pregnancy test	Prepubertal		Suppressed
GnRH Test - LH response		Absent or prepubertal	Suppressed	Absent
Serum sex steroid levels	Pubertal	Raised androgens relating to the enzyme deficiency	High DHEAS, Androstenedione and testosterone	Very high testosterone levels
Others – clinical and imaging	Hepatomegaly in hepatoblastoma; radio-imaging US, CT. The MRI in CNS tumors secreting hCG	After initiation of glucocorticoids, development of complete PP needs therapy	US abdomen; CT and MRI; selective venous sampling	
Clinical condition	Familial Leydig and germ cell maturation		McCune-Albright Syndrome	Premature adrenarche
Gonad size	Symmetrical, >2.5 cm; smaller in relation to pubertal development; spermatogenesis +/-	Symmetrical, > 2.5 cm; smaller in relation to pubertal development	Prepubertal	
Plasma gonadotropin levels - assay by 3rd generation	Suppressed	Prepubertal at first stage	Prepubertal	
GnRH test- LH response	Absent	Absent		
Serum sex steroid levels		Pubertal levels of testosterone	Prepubertal testosterone; DHEAS : pubic hair stage 2	
Others – clinical and imaging	Familial; sex-limited AD trait	Café au lait spots; polyostotic fibrous dysplasia; other hyperendocrinopathies - thyrotoxicosis, gigantism, etc.	Usual onset: Beyond 6 years of age	

GnRH Test

This test is indicated in the diagnosis of central precocious puberty (CPP) in suspected children. A pubertal response of LH will differentiate CPP from other peripheral causes. The determination of gonadotrophins LH and FSH in a single blood sample drawn after GnRH administration has simplified the diagnostic work-up of CPP. A definitive central precocious puberty (CPP) diagnosis is confirmed by a brisk rise in LH 20 to 40 minutes after infusion of 100 mcg of GnRH, which is more than the rise in FSH. No increase in LH and FSH after infusing GnRH suggests precocious pseudopuberty. Prepubertal girls with premature thelarche sometimes show an exaggerated rise in FSH after GnRH. A FSH rise more than the LH rise does not indicate CPP.

Sex Steroid Levels

For girls, because of weekly fluctuations of levels, estradiol measurements are less reliable indicators of the stage of puberty. Though levels exceeding 20 pg/ml usually indicate puberty, some girls who are definitely pubertal may have levels less than 20 pg/ml. Girls who have ovarian tumors or cysts often have estradiol levels that exceed 100 pg/ml.

Serum testosterone evaluation is useful for boys with suspected precocious puberty. Table 4 outlines the approximate correlation of this test with the stage of puberty. Note that because LH and testosterone rise with sleep onset in early puberty, early morning testosterone is higher than afternoon levels.

Adrenal androgen levels are helpful in the evaluation of PPP only when an adrenal tumor is considered to be present because of rapid virilization as it is generally associated with extremely elevated DHEA and DHEAS. Levels of adrenal androgens (e.g. dehydroepiandrosterone [DHEA], dehydroepiandrosterone sulfate [DHEAS]) are elevated modestly in boys and girls with early growth of pubic hair. If congenital adrenal hyperplasia is suspected, serum levels of 17-OH progesterone are estimated. For greatest accuracy of diagnosis, an adrenocorticotrophic hormone (ACTH) stimulation test gives the greatest diagnostic accuracy. A high-normal random 17-OH progesterone finding with an elevated level 30 to 60 minutes after ACTH injection may be seen.

Thyroid hormonal tests are not a routine requirement. Severe hypothyroidism rarely leads to precocious puberty. Major clues of severe hypothyroidism are growth arrest instead of growth acceleration, galactorrhea, and signs of thyroid hormone deficiency. In primary hypothyroidism, mild testicular enlargement is likely because of raised FSH; Free T4 will be low and TSH is elevated; LH levels will be prepubertal.

Treatment

Treating early puberty is important for physical as well as emotional and social reasons. Children with precocious

puberty may initially appear taller than their peers, but they stop growing too soon and end up at a shorter height than normal. If untreated, boys typically grow no taller than 160 cm (5 feet 4 inches) and girls rarely reach 150 cm (5 feet). Hence, the main goals of therapy in PP are to preserve adult height and alleviate potential psychosocial effects of precocious puberty.

Objectives of treatment in precocious puberty	Determinants for initiation of specific treatment in precocious puberty
To arrest and cause regression of existing secondary sexual characteristics	Age, overall health status and medical history of the child
To arrest premature sexual maturation until normal age of puberty	Time of onset, extent and degree of advancement of the condition
To halt the rapid rate of skeletal maturation and to prevent early epiphyseal fusion, so as to prevent final short stature and attain near normal mature height	Expectations for the course of the condition
To alleviate the emotional and psychosocial problems identified in the child	Affordability (cost), availability and accessibility (local) and acceptability
To detect and treat the primary etiological condition	Tolerance of the child for specific drugs and therapies
To counsel and relieve the parental anxiety	Pediatrician's or endocrinologist's preference based on evidence, experience, familiarity and recent advances

Treatment of Central Precocious Puberty

Gonadotropin Releasing Hormone Agonist

GnRH agonists remain the mainstay of treatment for centrally mediated gonadotropin dependent precocious puberty. These potent long-acting synthetic analogs of natural GnRH, suppress pituitary gonadotropin secretion by providing continuous stimulation, whereas the pulsatile stimulation of endogenous GnRH is the cause for pubertal progression. This downregulation of the pituitary–gonadal axis by the administration of these GRnH analogs limits pubertal progression and arrests and/or regresses physical pubertal development thereby slowing the accelerated pubertal growth rate and bone maturation.²⁸⁻³² The rate of growth and bone maturation during treatment slows, but this rate depends upon the advancement of bone age and skeletal maturation at the time of initiating the therapy. Adult height potential can be preserved by GnRH analog therapy, if treatment is started early enough. Height lost however cannot be regained and so early, prompt treatment is considered essential. Various formulations (intramuscular, subcutaneous, and intranasal) of short- (daily)

and long- (monthly) acting GnRH agonists are available, with depot leuprolide being the most commonly used preparation in the United States. Newly developed 3-month depot formulations also have been shown to be effective.

Gonadotropin-releasing hormone agonists have been shown to improve adult height compared with pretreatment predicted height in children with CPP,^{32,33} but outcomes are variable with children younger than 6 at initiation of therapy gaining the most height and those over 8 showing little benefit. GnRH agonists generally are tolerated well, but occasionally, an initial, temporary flare of GnRH activity can occur and result in transient advancement of secondary sexual characteristics and even vaginal bleeding. Initial concerns about long-term effects of GnRH agonists on bone mineral density have been alleviated,³⁴ GnRH agonist therapy does not lead to obesity, a serious reported and voiced concern.^{35,36}

Leuprolide (leuporelin), triptorelin, goserelin, histrelin acetate and deslorelin are available for subcutaneous and depot intramuscular injection, nafarelin and buserelin are available for subcutaneous and nasal applications.

Drug	Leuporelin	Triptorelin	Goserelin
Preparation	Microsphere suspension	Microsphere suspension	Implant
Injection site and route	Abdomen-SC; Buttocks, thigh - IM	Abdomen-SC; Buttocks, thigh - IM	Abdomen, buttock-SC
3-4 weekly Prep.	Yes	Yes	Yes
10-12 weekly Prep.	Yes	No	Yes

Depot Formulations of Long-acting GnRH Analogs

These maintain fairly constant serum concentration of the drug for weeks, constitute the preparations of choice for treatment of central precocious puberty. Leuprolide acetate, a depot preparation is given in a dose of 0.25 to 0.30 mg/kg/month (minimum, 7.50 mg) intramuscularly. In five percent of children with local reactions like sterile fluid collection at the site of injection, treatment should be changed to subcutaneous injections of aqueous leuprolide, given once or twice daily (20-50 mcg/kg/mo; total dose 600 µg/kg/24 hr), or intranasal administration of the GnRH agonist nafarelin 400 µg to 800 µg bid. The dose of triptorelin is 60 mcg/kg/month. Goserelin acetate is approved for treatment of precocious puberty in other countries. A 12-month implant (histrelin) is also available for use in USA.

Treatment is usually started with a monthly depot preparation given by SC or IM injection. Cyproterone acetate is given initially for a few weeks to counter the effects of the initial 'flare' in gonadotrophin secretion. The acute

GnRH stimulation test is repeated after a few months to determine whether LH and FSH levels are suppressed. Later, it may be possible to maintain adequate gonadotrophin suppression using a 3-monthly long-acting preparation. The duration of therapy is individualized according to age of child, maturity of child, predicted adult height. Usually the treatment is continued until 10 years of age. A withdrawal bleed may occur in some girls following the first GnRH a injection.

GnRH Antagonists

The GnRH antagonists have only recently become commercially available and are currently under study for treatment of sexual precocity. The GnRH antagonist act by competitive binding to GnRH receptors and suppresses pituitary gonadotrophin secretion without any initial outbursts.

Monitoring the Response and Follow-up

The follow-up should be done every 3 to 4 months to ensure that progression puberty has been arrested. Height and height velocity should be monitored. A decrease in testicular size and serum testosterone are sufficient indicators of efficacy of treatment in boys. In girls, a GnRH test should be done initially at 3 to 4 months and then it can be done on yearly basis.

Other Treatment Options

Historically, medroxyprogesterone and cyproterone acetate were used in an attempt to suppress activation of the hypothalamic-pituitary-gonadal axis. In addition, cyproterone acetate has antiandrogenic effect. Neither of these agents was satisfactory as they were not fully effective in inhibiting pubertal or skeletal maturation or improving adult height.

1. Medroxyprogesterone acetate.
2. Cyproterone acetate.

Treatment of Peripheral Precocious Puberty

Treatment of peripheral precocious puberty involves treating the underlying disorder and limiting the effects of elevated sex steroids. Testotoxicosis is often treated with ketoconazole, which is a nonspecific inhibitor of steroidogenesis. Alternative therapies include spironolactone (androgen receptor inhibitor)/flutamide with letrozole, medroxyprogesterone acetate, testolactone and anastrozole (aromatase inhibitor), and tamoxifen (estrogen receptor inhibitor). Recently, tamoxifen has shown particular promise for treatment of McCune-Albright syndrome, but long-term efficacy and safety data are needed.³⁷

McCune-Albright syndrome with multicystic ovaries, elevated estradiol, low basal LH and prepubertal response to GnRH stimulation is treated with tamoxifen, testolactone/aromatase inhibitor.

Surgery of Adrenal or Gonadal Tumors

In most cases, hormone-producing tumors, specifically granulosa cell tumors in girls, should be excised. However, prolonged follow-up is necessary in case of recurrence in the contralateral ovary. Excision is also an option for the various neoplasms causing pseudopuberty in males. However, some of these tumors are aggressively malignant and associated with high mortality.

Testicular/Ovarian/Adrenal Tumors

These tumors are mostly unilateral and should be removed surgically, once removed the remaining contralateral testis, ovary and adrenal glands should recover from suppression and be adequate for normal function.

Congenital Adrenal Hyperplasia

The classic and simple virilizing CAH requires lifelong therapy with glucocorticoids and mineralocorticoids in both males and females.

Psychological Counseling and Emotional Support

Indication for such a treatment on the basis of psychologic and behavioral anomalies has to be determined on an individual basis. Parents who are anxious and worried must be counseled and the evaluation and treatment plan must be discussed with them.

Prognosis of CPP with GnRH Analog Treatment

The adult heights attained by untreated children with CPP often are below the fifth percentile. The cause of the precocious puberty, as well as the age at onset, rapidity of progression through puberty, and age when therapy is initiated, affects the height outcome. Several long-term studies of the treatment of CPP with GnRHa, now indicate that treatment results in improved adult height in most patients. Though some patients attain adult heights that surpass their target heights, a substantial number of treated children with GnRH analogs do not attain their targeted adult heights. Deceleration in growth is expected during GnRHa therapy, but in some patients the decrease during therapy is so great that the expected improvement in predicted adult height is not achieved. Even after several years of therapy, they attain adult heights that are significantly less than their target heights.

SUMMARY

Precocious puberty is not uncommon in pediatric practice. The definition of precocious puberty in girls, i.e. the cut-off age before which there is appearance of secondary sex characters has been modified in the USA, because of advancement of menarche in American black and white girls. The clinical and investigative approach towards this endocrinal problem differs in boys and girls with early development of pubertal features. Advanced bone age results in earlier

epiphyseal fusion causing ultimate short stature. After ruling out the normal variant precocious thelarche and pubarche, the clinician must refer the child to competent experts to have proper investigational work-up and treatment, so that their pubertal features can regress and the final adult height does not get reduced. There are contradicting recommendations regarding the routine need for neuroimaging of girls with central precocious puberty, because majority of them has no identifiable lesion and hence considered idiopathic. Boys with CPP must have total work-up as they have a definite, identifiable cause. The GnRH analogs have become the drug of choice to treat CPP. The peripheral precocious puberty, with its identifiable cause, must be treated accordingly. These children and parents need appropriate counseling and psychological support. These children also need regular follow-up—monitoring of height, bone age, regression of pubertal features and psychosocial adjustment till they attain their regular age of puberty.

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Metabolic Syndrome in Children and Adolescents

Archana D Arya

The *Metabolic Syndrome* also known as syndrome X is characterized by:

- *Obesity* (abdominal)
- *Atherogenic dyslipidemia* (elevated triglyceride [TG] levels, high low-density lipoprotein [LDL] particles, and low high-density lipoprotein cholesterol [HDL-C] levels)
- *Raised blood pressure*
- *Insulin resistance* (with or without glucose intolerance),
- *Prothrombotic inflammatory vascular environment*.

Obesity plays a central role in the development of the metabolic syndrome. As childhood obesity has increased, the complications associated with it have become more common. Doctors are witnessing the first consequences of this epidemic in the form of increased incidence of Type 2 Diabetes Mellitus (T2DM) among adolescents, hepatic steatosis, orthopedic problems, sleep apnea and others.^{1,2}

Diseases such as diabetes mellitus, systemic arterial hypertension and dyslipidemia, increase the risk of cardiovascular events. The association between obesity and coronary disease is already well established in adults.³

This association led to the term “metabolic syndrome” being created to define the condition of those people who are at greatest risk of cardiovascular events.⁴ The fact that the metabolic syndrome is being identified in children suggests that the development of cardiovascular disease will also occur earlier, increasing the risk of early death, therefore, raising a great health concern. Early identification of the metabolic syndrome may help target interventions to improve future cardiovascular health. Unless action is taken, diabetes experts agree that this is the first generation where children may die before their parents.

Recent studies suggest that the metabolic syndrome may originate *in utero*.

Intrauterine events for the unborn child and factors during early development years predispose a child to disorders such as obesity, prediabetes, and metabolic syndrome.

The presence of maternal gestational diabetes,⁵ low birth weight,⁶ and infant feeding practices⁷ for example contribute to a child's future level of risk. Other factors can be genetic, socioeconomic or environmental (an obesogenic environment for example).⁸

DEFINITION

There is no formal definition of metabolic syndrome in children and adolescents. Adaptation of the criteria used for adults is complicated because of the multiple definitions proposed by different organizations and because normal ranges for each criterion must be adjusted for each age group. However, the rapid rise in obesity trends underlines the urgency for a definition that could be used to further understand who is at high-risk of health complications and to distinguish them from those with “simple” uncomplicated obesity.

The wide variety of cut-off points used highlighted the need for a single definition that would use a consistent set of criteria, which would be easily measurable, with age-specific and sex-specific cut-off points.

Third Report of the Adult Treatment Panel (ATP III) defined metabolic syndrome (Met S) by using criteria easily applied by clinicians and researchers⁹ in 2001.

The Third National Health and Nutritional Survey (NHANES) carried out in children from 1988 to 1994, defined pediatric Met S using criteria analogous to ATP III as 3 or greater than 3 of the following criteria¹⁰ (Table 1).

Goodman et al. proposed a definition with BMI as a base, justifying that it would be less dependent on ethnic variations - we are aware that abdominal circumference may vary according to the race. The prevalence in moderately obese patients (considering those who had Z of 2 and 2.5) was 38.7 percent, and in severe obese patients (with Z over 2.5 of pattern deviations), it was 49.7 percent.¹¹

Table 1: Criteria for metabolic syndrome

<i>Fasting Triglycerides</i>	<i>HDL cholesterol</i>	<i>Fasting glucose</i>	<i>Waist circumference</i>	<i>Systolic blood pressure</i>
≥ 100 mg/dl	≤ 50 mg/dl Boys 15-19 years: <45 mg/dl	≥ 100 mg/dl	>75th % ile for age and gender	>90th % ile for gender, age and height

Table 2: The IDF consensus definition of metabolic syndrome in children and adolescents

<i>Age group (years)</i>	<i>Obesity (WC)</i>	<i>Triglycerides</i>	<i>HDL-C</i>	<i>Blood pressure</i>	<i>Glucose (mmol/L) or known T2DM</i>
6-<10	≥90th percentile	MS cannot be diagnosed, but further measurements should be made if there is a family history of MS, T2DM, dyslipidemia, CV disease, HT and/or obesity			
10-<16	≥90th percentile or adult cut-off if lower	≥150 mg/dl (≥1.7 mmol/L)	≤40 mg/dl (≤1.03 mmol/L)	Systolic≥130/ diastolic≥85 mm Hg	100 mg/dl If ≥ 100 mg/dl or known T2DM, recommend an OGTT
16+ MS	Use existing IDF criteria for adults i.e. Central obesity(WC≥94 cm and 80 cm for Europid men and women respectively, with ethnicity specific values for other groups) Plus any 2 of the following 4 factors: –raised triglycerides: ≥150 mg/dl –reduced HDL cholesterol: <40 mg/dl in males and <50 mg/dl in females, or specific treatment for these lipid abnormalities –raised BP: systolic=130 or diastolic=85 mm Hg or treatment of previously diagnosed hypertension –impaired fasting glycemia: FPG ≥100 mg/dl, or previously diagnosed type 2 diabetes				

MS: metabolic syndrome; WC: waist circumference; HDL-C: high-density lipoprotein cholesterol; T2DM: type 2 diabetes mellitus; OGTT: oral glucose tolerance test.

BMI is the most practical method for assessing obesity in children in a clinical practice. The WHO has recommended using BMI as an index of being overweight or obese.

Obesity is defined as a BMI > 95th percentile for age and sex. Those between the 85th and the 95th percentile are considered to be at risk for obesity. There are percentile charts available for BMI, related to age and sex, from NCHS that have been accepted widely. (<http://www.cdc.gov>)

In studies of lean and obese adolescents, it has been shown that the BMI correlates strongly with the visceral lipid depot. The BMI also correlates with blood pressure and dyslipidemia better than the waist circumference and hence may be a better indicator for obesity in children than waist circumference.

On the other hand the new IDF definition of metabolic syndrome in children and adolescents (Table 2) is inspired, in part, by the IDF worldwide definition of metabolic syndrome in adults.¹² The IDF definition has taken waist circumference (WC) as criteria for metabolic syndrome instead of BMI, similar to the adult criteria, because it is an independent predictor of insulin resistance, lipid levels, and blood pressure.¹³⁻¹⁷ Moreover, in young people who are obese and have similar body mass index (BMI), insulin sensitivity is lower in those with high

amounts of visceral adipose tissue and high waist/hip ratio than in those with low amounts.¹⁸⁻¹⁹

Although there has not been universal agreement as to which level to use for the criteria for the metabolic syndrome, several studies,^{12,20,21} have used the 90th percentile as a cut-off for waist circumference. Children with a WC higher than the 90th percentile are more likely to have multiple cardiovascular disease risk factors than are those with a waist circumference below this level.²²⁻²⁴ IDF has chosen to use the 90th percentile as a cut-off for WC, which will be reassessed when more outcome data become available.

Waist circumference in children is a good predictor of visceral adiposity,²⁵ but since body proportions normally change during pubertal development and may vary among persons of different races and ethnic groups.²⁶

Kuriyan et al. developed waist circumference percentiles based on a study on 9060 urban children (5172 boys and 3888 girls) in the age group of 3 to 16 years in Bangaluru in 2010. The waist circumference of the Indian children from the present study was higher than age and sex matched European children.

These curves represent the first waist and waist height ratio percentiles for Indian children but do not have national geographical representation.²⁷

The author suggested that for a start, the 75th percentile of waist circumference from this study be used as an “action point” for Indian children to identify obesity.

Virani studied 320 affluent children longitudinally from 5 major geographical regions in India for their waist circumference and developed WC percentiles.²⁸

Pandey et al published WC percentiles for Indian children from 14 to 18 years of age.²⁹

The WC percentiles of Indian children published recently have their limitations in terms of national representation and age groups. Method of measuring WC can also vary and most pediatricians are more comfortable with BMI as a parameter rather than measuring WC, hence it is suggested that pediatricians can continue to use BMI cut-offs at present for defining Met S.

Prevalence of Metabolic Syndrome in Adolescents

The NHANES III survey (1988-1994) revealed that the prevalence of metabolic syndrome was 6.8 percent among overweight adolescents and 28.7 percent among obese adolescents.¹⁰ However, these rates may underestimate the current extent of the problem, because both the magnitude and the prevalence of childhood obesity have increased in the past decade.

Epidemiologic data show that 4 percent of all adolescents and 30 percent of overweight adolescents in the United States have the metabolic syndrome.⁹ Prevalence among 12 to 19 year olds in the United States is about 4.2 percent.¹⁰ The risk of the metabolic syndrome is nearly 50 percent in severely obese (BMI >40.6 kg/m²) adolescents.³⁰

The prevalence of the metabolic syndrome also increased significantly with increasing insulin resistance.

The Medline and Embase databases were searched for articles published between August 2007 and January 2009, in which the prevalence of the metabolic syndrome was analyzed in populations aged between 2 and 19 years, using several recognized definitions. Diagnostic criteria were extracted for the Met S and prevalence rates by sex, age group, body mass index status and ethnicity. A total of 36 studies were included. The prevalence estimates from general population and community-based sampling ranged from 1.2 to 22.6 percent with rates of up to 60 percent observed in the overweight and obese.³⁰

Singh et al screened 1083 adolescents between 12 to 17 years of age in Chandigarh, India. The overall prevalence of MS in adolescents was 4.2 percent. However, the prevalence rose to 5.8 percent when the fasting plasma glucose cut-off was lowered to 5.5 mmol/L. There was no gender difference in the distribution of MS. When stratified by body mass index (BMI), 5.5 percent adolescents had a BMI >95th percentile, while 4 percent had a BMI between 85th and 95th percentile. Of the adolescents with BMI >95th percentile, 36.6 percent met the criteria for MS, while 11.5 percent met the criteria in those with a BMI between 85th to 95th percentile. Only 1.9 percent of the normal population had MS (P <0.0001).

Low high-density lipoprotein was the most common and abdominal obesity the least common constituent of MS.³¹

COMPONENTS OF METABOLIC SYNDROME IN CHILDREN

Obesity

Etiological Role of Weight Gain and Obesity in Metabolic Syndrome

For most patients, the root causes of the metabolic syndrome are improper nutrition, inadequate physical activity, and subsequent increases in body weight.

As the degree of obesity increases, the prevalence of Met S increases, with obesity occurring in 38.7 percent of moderately obese (mean body mass index [BMI] 33.4 kg/m²) and 49.7 percent of severely obese (mean BMI 40.6 kg/m²) children and adolescents.

Among obese children, the prevalence of the metabolic syndrome is high and increases with worsening obesity.^{10,20} This was illustrated in a study of 439 obese, 31 overweight, and 20 normal-weight children and adolescents who underwent a comprehensive metabolic assessment.²⁰ The metabolic syndrome was present in 39 and 50 percent of the moderately and severely obese subjects, respectively. In contrast, no overweight or normal-weight children met the criteria for the metabolic syndrome.

Morrison et al³² carried out a prospective assessment of 814 children and adolescents as part of a 25 to 30 year follow-up. Metabolic syndrome in adulthood was strongly associated with presence of metabolic syndrome and with body mass index (BMI) in childhood, with each increase in BMI percentile of the order of 10 points being linked to a 25 percent increase in the risk of metabolic syndrome in adulthood. Another important finding from this study was that metabolic syndrome in childhood was an independent predictor of DM2 in adulthood.³²

DYSLIPIDEMIA

The lipid profile associated with the metabolic syndrome puts individuals at increased risk for cardiovascular disease. Several deleterious changes in lipid metabolism are often seen in obese individuals. These changes are more closely correlated with the amount of visceral fat than total body fat. In general, obesity tends to elevate fasting plasma total cholesterol and TGs, and reduce plasma HDL-cholesterol levels. Though plasma LDL-cholesterol levels remain slightly elevated or normal, small, dense atherogenic LDL particles tend to increase, particularly in patients with insulin resistance associated with visceral adiposity. The low HDL-C levels, high LDL-C to HDL-C ratio, and high proportion of small, dense LDL particles increase risk for atherosclerosis.

The Bogalusa Heart Study, a community-based study of risk factors for cardiovascular disease, pooled data from 9167 subjects aged 5 to 17 year. These investigators found that children with a BMI above the 85th percentile for age and gender were more likely to have adverse levels of cholesterol, LDL-cholesterol, HDL-cholesterol, TG, and blood pressure, respectively, than normal weight subjects.³³

Insulin Resistance

Hyperinsulinism and insulin resistance are characteristic features of obesity.³⁴ It has been demonstrated that insulin secretion increases as the severity of obesity increases and this increase in insulin secretion is accompanied by varying degrees of resistance to insulin mediated glucose uptake, resulting in abnormalities in glucose tolerance in some obese adolescents.³⁵ Insulin resistance results in the development of acanthosis nigricans, a raised hyperpigmentation of the skin often present at the back of the neck, axillae and other flexural areas. Girls with hyperinsulinism may develop hyperandrogenism and hirsutism. Occasionally, some adolescents with a familial predisposition to type 2 diabetes develop the disease.

About 25 percent of children or adolescents with obesity have insulin resistance, and 4 percent have silent type 2 diabetes.³⁶ As in adults, insulin resistance and diabetes are associated with other elements of the metabolic syndrome, including hypertension and abdominal fat distribution. Studies in children have shown a relationship among fasting insulin and lipids³⁷ blood pressure³⁸⁻⁴⁰ and BMI.^{41,42} Furthermore, high insulin levels have been shown to precede the development of the atherogenic profile characterized by low HDL-cholesterol, high triglycerides, and high systolic blood pressure. Hyperinsulinemia, through stimulation of arterial smooth muscle proliferation, has been implicated in the development of atherosclerotic plaque and degree of insulin resistance is significantly correlated with coronary artery disease.

The mechanism through which insulin resistance and the accompanying hyperinsulinemia may alter blood pressure is less clear but may relate to direct effects on the sympathetic nervous system and renal sodium reabsorption. High blood pressure may develop due to the lack of resistance to these secondary effects of insulin or alternatively, insulin resistance may lead to endothelial dysfunction through the nitric oxide pathway.

Systemic Arterial Hypertension

The association between arterial hypertension and obesity is valid for all age groups. In the pediatric population, obesity is the primary cause of hypertension. Systolic hypertension is positively correlated with BMI and the waist- to-hip ratio in both children and adolescents.^{43,44}

Arterial hypertension in children is defined statistically on the basis of a distribution curve from healthy

children. Body composition is the greatest determinant of arterial blood pressure in children and adolescents. For this reason, arterial blood pressure measurements must be adjusted for height, age and sex. ([http://www.nhlbi.nih.gov/guide lines/hypertension/child_tbl.htm](http://www.nhlbi.nih.gov/guide%20lines/hypertension/child_tbl.htm)).

Endothelial Dysfunction

Endothelial dysfunction is one of the earliest signs of increased risk for cardiovascular disease and has been shown to be predictive of cardiovascular events. Endothelial dysfunction develops in the milieu of cardiovascular risk factors such as obesity, hypertension, dyslipidemia, insulin resistance, and type 2 diabetes. Moreover, obese children have increased levels of hemostatic and inflammatory factors, including fibrinogen, plasminogen activator inhibitor 1, and C-reactive protein.^{43,45,46} These factors may contribute to endothelial dysfunction and early atherogenesis in obese youth. In obese children, endothelial dysfunction is related to the severity of obesity, as well as to the degree of insulin resistance.

ASSOCIATIONS AND FUTURE OUTCOMES OF METABOLIC SYNDROME

Hepatic Manifestations

Recent studies have revealed the hepatic manifestations of the metabolic syndrome, which include nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH).^{47,48}

A valuable biomarker for both of these disorders is an elevated alanine aminotransferase (ALT) level.⁴⁹

Between 10 and 25 percent of obese children have elevated transaminases, primarily ALT; the degree of obesity is related to the prevalence of elevated ALT levels; studies have shown that 11 percent of the moderately obese subjects and 21 percent of the severely obese subjects have elevated ALT levels.

Abdominal sonography can detect a fatty liver, which is also associated with a greater BMI, in 52 percent of obese children. In an autopsy study, the incidence of fatty liver was 38 percent in obese children 2 to 19 years of age. Morbidly obese children are particularly prone to fatty liver. Weight reduction is an effective treatment for NAFLD. Although a benign clinical course is typical of NAFLD, it may be associated with increasing fibrosis and, rarely, progression to cirrhosis.

Cardiovascular Consequences of Obesity (Relationship between Components of MS and Future CV Outcomes)

A recent study prospectively analyzed a cohort of 276,835 children for coronary disease. The risk of a coronary event in adulthood had a positive correlation with BMI between

7 and 13 years of age for boys and between 10 and 13 years of age for girls, with a linear relationship between BMI and the rate of cardiac events.⁵⁰

Another interesting study estimated the prevalence of obesity among 35-year-old in the United States in 2020 (projected from current data and secular trends) and the future incidence of coronary events between 2020 and 2035 (using a computerized statistical simulation program). The study concluded that in 2035 the prevalence of coronary disease would have risen by 5 to 16 percent, with an excess of 100,000 cases being attributable to the increase in obesity.⁵¹

The greatest concern aroused by childhood obesity is probably cardiovascular diseases. The Bogalusa Heart Study⁵² analyzed data from autopsies of people who died aged from 3 to 31 and who had previously been assessed for risk factors (lipid profile, arterial blood pressure, anthropometric data). The study results showed that the presence of fatty streaks (one of the earliest stages of atheromatous plaques) in the aorta was strongly related to total cholesterol and LDL-cholesterol levels and correlated inversely with HDL-cholesterol. Fibrous plaques were observed in the coronary arteries of people who had high LDL-cholesterol, triglycerides and arterial blood pressure and low HDL. Microscopic histological analysis of the aortic and coronary intima confirmed these findings.

The Muscatine Study demonstrated that cardiovascular risk in adults is related to childhood LDL-cholesterol levels and childhood BMI in females.⁵³

The Cardiovascular Risk in Young Finns Study also showed that childhood LDL-cholesterol and BMI correlated with adult cardiovascular disease. The increased cardiovascular risk in adulthood was irrespective of adult risk factor status, indicating that permanent damage to the arterial wall may occur during childhood.

Postmortem studies in children showed that 50 percent of children age 2 to 15 year had fatty streaks in their coronary arteries, and 8 percent of these children had raised fibrous plaques in their coronary arteries. The Pathobiological Determinants of Atherosclerosis in Youth study found that 12 percent of adolescents age 15 to 19 year had raised lesions or advanced lesions of atherosclerosis in their right coronary arteries.⁵⁴ In both of these postmortem studies, the extent and severity of lesions correlated with BMI and lipoprotein levels.

Evaluation of the Obese Child for Metabolic Syndrome

A comprehensive medical evaluation must be done in all obese children and adolescents to screen for metabolic syndrome and other associated complications.

Approach to evaluation of an obese child, screening for complications that comprise the metabolic syndrome

and management and prevention of obesity have been discussed in the chapter on "obesity".

Management of Metabolic Syndrome

The main goal of therapy should be to achieve the objective of lifelong weight control.

The combination of dietary and physical activity interventions appears to provide the most beneficial improvements in components of the Met S. Comprehensive behavioral modification in overweight children reduces body weight, improves body composition, and positively modifies many of the components of the Met S within 3 months, and these effects are maintained at 1 year.⁵⁵ Similar effects have been observed for endothelial dysfunction, with the greatest improvements occurring when combined dietary and exercise interventions are used in overweight children.⁵⁶

Therefore, it is reasonable to suggest that early intervention aimed at managing obesity could reduce the risk of developing the MS. It is conceivable that even in the absence of weight loss, overweight and obese children may improve their cardiovascular risk profile by lifestyle changes and therapies targeted toward individual components of the syndrome.

At the present time, there is no specific treatment for this clustering of risk factors in children, other than reducing obesity, increasing physical activity, and treating the various components of the Met S such as hypertension or hyperlipidemia. Weight control improves glucose tolerance, with a recommended weight loss in adults of 10 percent to 15 percent. Exercise training improves insulin sensitivity and endothelial vascular function beyond the benefits of glycemic control and blood pressure reduction in adults and children.^{57,58} In small studies, metformin has been used effectively in adolescents with T2DM to decrease BMI and improve glucose tolerance.^{59,60}

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Disorders of Sexual Differentiation

Anurag Bajpai

INTRODUCTION

Disorders of sexual differentiation (DSD) are one of the most challenging conditions encountered by the pediatrician. The condition is relatively common with a prevalence of 1 in 300 to 5000 live births depending upon the criteria used. Genital ambiguity is not only a medical but also a social emergency. The first question that comes to the mind after the birth of the child invariably pertains to the gender of the newborn child. Inappropriate counseling in the immediate postnatal period therefore, leaves permanent scars in the minds of the parents. The management of an infant with DSD is thus as much an art as science. An understanding of physiology of sexual differentiation is mandatory for comprehensive management of the condition.

SEXUAL DIFFERENTIATION

The major steps in sexual differentiation include determination of genetic sex, development of gonads in accordance to genetic signals and subsequent differentiation of sexual characteristics. Deviation at any of these levels results in discordance of genetic, gonadal and phenotypic sex culminating in DSD.

Gonadal Development

The process of sexual differentiation begins with the development of bipotential gonad. Germ cells arise from the celomic epithelium of allantois, a part of hind gut and migrate to the urogenital ridge at four to six weeks of gestation. There they combine with somatic cells to give rise to the bi-potential gonad. Sex determining region of Y chromosome (SRY), a transcription factor in the short arm of Y chromosome is the chief regulator of sex determination. In boys, SRY gene induces testis determining genes like SOX9 while inhibiting anti testis gene DAX1 resulting in the development of gonad into testis. In the absence of

SRY, the gonads develop into ovaries under the influence of *DAX1* genes. The somatic cells give rise to Sertoli and Leydig cells in males in the presence of SRY gene and into granulosa and theca cells in females in its absence.

Development of Internal Genitalia

Sertoli cells secrete anti-mullerian hormone (AMH), which is responsible for the regression of mullerian duct in males. Testosterone secreted by Leydig cells stabilizes wolffian structures and induces their differentiation into epididymis, vas deferens, ejaculatory ducts, and the seminal vesicles. In the absence of AMH and testosterone mullerian ducts differentiate into fallopian tubes, uterus and the upper third of the vagina along with regression of the wolffian ducts.

Development of External Genitalia

Dihydrotestosterone (DHT), potent androgen produced by the action of enzyme 5 α reductase on testosterone, is the chief regulator of external genitalia development in males. DHT induces the development of corpus spongiosum, penile corpus cavernosa and scrotum. In girls, the labioscrotal swellings and urethral folds do not fuse in the absence of androgens and give rise to labia majora and minora, respectively. The genital tubercles form the clitoris while canalization of the vaginal plate creates the lower portion of the vagina.

CLASSIFICATION

DSD can result from disorders of gonadal development, gonadal function or hormone action. Traditionally a morphology based classification of DSD has been employed that divided these patients into virilization disorders, feminization disorders and true hermaphroditism. Besides being ambiguous, these terms have the disadvantage of negative connotations. There was thus a move towards

developing culturally acceptable classification of these disorders. This culminated in the consensus statement on disorders of sexual development with etiopathological classification of DSD (Table 1, Flow chart 1).

46 XX DISORDERS OF SEXUAL DIFFERENTIATION

These disorders are most commonly caused by fetal or maternal androgen excess; SRY insertion and 46 XX gonadal dysgenesis are rare cause of 46 XX DSD.

Androgen Excess

Intrauterine androgen excess could due to increased fetal androgen production or transplacental passage of androgens. *Congenital adrenal hyperplasia* is the most common

cause of DSD (Table 2). 21-hydroxylase deficiency, accounting for 95 percent of children with CAH, is characterized by glucocorticoid and mineralocorticoid deficiency on one hand and androgen excess on the other. Patients with the most severe form present in the neonatal period with life-threatening salt wasting. 11-hydroxylase deficiency, 3 β -hydroxysteroid dehydrogenase deficiency and *P450 oxidoreductase deficiency* are other forms of CAH presenting with 46 XX DSD. These disorders are diagnosed by the estimation of basal and ACTH stimulated 17OHP levels (21-hydroxylase deficiency) or 11 hydroxy DOC (11 hydroxylase deficiency). Mullerian structures are normally developed providing an opportunity for fertility. *Aromatase deficiency*, deficiency of enzyme converting testosterone to estrogen, results in androgen excess and maternal and fetal

Table 1: Classification of DSD ESPE-LWPES consensus statement 2005

Category	Previous names	Disorders
Sex chromosome DSD		45 XO Turner syndrome 46 XX/XY gonadal dysgenesis
Ovotesticular DSD 46 XY DSD	True hermaphroditism Male pseudohermaphroditism Feminization Undervaluation	Gonadal dysgenesis Steroidogenic defects AIS, 5 AR II deficiency
46 XX DSD	Female pseudohermaphroditism Variation	Androgen excess Aromatase deficiency SRY insertion

AIS- Androgen insensitivity syndrome, CAH- Congenital adrenal hyperplasia

Flow chart 1: Etiology based classification of DSD

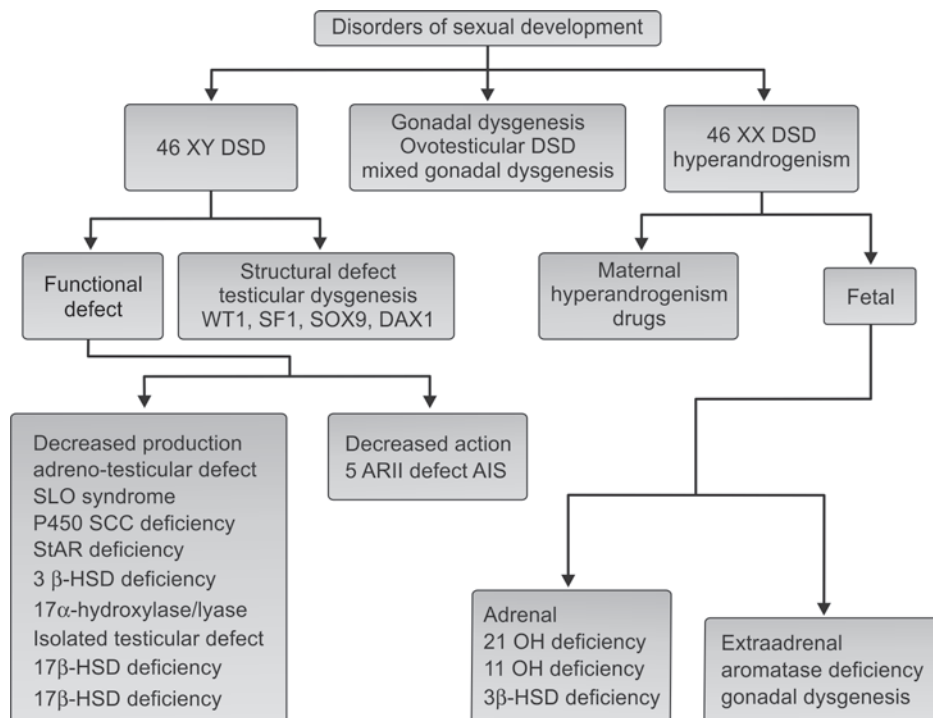


Table 2: Steroidogenic defects associated with DSD

Enzyme	Features	Diagnostic test
Associated with under civilization		
7 DHC dehydrogenate SLO syndrome	Polydactyly, microcephaly Sex reversal	High 7 dehydrocholesterol
P450 SCC deficiency	Adrenal insufficiency Complete sex reversal	Low DHEA, pregnenolone, 17OHP
StAR	Adrenal insufficiency Complete sex reversal	Low DHEA, pregnenolone, 17OHP
17 hydroxylase	Hypertension	Low 17OHP, high deoxycorticosterone
17β-HSD III	Complete sex reversal	Low testosterone, high androstenedione
5 α reductase	Virilization at puberty	High testosterone to DHT ratio
Associated with virilization		
21 hydroxylase	Adrenal insufficiency	High 17OHP
11β-hydroxylase	Hypertension	High deoxycortisol
Associated with both virilization and under virilization		
3β-HSD	Adrenal insufficiency	High 17 OH pregnenolone, DHEA
P450 Oxidoreductase deficiency	Adrenal insufficiency	High 17OHP and low androstenedione
SLO- Smith-Lemeli-Optiz syndrome, 17OHP-17-hydroxyprogesterone, DHEA- Dehydroepiandrosterone, DHT- Dihydrotestosterone		

virilization. *Transplacental* exposure to androgens is most commonly associated maternal medications or hyperandrogenism in mother due to luteoma of pregnancy or androgen producing tumor.

Gonadal Dysgenesis

46 XX males have a prevalence of 1 in 25000 males and usually present with infertility. The condition is most commonly associated with SRY insertion.

46 XY DISORDERS OF SEXUAL DIFFERENTIATION

These disorders are caused by abnormalities in testicular development, androgen production and androgen action. Unfortunately, the diagnosis of a substantial number of these individuals can not be identified despite extensive evaluation.

Gonadal Dysgenesis

Gonadal dysgenesis is the most common cause of 46 XY DSD. SRY deletion is however identified in only 15 to 20 percent of 46 XY females. Multisystem involvement is observed in gene defects affecting the WT1 (glomerulopathy and hemihypertrophy), SF1 (adrenal insufficiency) and SOX9 genes (skeletal dysplasia). There is a high risk of development of gonadoblastoma in 46 XY DSD mandating the need for gonadectomy. *Vanishing testis syndrome* is characterized by destruction of testis during an embryonic period. Genital ambiguity may occur if testes are destroyed between 8 to 14 weeks of gestation. These patients may be differentiated from those with cryptorchidism based on undetectable AMH levels.

Defective Androgen Synthesis

Fetal androgen deficiency could be related to LHCG receptor mutation, defective adrenal and testicular steroidogenesis (P450 side chain cleavage enzyme, StAR, P450 SCC, 17-hydroxylase/lyase and 3 β -hydroxysteroid dehydrogenase deficiency) or isolated testicular steroidogenic defect (17 β -hydroxysteroid dehydrogenase deficiency). Adrenal steroidogenic defects presents with salt wasting mandating early identification of the condition. 17 β -hydroxysteroid dehydrogenase deficiency is characterized by virilization during puberty due to extra gonadal conversion of androstenedione to testosterone.

Inefficient Androgen Action

Inefficient androgen action may be due to androgen resistance (androgen insensitivity syndrome) or impaired conversion of testosterone to dihydrotestosterone (5 alpha reductase deficiency) *Androgen insensitivity syndrome (AIS)* is an X-linked disorder characterized by resistance to androgen action. The disease forms a spectrum ranging from apparently normal phenotypic female (complete AIS) to genital ambiguity to a male with hypospadias (partial AIS). Complete AIS may present with inguinal hernia in young girls or primary amenorrhea in older girls. Absent or sparse pubic and axillary hairs are characteristic of the condition due to the pivotal role of androgens in their development. Genital ambiguity or infertility in maternal relatives may be present suggesting X-linked inheritance. Mullerian structures are absent as AMH action is normal. High testosterone and DHT levels are suggestive; the diagnosis is established by demonstration of decreased

enzyme activity on skin fibroblast. 5 Alpha reductase deficiency presents as a spectrum of disease ranging from a male with penoscrotal hypospadias to an under feminized female. Increased testosterone during puberty acts on the androgen receptor leading to virilization. Elevated testosterone in the setting of low DHT is diagnostic (Table 2).

Ovotesticular Disorders of Sexual Differentiation

The condition is characterized by the presence of both testicular and ovarian tissue in the same individual. The most common karyotype is 46 XX. Other combinations include 46 XX/XY, 46 XYY and others. The presentation is usually with genital ambiguity. Genital asymmetry is characteristic. Thus, mullerian structures may be present on the side of ovary while wolffian structures may develop along side the testis.

EVALUATION

Evaluation of a child with DSD begins from the labor room. Compassionate and patient counseling is mandatory to achieve parental confidence. 21-hydroxylase deficiency should be excluded to prevent life threatening consequences.

When to suspect?

Most children with DSD have obvious genital ambiguity. DSD should however also be considered in girls with clitoromegaly and posterior labioscrotal fusion, boys with penoscrotal hypospadias (suspected 46 XY DSD) and cryptorchidism (46 XX DSD with hyperandrogenism) and girls with bilateral inguinal masses or primary amenorrhea with normal pubertal development (complete AIS). Discordance between karyotype and phenotypic sex should prompt evaluation for DSD even if genital appearance is normal. It is also important to identify normal variants like prominent but not enlarged clitoris (Fig. 1), apparent small penis embedded in suprapubic fat, appearance of clitoromegaly in preterm girls and labial adhesion without clitoromegaly to avoid unnecessary work-up.

Clinical Evaluation

Family history of consanguinity and genital ambiguity should be recorded. Congenital adrenal hyperplasia is likely if there is a family history of sibling deaths and consanguinity. Exaggerated pubertal gynecomastia and DSD in maternal relatives (brothers and maternal uncle) is suggestive of androgen insensitivity syndrome. Gonads in patients with complete androgen insensitivity are often mistaken for inguinal hernia and operated upon. Intake of progestational drugs during first trimester and features of virilization in mother should be enquired. Failure to thrive, polyuria and lethargy suggest the possibility of 21-hydroxylase deficiency (Fig. 2).



Fig. 1: This two-week-old girl was referred for evaluation of clitoromegaly. She was diagnosed as prominent clitoris. On follow-up at the age of six months, the girl had normal genital appearance (For color version see plate 13)



Fig. 2: This three-week-old neonate presented with genital ambiguity. Examination revealed Prader stage IV genitalia, single urogenital opening, no palpable gonads and generalized hyperpigmentation. Investigations showed hyponatremia (sodium 112 mmol/L), hyperkalemia (potassium 6 mmol/L) and elevated 17OHP levels (200 nmol/L, 6000 ng/dl) confirming the diagnosis of salt wasting 21-hydroxylase deficiency (For color version see plate 13)

Virilization during puberty is suggestive of 5 α reductase and 17 β -hydroxysteroid dehydrogenase deficiency, while feminization during this period points to androgen insensitivity syndrome.

General Examination

General examination should be guided towards identification of pointers to disease (hyperpigmentation in steroidogenic defects, hemihypertrophy in WT1 defect, skeletal dysplasia in SOX 9 defect, polysyndactyly and mid facial narrowing in Smith-Lemeli-Optiz syndrome, Table 3). Pubic and axillary hairs are sparse in complete AIS while other secondary sexual characters are well developed.

Table 3: Pointers to diagnosis in DSD

<i>Pointer</i>	<i>Likely diagnosis</i>
Pigmentation	Congenital adrenal hyperplasia, SF1 defect
Genital asymmetry	Mixed gonadal dysgenesis, ovo testicular DSD
Skeletal dysplasia	SOX 9 defect
Polydactyly, microcephaly	Smith-Lemeli-Optiz syndrome
Hypertension	11 or 17 hydroxylase defect
Hemihypertrophy	WT1 mutation
Renal failure	Denys-Drash syndrome

This helps in differentiating this disorder from primary mullerian agenesis as a cause of primary amenorrhea in the presence of normal breast development. Examination of a neonate with genital ambiguity is incomplete without the examination of mother for features of hyperandrogenism in the form of hirsutism, acne and change in voice.

Genital Examination

Initial step in genital evaluation is directed towards identification of gonads. Bilaterally rounded structures below the inguinal canal are most commonly testis but may rarely be streak gonads or ovotestis. Unilateral gonads and genital asymmetry is suggestive of ovotesticular DSD. The labioscrotal region should be evaluated for the extent of fusion using the anogenital ratio (ratio of distance of anus from the posterior forchette to that anus to the base of phallus). Values above 0.5 are suggestive of virilization. The presence of mullerian structures can be confirmed by per rectal examination. The length and breadth of phallus should be measured. The number of openings in the urogenital region is helpful in deciding the presence of urogenital sinus. Asymmetrical labioscrotal region is suggestive of ovotesticular DSD (Fig. 3). The genitalia should be staged according to the classification proposed by Prader et al which divides these patients from grades I to V with grade I representing female with clitoromegaly and V male with cryptorchidism.

INVESTIGATIONS

Step-wise evaluation is required to establish the cause of DSD. Karyotype is the cornerstone of diagnosis of DSD but the results are usually available only after three to four weeks. Identification of Y and X material using FISH is helpful in rapid assessment. Ultrasound for mullerian structures and electrolytes should be done. Further evaluation is guided by the karyotype and presence/absence of palpable gonads and mullerian structures (Flow chart 2).

46 XX DSD with mullerian structures and no palpable gonad: The most important investigation is 17OHP with levels above 100 nmol/L (3000 ng/dl) suggesting the diagnosis of 21OHD while those between 20 to 100 nmol/L being



Fig. 3: This three-month-old boy presented with small phallic size (stretched penile length 1.5 cm), penoscrotal hypospadias and asymmetric genital appearance. Investigations were suggestive of gonadal dysgenesis (karyotype 46 XY/XO) (For color version see plate 13)

indicative of 11 β OHD. Urinary steroid profile is diagnostic in individuals with borderline 17OHP levels. Gonadal biopsy is indicated if 17OHP levels are normal to exclude gonadal dysgenesis.

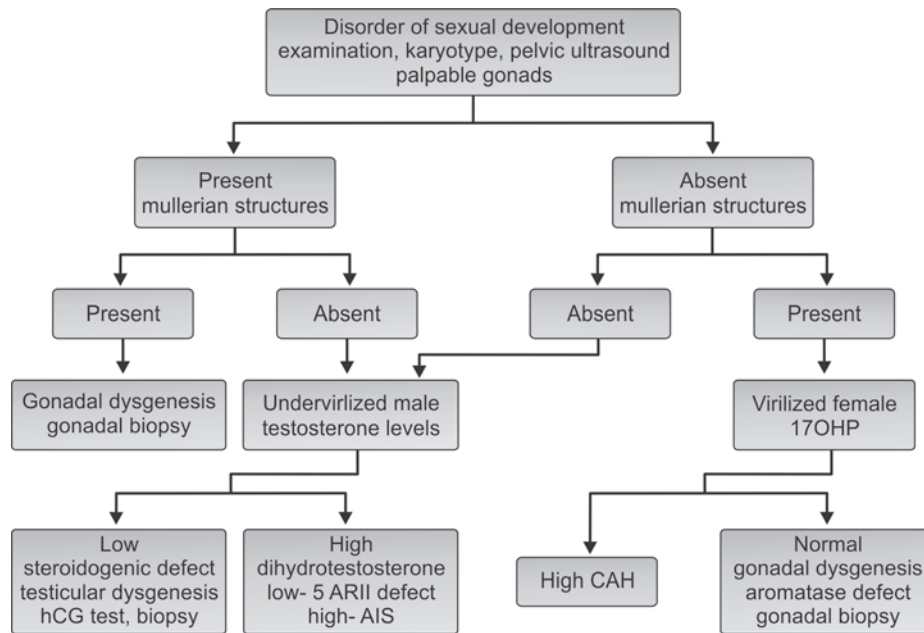
46 XY DSD with no mullerian structures with/without palpable gonads: Work-up is guided by serum testosterone levels. Low testosterone indicates gonadal dysgenesis or steroidogenic defects while high levels are suggestive of inefficient testosterone action. Antimullerian hormone should be done in children with low testosterone to detect sertoli cell functions. Abdominal ultrasound and urine protein should be measured to assess association with Denys Drash syndrome and WT1 gene defect. HCG stimulated testosterone to DHT ratio are indicated in individuals with elevated testosterone levels with elevated ratio suggesting 5 alpha reductase deficiency.

46 XX/XY karyotype with mullerian structures and palpable gonads: This constellation of findings indicates the diagnosis of ovotesticular DSD and mandates gonadal biopsy.

MANAGEMENT

Components of management include management of life-threatening conditions, initiation of specific treatment, parental education and decision about gender of rearing. The managing team should include pediatric endocrinologist, pediatric surgeon with expertise in DSD, social worker and geneticist. Salt wasting CAH should be identified and treated. Premature gender assignment and mention of gender specific words should be avoided. Parents should be reassured that the child should be able to achieve normal outcome. Parental education should include physiology of sexual development, disorders of

Flow chart 2: Approach to a child with DSD



DSD-Disorder of sexual development, StAR- Steroidogenic acute regulatory protein, OHD-Hydroxylase deficiency, β -HSD-Beta hydroxysteroid dehydrogenase, SLO-Smith-Lemeli-Optiz syndrome, 5 AR II-Alpha reductase II, AIS- Androgen insensitivity syndrome

sexual differentiation, presumptive diagnosis, and potentials for sexual function and fertility.

Decision Regarding Gender of Rearing

The considerations include ability to perform sexually, fertility prospects, feasibility of genital reconstruction and social considerations (Table 4). Fertility prospects are limited to individuals with 46 XX DSD who should be reared as females. Rarely male gender of rearing may be considered in extremely virilized 46 XX DSD individuals (Prader IV and V) with delayed diagnosis. 46 XY individuals with complete AIS should be reared as females. In all other 46 XY individuals with DSD male sex of rearing is preferred given the programming effects of intrauterine androgen exposure. A trial of androgens could be given in individuals with very small penile size with increase in size indicating male sex of rearing.

Medical Management

Steroid replacement should be done in children with congenital adrenal hyperplasia. Trial of testosterone should be given in patients with 46 XY DSD. Age and gender appropriate pubertal induction and hormone replacement therapy is required to achieve normal long-term outcome.

Table 4: Guidelines for gender of rearing for DSD

Disorder	Considerations	Gender of rearing
CAH with virilization	Fertility as female Usually gender appropriate	Female
Undervirilized male	Usually infertile Variable gender preference	Testosterone response Present—as male Absent—as female
Complete AIS	No prospect of fertility Risk of gonadoblastoma	Female Gonadectomy
Partial AIS	No fertility prospect May respond to androgens	Male
5 α Reductase defect	Virilization during puberty	Male

Surgical Procedures

Surgical reconstruction should be considered only when necessary. Mild clitoromegaly does not require surgery. Clitoroplasty should be done as soon as feasible. Vaginal size should be assessed during puberty to decide about

the need for vaginoplasty. Undervirilized boys should be taken up for hypospadias and cordee correction after a course of testosterone (25 mg intramuscularly monthly for three doses). Gonadectomy is indicated in individuals with Y line at risk for gonadoblastoma. Prophylactic gonadectomy should be performed at an early age in 46 XY gonadal dysgenesis. The risk of gonadoblastoma is low in complete AIS and the procedure may be deferred till puberty to allow for estrogenization.

There has been a tremendous increase in the understanding of the process of sexual differentiation. This has resulted in identification of specific etiology in a large number of cases. Careful clinical assessment and patient counseling however remains cornerstone to successful management of a child with DSD.

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Newborn Screening for Endocrinopathies

Sudha Rao Chandrashekhar

INTRODUCTION

Newborn screening (NBS) is a race against time. It is a diversified and ever expanding aspect of child health care. Screening for treatable congenital endocrinopathies is an important preventive health measure which not only prevents mortality and improves quality of life of the affected individual but also the social health. Effective newborn screening requires an adequate public health infrastructure integrated with the health care delivery system. In India, we still do not have a health mandate for universal newborn screening.

The universal screening of all newborns dates back to the history of phenylketonuria (PKU) a metabolic error with devastating effects. Horst Bicket in 1953, first described an effective dietetic therapy for PKU. It was soon realized that treatment prior to the onset of symptoms helped long-term outcome. In early 1960s Robert Guthrie and Ada Susi developed a biological test for phenylalanine and the now famous Guthrie card, and thus began the concept of universal newborn screening.¹ A major breakthrough occurred in the early 1970s when Dussault et al added a radioimmunoassay for thyroxine (T_4) and later thyrotropin (TSH) and screening for congenital hypothyroidism (CH) was added.² In 1977, serum 17 hydroxy progesterone (S-17OHP) was added to screen for congenital adrenal hyperplasia (CAH).² As more and more diseases were found to be treatable, if detected in presymptomatic stage, an ever expanding list of conditions were included which were diverse and rare. Introduction of tandem mass spectrometry (TMS), in 1980s, made it possible to test for a large number of metabolic disorders. Presently more than 30 diverse disorders can be screened in the various 206 NBS programs worldwide.

NEWBORN SCREENING GUIDELINES

Screening of newborns is not only about the test but also follow up, treatment and evaluation. There have been many guidelines issued regarding the same.^{3,4}

The principles of population-wide screening for disease formulated by Wilson and Jungner in 1968 (WHO guidelines) remain valid today. Any disease for which screening is performed must be a serious condition whose etiology and pathogenesis are understood, which becomes clinically manifest only after a latent or early symptomatic stage, which can be treated successfully with the available medical and organizational resources, and for which suitable testing methods exist.³

These fundamental pre-requisites are fulfilled by CH and CAH the two congenital endocrine disorders which are included in the NBS panel in many countries.

CONGENITAL HYPOTHYROIDISM

Congenital hypothyroidism (CH) is one of the most common preventable causes of mental retardation when treated early and adequately. The incidence of CH is one in 2,500 to 4,000 newborns in most populations, and is more common in India with an incidence of one in 1,100 to 1,200 newborns.⁵ CH can be transient or permanent. Permanent disorders are more common and are due either to structural defects like thyroid gland agenesis/dysgenesis or functional defect of thyroid hormonogenesis. Transient hypothyroidism is less common and occurs due to trans-placental transfer of maternal antibodies, drugs or states of iodine deficiency or excess. A small number of children have CH due to hypothalamo pituitary dysfunction.

Only 10 to 15 percent of hypothyroid neonates present with diagnostic clinical features and often the signs and symptoms are nonspecific.⁵ Many clinical scores have been developed to assist in diagnosis. The following clinical score used in the newborn period, is suggestive of hypothyroidism at a score of more than 5.

Studies have revealed that about 10 percent children are diagnosed clinically in the first month of life and 30 percent in the first 3 months. L-thyroxine replacement

Apgar score for hypothyroidism	Score
Open posterior fontanelle	1
Umbilical hernia	2
Typical edematous facies	2
Constipation	2
Female sex	1
Pallor, hypothermia	1
Macroglossia	1
Hypotonia	1
Prolonged jaundice	1
Rough, dry skin	1
Postmaturity	1
Large baby (weight >3.5 kg)	1

therapy if started before 3 months of age, the mean intelligence quotient (IQ) is 89 and drops to 70 when treated between 3 to 6 months of age and is as low as 54 if initiated therapy after 6 months of postnatal life.⁶ Hence, there is a high-risk of delayed diagnosis and treatment based on clinical examination alone.

In addition to the profound clinical benefit, it has been estimated that the cost of NBS for CH is much lower than the cost of diagnosing CH at an older age thus, having the highest cost benefit ratio. In India, we still do not have a health mandate necessitating CH screening of every newborn by law. Hence newborn screening for CH is done differently at different centers across the country.

Screening two Strategies for Congenital Hypothyroidism

There are two primary approaches to neonatal screening for hypothyroidism:

- *Primary measurement of T_4* , followed by determination of TSH if the T_4 value is low. This approach is being used in North America for screening.
- *Primary measurement of TSH*, followed with T_4 measurement if TSH levels are high. This method is followed in most parts of Canada, Europe and Japan.

Both approaches have their advantages and disadvantages and may miss out on a small number of cases.

A Third Approach is to Use Both T_4 and TSH at the First Screen

It is important to note that positive predictive value (PPV) depends on the prevalence of CH regardless of the choice of the screening strategy used.

T_4 Screening

Advantages

- Detects secondary and tertiary hypothyroidism
- Detects TBG deficiency
- Detects hyperthyroxinemia.

Disadvantages

- Can miss compensated hypothyroidism
- Can miss late onset hypothyroidism as occurs in Down syndrome
- Recall rate is higher 0.3 percent.

TSH Screening

Newer generation of TSH assay techniques have improved the sensitivity with lower recall rates and very less false negative test results.

Advantages

- Can detect compensated hypothyroidism
- Recall rate is 0.05 percent.

Disadvantages

- Can miss secondary or tertiary hypothyroidism
- Can miss TBG deficiency
- Hypothyroxinemia
- Hyperthyroidism may be missed
- Miss delayed TSH rise as seen in LBW or VLBW babies.

Combined T_4 and TSH screening is ideal with can be undertaken in combined filter paper with multiplex bio-marker system. This method is more expensive.

AGE AT SCREENING

The preferred time for blood sampling is after 72 hours of life to decrease the number false positives which occurs due to physiological TSH surge.

In infants discharged from the nursery before 48 hours of age, blood should be obtained before discharge. In instances such as home births or in the case of a critically ill or preterm neonate, blood should be obtained by 7 days of age, recognizing that samples obtained after 4 days of age are late for screening of congenital adrenal hyperplasia or metabolic disease. Some centers in USA use two time periods, the second collection being done at 2 weeks of age. Infants with CH detected at the later screening time tend to be of LBW or VLBW, with mild or delayed TSH elevations.⁴

In most NBS, for CH the false positive to case ratio is 2 to 3:1.⁵ False negative results may be found if screening is done in very sick neonates or after having received blood transfusion.

Screening Sample

Either cord blood sample or heel prick sample on/after day 3 of life is collected on filter paper and checked for T_4 , TSH or both. If cord blood is collected it should be from the placental end. The filter paper designed for newborn screening bears printed circles. Capillary blood samples are placed in these circular areas to fill and saturate them. Spotting blood over a previous blood spot, or

double spotting, causes invalid results, and these blood spots should not be used.^{1,4}

Rescreening

As babies develop hypothyroidism despite a normal initial screen, many centers retest all the infants with normal thyroid screen at 4 to 6 weeks of age. Many affected infants are (1:30,000) detected by the second screening.

The American Academy of Pediatrics (2006)⁴ recommends that thyroid functions should be repeated during infancy, when there is a clinical suspicion of hypothyroidism

- History of thyroid disease during pregnancy
- Family history of thyroid dysmorphogenesis
- Infants with Down syndrome (high prevalence of late onset CH).

Interpretation of Results (Table 1)

Correct interpretation of the test results is very important and the pediatrician must be familiar with the normal changes occurring in the thyroid hormones soon after birth.

During the first hours after birth, there is an abrupt increase in pituitary TSH secretion, reaching levels of 60 to 80 mIU/ml within 30 minutes after delivery. This rise in TSH stimulates a 2 to 6 fold increase in secretion of T_4 and T_3 from the thyroid gland, by 24 hours of life. The T_4 levels are in the 15 to 19 $\mu\text{g/dl}$ range and T_3 levels in the 300 ng/dl range. TSH levels decline slowly over the next 72 to 96 hours, to <8 mIU/L by 5 to 7 days.

Babies with cord blood TSH of more than 35 mIU/ml or day 3 TSH of more than 20 mIU/ml should be retested for T_3 , T_4 and TSH.

Criteria for the Diagnosis of Congenital Hypothyroidism

Serum T_4 level <10 mcg/dl

Serum TSH >20 mIU/ml

Preterm babies have higher TSH with lower T_4 and T_3 values as compared to term babies due to immaturity of the hypothalamo-pituitary-thyroid (H-P-T) axis which occurs

in the second half of gestation and the feedback system which is complete only by second month of postnatal life.

Abnormal screening results may fall into the following categories:

- Low T_4 and increased TSH
- Low T_4 and normal TSH
- Normal T_4 and elevated TSH
- Low T_4 with delayed rise in TSH
- Transient TSH elevation.

LOW T_4 AND INCREASED TSH

Elevated TSH with low levels of T_4 and T_3 are suggestive of primary congenital hypothyroidism which may be permanent or transient.

Permanent primary CH (PPCH)

This is due to thyroid dysgenesis (80-90%) or dysmorphogenesis (10-20%).

Transient CH

In transient CH, T_4 levels are low and TSH is elevated, but they normalize spontaneously. These individuals are usually started on thyroxine replacement, only to be found to have normal thyroid functions later in life. This picture could be due to transplacental passage of thyroid antibodies, maternal iodine deficiency, excess exposure to iodine by the mother during pregnancy (iodine crosses the placenta and suppresses the fetal thyroid gland) or infant during the postnatal period, antithyroid drugs and dietary goitrogens.

LOW T_4 AND NORMAL TSH

Congenital TBG Deficiency

An X linked condition diagnosed by low TBG levels and normal free T_4 values. They are clinically euthyroid and do not need to be treated.

Transient Hypothyroxinemia of the Newborn

This is more common in low birth weight infants with or without prematurity, especially if they are sick, but may be present in a small number of normal newborns. This may not cause significant ill effects on the development of the newborn, hence routine supplementation may not be required, but they need to be followed up closely.

Central (Secondary-Tertiary or Hypopituitary Hypothalamic Hypothyroidism)

This results in deleterious effects on development if untreated. More often central hypothyroidism is associated with deficiency of other pituitary hormones. Patients with hypoglycemia, prolonged jaundice, micropenis, hypogonadism, diabetes insipidus, and other midline deformities must be worked up to rule out hypopituitarism.

Table 1: Interpretation of Results

T_4	Free T_4	TSH	Disorder
L	L	H	Primary hypothyroid
N	N	H	Transient/compensated hypothyroid
L	N	N	TBG low
L	L	N	Central hypothyroid; delayed TSH rise; transient hypothyroidism
H	H	N	Hyperthyroxinemia
H	H	H	T_4 resistance

Normal T_4 and Elevated TSH

Compensated hypothyroidism is the term used for patients with normal levels of T_4 and T_3 and elevated TSH. Such patients are clinically asymptomatic as long as their T_4 levels remain normal. TSH levels may remain elevated for a prolonged period of time or may normalize spontaneously later in life or may decompensate to develop full blown hypothyroidism. It is impossible to predict the course of these patients and they need to be evaluated thoroughly by an experienced pediatric endocrinologist to determine the need for treatment.

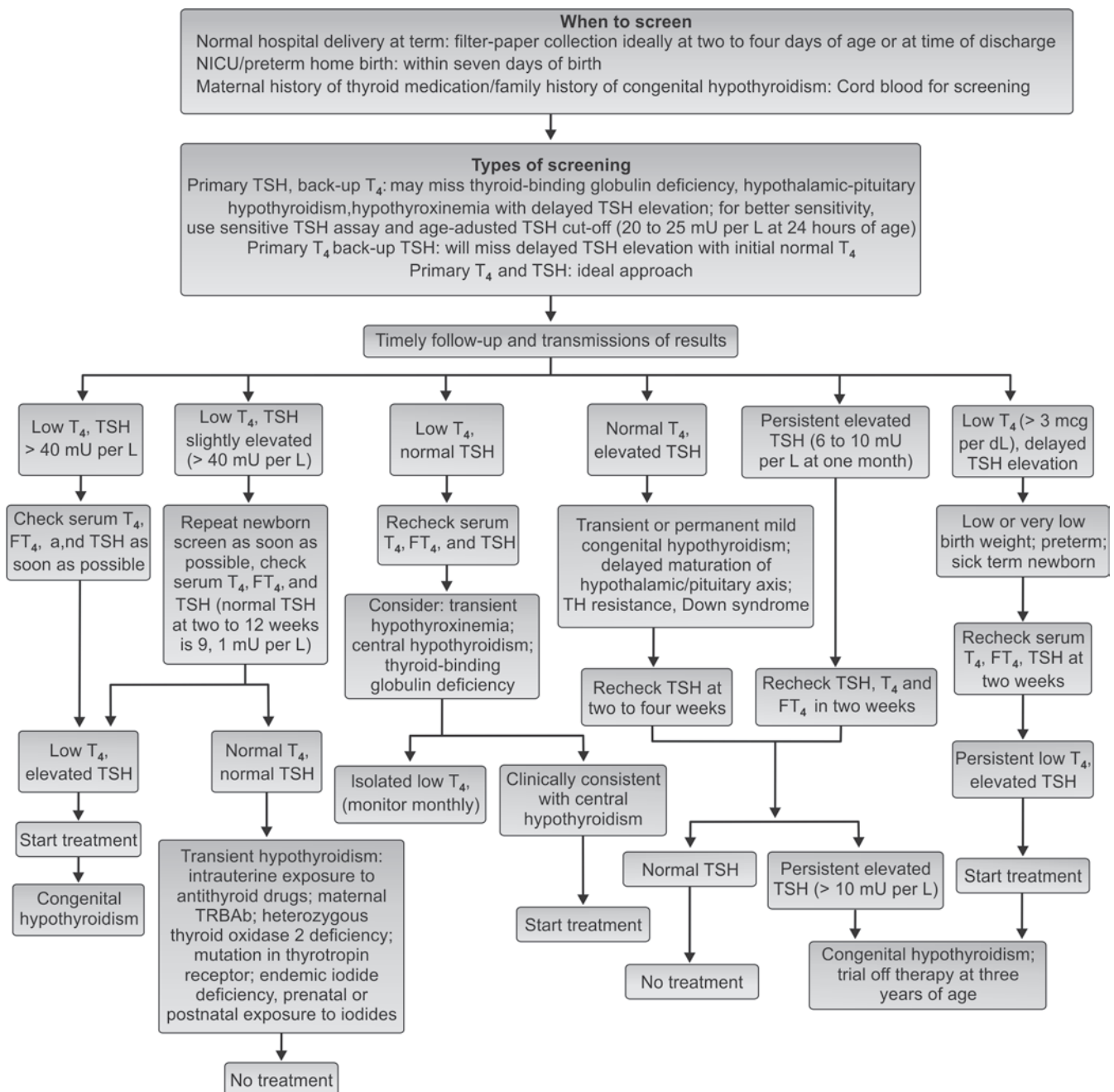
CLINICAL MANAGEMENT

As soon as the test results are available the infant must be seen by the pediatrician without delay. Pediatric endocrinologist referral is recommended (Flow chart 1).

Detailed history including prenatal thyroid status, maternal medications, maternal thyroid status and family history of thyroid disorders must be obtained. A thorough clinical examination must be done. Blood sample must be collected to recheck the thyroid status.

Thyroid ultrasonography, or iodine 123 (^{123}I) or sodium technetium 99m pertechnetate ($^{99\text{m}}\text{Tc}$) thyroid

Flow chart 1: Approach to newborn screening for congenital hypothyroidism



uptake scan may be undertaken to identify functional thyroid tissue.

Treatment need not be delayed to perform the scan. A thyroid scan can be performed within the first few days of treatment, because the elevated TSH found in patients with permanent CH rarely normalizes within this time period. A serum TSH measurement should be obtained at the time of the scan. If L-T4 therapy has caused the TSH concentration to be <30 mU/L, ultrasonography can still be performed. A scan can be performed after the child is 3 years of age, when TH treatment can be interrupted without danger to the developing central nervous system.⁴

TREATMENT

All infants with hypothyroidism should be rendered euthyroid as promptly as possible by thyroid hormone (L-T4) replacement therapy. An optimal TH therapy helps in optimal cognitive outcome. The goal of therapy is to normalize T4 within 2 weeks and TSH within 1 month. TSH levels should be maintained between 0.5 and 2.0 mU/L during the first 3 years of life.⁴⁻⁶

Administration of L-T4 is the treatment of choice. Although T3 is the more biologically active, most brain T3 is derived from local monodeiodination of T4, so T3 should not be used. The tablet should be crushed and suspended in a few milliliters of formula, breast milk, or water and taken empty stomach. Care should be taken to avoid concomitant administration of soy, fiber, or iron. Breastfeeding can continue.

The L-T4 dose should be adjusted according to the infant's clinical response and serum FT4 and TSH concentrations. During therapy, the serum total T4 or FT4 should and might be in the upper half of the reference range during the first 3 years of life with a low normal serum TSH.

FOLLOW-UP AND OUTCOME

Clinical evaluation of the infant by the practitioner should be conducted at frequent intervals during the first 3 years of age.

Infants need to undergo frequent laboratory and clinical evaluations of thyroid function, growth, and development to ensure optimal T4 dosage and adherence to their therapy regimen.⁵ Serum T4 and TSH measurements should be performed:

- At 2 and 4 weeks after the initiation of L-T4 treatment
- Every 1 to 2 months during the first 6 months of life
- Every 3 to 4 months between 6 months and 3 years
- Every 6 to 12 months until growth is completed; and at more frequent intervals when compliance is poor, abnormal values, or dose has been changed.
- FT4 and TSH measurements should be repeated 4 weeks after any change in dosage.

The outcome in infants with CH who are treated early is excellent. The prognosis for normal mental and neurologic performance is doubtful for those not detected early. Although physical recovery is good and stature is normal when replacement therapy is begun late 80 percent of infants given replacement therapy before 3 months of age have an IQ greater than 85, 77 percent of these infants show some signs of minimal brain damage, including impairment of arithmetic ability, speech, or fine motor coordination in later life^{7,8}. Long-term studies have shown that children with inadequate or delayed therapy also have cardiovascular morbidity in the form of left ventricular diastolic dysfunction, impaired exercise capacity, increased intima media thickness.

Key Point

- Universal screening of all newborns for CH is mandatory.
- The CH screening has a high benefit cost ratio.
- Either heel prick sample after 72 hours of life or cord blood can be used to perform TSH, T4 or both.
- Interpretation of results has to be done in relation to gestational age, age of life, presence of illness and established cut-offs.
- Early initiation of therapy to aim at normalizing T4 by 2 weeks and TSH by 4 weeks helps optimizing outcome.

CONGENITAL ADRENAL HYPERPLASIA

Congenital adrenal hyperplasia (CAH) is one of the common inborn errors of metabolism. It consists of a family of inherited disorders caused due to the loss or severely decreased activity of one of the five enzymes required for cortisol biosynthesis in the adrenal cortex (Flow chart 2). The various forms of CAH are due to mutations in the steroidogenic enzyme genes involved in cortisol biosynthesis. These enzymes are Desmolase, 3 β -hydroxysteroid dehydrogenase (*HSD3B2*), 21-hydroxylase (*CYP21*), 11- β -hydroxylase (*CYP11B1* and 2), 17 α -hydroxylase (*CYP17*).

Steroid 21-hydroxylase deficiency (21-OHD) is the most common enzymatic defect and accounts for more than 90 percent of cases of CAH. This autosomal recessive, monogenic, inherited defect of adrenal steroidogenic pathway results in inadequate corticosteroid production and excess of androgens. The phenotype is a manifestation of the degree of affection of glucocorticoid and mineralocorticoid synthesis and the presence of androgen excess. Thus, the phenotypic presentation can be one of salt wasters (SW) or nonsalt wasters (NSW) which can manifest as the severe classic (C) form or the milder nonclassic (NC) form depicting the residual enzyme activity.⁹ In females, androgen excess due to a severe defect causes prenatal virilization presenting as ambiguous genitalia at birth, the

this test, which remains the lowest of all screening conditions.^{13,14}

Compared with other newborn screening tests, the specificity of screening for CAH by immunoassay is low. Cross-reactivity of the specific antibody with other steroids, particularly pregnenolone, increases the number of false-positive results, which have been reported to be as high as 8 percent for different steroids and for several medications, greatly reducing discrimination between normal neonates and those with CAH.^{9,14} The 17OHP test shows a high false positive rate and it is difficult to interpret blood spot 17OHP levels because these values change with gestational age.

Despite the fact that CAH screening fulfills the WHO criteria for screening, it has not been universally included in NBS programs. This could be because, approximately 50 percent of CAH newborns are identified before the screening result is available (virilized CAH girls and patients with siblings with CAH) and the salt crisis may occur as early as 2 weeks of life. This emphasizes the need for rapid turnaround time (i.e. the result must be available before 10 days of life). Nevertheless, 50 percent of CAH infants (mainly boys) will get their diagnosis earlier by screening so that life-threatening salt crisis can be avoided. Furthermore, patients with milder variants of CAH may be detected early and precocious puberty and short stature can be avoided. In a recent review of CAH screening Brosnan et al concluded that published data clearly show that diagnosis can be made earlier by screening and serious salt crises can be avoided.¹⁵

It remains to be established that screening has a positive effect on mortality. Guidelines for neonatal CAH screening have recently been issued.

TREATMENT

Treatment is based on the principle of replacing normal glucocorticoid and mineralocorticoid needs, to suppress over secretion of adrenal androgens and to provide psychological support. Most female patients also need surgical reconstruction of the external genitalia.

The therapeutic dose of glucocorticoid and the type of glucocorticoid used are important. Ideally the replacement dose required is slightly higher than the endogenous cortisol secretion rate (6–8 mg/m²/day). In newly diagnosed patients and neonates the initial dose required might be much higher. Thus, the widely cited dose of 15 to 20 mg/m²/day of hydrocortisone is initiated but adjusted to the smallest dose that is able to normalize growth and physical maturation besides maintaining metabolic control. Oral hydrocortisone is the preferred glucocorticoid used and is given in three divided doses.

In SW patients' lifelong mineralocorticoid treatment is necessary, and additional salt supplements are needed to maintain plasma sodium concentration and renin in the

normal ranges during infancy. Salt supplementation (2–3 g/day) is given from birth to late childhood. Often, older children acquire a taste for salty food and do not require daily supplements of sodium chloride. Fludrocortisone in a dose of 0.1 to 0.2 mg/day as a single or two divided doses is recommended to maintain the salt balance. The doses may often be decreased after early infancy.¹⁰

Treatment of infants and children affected by the non-classic form of the disease is not recommended until and unless symptoms and signs of androgen excess become evident.

Adverse outcomes can occur in babies with false-positive results for CAH who receive treatment.

KEY POINTS

- Congenital adrenal hyperplasia (CAH) is a common inherited inborn error of metabolism leading to life-threatening crisis
- CAH screening helps identify infants at risk for the development of life-threatening adrenal crisis and to prevent the incorrect male sex assignment of affected female infants with ambiguous genitalia.
- Elevated levels of S-17-OHP adjusted for age, gestational age, weight, illness or stress helps diagnose CAH 21-OHD.
- Compared with other newborn screening tests, the specificity of screening for CAH by immunoassay is low and hence high false positive results.
- Additional steroid hormone assay and/or mutational studies besides CAH screening helps decrease the false positives.

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Polycystic Ovary Syndrome in Adolescence

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INTRODUCTION

Adolescence is a time of enormous physical and psychological change for young women. Polycystic ovary syndrome (PCOS) is the most common endocrine metabolic disorder affecting 11 to 26 percent of all adolescent girls¹ and has significant impact on quality of life and psychological morbidity. It has its origins in utero, seeds in adolescence, grows in reproductive phase and shadows the geriatrics. Polycystic ovary syndrome treatment not only needs multidisciplinary but multidimensional approach is required for the positive outcome.

Polycystic ovary syndrome is now a growing epidemic in developing countries because of changing life style and better nutrition patterns. The prevalence of overweight/obesity in urban children in Delhi has shown an increase from 16 percent in 2002 to about 24 percent in 2006.² The polycystic ovary syndrome (PCOS) in a teenager is characterized by irregular menstrual cycles, generally less than six menses per year, and by clinical or biochemical features of hyperandrogenism. More than 50 percent of PCOS patients have the metabolic syndrome

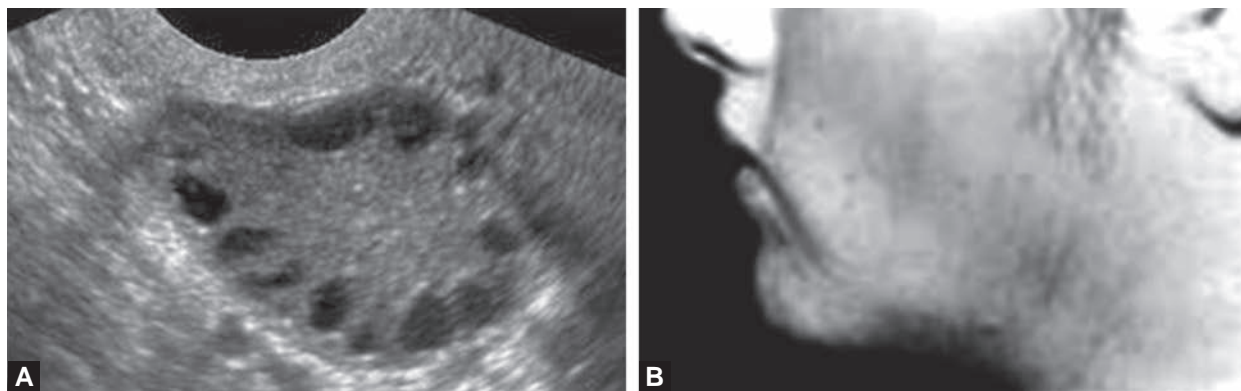
simultaneously, including obesity, insulin resistance and dyslipidemia.³

PCOS was first described by Stein and Leventhal in 1935, its definition has been readdressed several times. In 1990 the National Institutes of Health established new criteria, based on presence of hyperandrogenism and chronic anovulation with exclusion of other causes of hyperandrogenism such as congenital adrenal hyperplasia, hyperprolactinemia and androgen secreting neoplasms.⁴

The inclusion of ultrasound morphology of the ovaries as a further potential criteria to define PCOS was proposed by the Rotterdam Consensus Conference in 2003. This has suggested a broader definition for PCOS, with two of the three following criteria being diagnostic of this condition:

- Polycystic ovaries (either 12 or more peripheral follicles or increased ovarian volume (greater than 10 cm³) (Figs 1A and B)
- Oligo- or anovulation
- Clinical and/or biochemical signs of hyperandrogenism.

A raised luteinizing hormone/follicle-stimulating hormone ratio is no longer a diagnostic criteria.⁵



Figs 1A and B: Ultrasound showing: (A) Polycystic ovary and; (B) Hirsutism associated

More recently the Androgen Excess Society in 2006 (AES) has provided a contemporary version of the definition of PCOS and the fundamental role of hyperandrogenism has been pointed out. Both the NIH and the AES have declared hyperandrogenism as the core characteristic of PCOS.⁶ Considering the clinically evident association of hyperandrogenism with metabolic abnormalities, these two definitions fit better the metabolic phenotype of PCOS than Rotterdam Consensus. Conversely the Rotterdam criteria are less selective in metabolic terms, as they embrace a wider spectrum of women with less pronounced endocrine and metabolic abnormalities.⁷

A quarter of the world's adults are considered to have the metabolic syndrome and polycystic ovary is the female counterpart of it.⁸

ORIGINS

PCOS is a heterogeneous disorder which is believed to result from an interplay between genetic and epigenetic factors compounded by environmental triggers.

Genetics and PCOS

Earlier studies have suggested an autosomal dominant⁹ or X linked mode of inheritance,¹⁰ but the prevailing concept is that PCOS is a polygenic trait and female sub type of metabolic syndrome.¹¹ The rates of PCOS in mothers and sisters of patients with PCOS were 24% and 32%, respectively.¹²

The PCOS susceptibility genes/ loci so far can be divided into two broad groups: (1) Gene associated with sex hormone regulation and (2) genes associated with insulin resistance. Genes associated with sex hormones regulation are Fibrillin 3 (FBN3), Sex binding globulin (SHBG), X-linked androgen receptor (The AR Gene), Adrenal steroid 21-hydroxylase (CYP21), Dopamine D3 receptor and FSH-Beta. So far FBN3 gene shows strongest evidence for association to PCOS. Genes associated with insulin resistance are Caplin10 (CAPN10), Insulin-like growth factor 2 (IGF2), Insulin receptor substrates 1 and 2 (IRS1, IRS2).¹³

INSULIN RESISTANCE AND PCOS

Insulin receptor function is probably normal in women with PCOS. Abnormal serine phosphorylation is thought to be one of the major molecular pathways for insulin resistance in PCOS. If there is dysfunction of IRS-1, IRS-2 becomes active in presence of increased insulin concentration. This abnormal serine phosphorylation is involved in post-translational regulation of 17 to 20 lyase activity (CYP17). Thus, there may be a common etiology for both insulin resistance and hyperandrogenism. Polymorphic alleles of both IRS-1 and IRS-2, alone or in combination, may have functional impact on the insulin-resistant component of PCOS.¹⁴

HYPERANDROGENISM AND IN UTERO FETAL PROGRAMMING

The role of androgen exposure early in life adds to complexity to the heritability of PCOS. Androgen excess or increased GnRH release can produce the reproductive phenotype of PCOS.

Fetal programming of PCOS by androgen excess may be related to the phenomenon of sexually dimorphic programming of tissues leading toward more masculine phenotype with regard to reproductive, neuroendocrine and metabolic traits. PCOS is driven by an inherent hyperandrogenic activity of ovarian theca cells and male type pattern of pulsatile GnRH secretion which is due to fetal exposure to high androgens in utero.

Normally, the female fetus is protected in utero from maternal androgens by increased placental sex hormone binding globulin (SHBG) and placental Aromatase. SHBG binds the androgens and the placental aromatase converts them into estrogens. Excess maternal glucocorticoids (active cortisol) are converted by fetoplacental 11 β -hydroxysteroid dehydrogenase type 2, to inactive cortisone. Theoretically, therefore, exposure of female fetus to gestational hyperandrogenism may occur due to increased maternal or endogenous fetal androgen production and decreased placental SHBG or aromatase activity.

Pregnant PCOS women were found to have higher concentration of androgens, low SHBG and hyperinsulinemia, than normal pregnant women thus potentially exposing their daughters to elevated androgen levels in utero.¹⁵ Maternal hyperinsulinemia may induce excessive placental HCG production leading to fetal ovarian hyperplasia and hyperandrogenism.¹⁶ Maternal PCOS may lead to decreased nutrient supply to placenta and fetus by altering energy homeostasis and resulting growth retardation further leading to hyperinsulinemia and PCOS. These girls follow a path through postnatal catch up weight gain, amplified adrenarche, premature pubarche and ovarian hyperandrogenism in adolescence. In girls with premature pubarche persisting hyperandrogenism gets exacerbated by onset of gonadarche and PCOS during adolescence.¹⁷

Epigenetic abnormality hypothesis suggested by Zhongxiang Li and Hefeng Huang has established a novel mechanism for PCOS development and inheritance. It states that in utero hyperandrogenism exposure may disturb the epigenetic reprogramming in fetal reproductive tissue, thereby resulting in postnatal PCOS phenotype in women of reproductive age. Meanwhile, the incomplete erasure of such epigenetic abnormality in germ cells after fertilization may promote the transgenerational inheritance of PCOS.¹⁸

OBESITY—DIETARY FACTORS AND PCOS

Although insulin resistance is considered an inherent feature of PCOS, obesity is recognized as a significant aggravating factor associated in 30 to 70 percent.¹⁹ It is recognised that insulin resistance is less frequent in lean PCOS compared to their obese counterparts.²⁰

Visceral adiposity seems to be more important in lean PCOS than obesity *per se*. Interestingly, Lord et al have reported visceral adiposity is the most significant variable correlating with insulin resistance and metabolic dysfunction in PCOS.²¹ In view of the influential role of total and central obesity, diet emerges as an important factor in the perpetuation of insulin resistance in PCOS. Chronic over-nutrition is a widely acknowledged triggering factor of insulin resistance, particularly in susceptible individuals, like women with PCOS.²²

Currently, the quality of food and specifically, diet enriched to advanced glycated end products (AGEs) are incriminated in metabolic abnormalities via the increasing oxidative stress.²³ Increased AGEs levels positively correlate with serum androgen levels and with indices of insulin resistance in PCOS women.²⁴

Chronic exposure to high glycemic index food and free fatty acids cause beta cell dysfunction, increase TNF alpha and resistin and decrease insulin sensitizing agent, adiponectin further increasing insulin resistance.²⁵

PATHOPHYSIOLOGY OF PCOS

Insulin acts on classic insulin sensitive tissues like adipose tissue and skeletal muscle as well as nonclassic target tissue like ovary and endothelium. Insulin binding to its receptor cause phosphorylation of insulin receptor substrates (IRS) resulting in activation of mitogen activated kinase and phosphoinositide3-kinase (PI3K) signalling pathways. The multiplicity of signalling pathways downstream explains the pathway specific defects of insulin action in insulin resistance states.²⁶ A key feature of insulin resistance is that it is characterised by specific impairment in PI3K-dependent signalling pathways.²⁷

Autocrine, paracrine and hormonal factors modulate the coordination of theca and granulosa cell function in terms of androgen synthesis. Androgens and estrogens are negative modulators of LH effects whereas IGFs play a positive modulator role. Insulin also augments LH stimulated androgen production either via its own receptors or via IGF-1 receptors. In PCOS, the ovarian theca cells are increased in number, and they have increased steroidogenic capacity caused by increased transcription and mRNA stability of steroidogenic enzymes. Cystic follicles have high androstenedione to estradiol activity in contrast to healthy follicle where estradiol activity is higher in comparison to androstenedione. Also the granulosa cell fail to

increase the expression of aromatase leading to decreased estrogen secretion and prematurely express LH receptors and cholesterol side chain cleavage enzyme activity leading to over responsiveness to LH.

The ovary is considered as the main source of androgens in women with PCOS, although excess adrenal androgen production may occur. The enzymes used in formation of androstenedione from cholesterol is same in both, but under control of LH in ovary and ACTH in adrenal.²⁸

Insulin resistance increases endothelin-1, the most potent endothelial vasoconstrictor and marker of endothelial dysfunction, this explains the accelerated atherosclerosis in PCOS.²⁹

PCOS—A Chronic Inflammatory State

Several studies have unveiled the bidirectional relationship of insulin resistance with wide array of inflammatory/oxidative markers, including C-reactive protein, reactive oxygen species (ROS), Interleukin-18, protein carbonyls, soluble CD36, oxidised LDL and AGEs.³⁰

Beyond a simple association, there are data to support a casual, reciprocal relationship between inflammation/oxidative stress and insulin resistance in PCOS. The migration of macrophages in adipose tissue is a major proinflammatory process that is accentuated in presence of visceral obesity, which is present even in lean PCOS. Visceral adiposity, independent of obesity has been incriminated as a major trigger of insulin resistance and low grade chronic inflammation.³¹

Adiponectin, the most abundant adipokine mainly secreted from visceral adipocytes cells, has been found decreased in lean PCOS and obese women with PCOS, as compared with BMI matched controls. This aberration is caused by hyperinsulinemia. Adiponectin correlates negatively with progression of atherosclerosis. Other adipokines like resistin, retinol binding protein (RBP)-4, Visfatin are also implicated in PCOS.³² Visfatin is increased in both obese and lean PCOS and role of RBP-4 is unclear in human.³³

ENDOCRINE DISRUPTING CHEMICALS AND PCOS

Environmental endocrine disrupting chemicals also might disrupt ovarian and metabolic function, causing PCOS-like abnormalities. Bisphenol A (BPA), a widely used estrogenic industrial plasticizer, is one such endocrine disrupting chemical that is detectable in most individuals with PCOS.³⁴

Multivariate analysis confirmed that the risk factors associated with PCOS were disposable plastic cup for drinking, cooking oil fume and indoor decoration (P value: 0.011, 0.012, 0.026, 0.011, OR value: 2.800, 3.027, 2.370, 2.478).³⁵

CLINICAL PRESENTATION

PCOS symptoms usually develop gradually and start showing in early teens, when it is important for mother and pediatricians to be aware and watchful so that timely intervention can prevent progression of symptoms and long-term morbidity.

- Weight gain and upper body obesity (apple shaped) is more significant than weight gain near hips (pear-shaped). This visceral fat is linked to high androgen levels and more adverse metabolic risk profile than subcutaneous fat. Measurement of waist circumference is thought to correlate more closely with obesity risk than BMI.³⁶

One-third of PCOS are at high risk for development of metabolic syndrome.³⁷

According to the American Heart Association and the National Heart, Lung, and Blood Institute, metabolic syndrome is present if three or more of the following signs:

- Blood pressure equal to or higher than 130/85 mm Hg
- Fasting blood sugar (glucose) equal to or higher than 100 mg/dl
- Large waist circumference (length around the waist):
- Men—40 inches or more, Women—35 inches or more
- Low HDL cholesterol:
- Men—under 40 mg/dl, Women—under 50 mg/dl
- Triglycerides equal to or higher than 150 mg/dl

Hyperandrogenism

PCOS girls may present as hirsutism, acne, male pattern baldness, hair thinning, oily skin and acanthosis nigricans. Exaggerated signs of hyperandrogenism or virilisation suggest the work-up to rule out androgen producing tumor.

Hirsutism

The original method of Ferriman-Gallwey used 11 body areas to assess hair growth, but was decreased to 9 body areas in the modified method:

- Upper lip
- Chin
- Chest
- Upper back
- Lower back
- Upper abdomen
- Lower abdomen
- Upper arms
- Forearms (deleted in the modified method)
- Thighs
- Legs (deleted in the modified method)

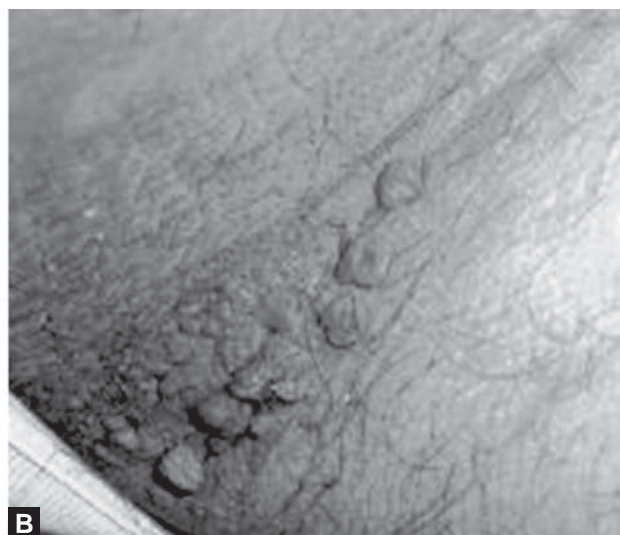
In the modified method, hair growth is rated from 0 (no growth of terminal hair) to 4 (extensive hair growth) in each of the nine locations. A patient's score may therefore range from a minimum score of 0 to a maximum score of 36. A score of 8 or higher is regarded as indicative of androgen excess. Another proposed predictor of hirsutism is that terminal hair on the chin or the lower abdomen (Ferriman-Gallwey score ≥ 2) is nearly 100 percent sensitive and 27 percent specific at predicting total-body hirsutism.³⁸

Acanthosis nigricans is characterized by symmetrical, hyperpigmented, velvety plaques that may occur in almost any location but most commonly appear on the intertriginous areas of the axilla, groin, and posterior neck. The posterior neck is the most commonly affected site in children. Acrochordons (skin tags) are often found in and around the affected areas (Figs 2A and B).

Acanthosis nigricans is found in 5 percent of women with PCOS, is the hallmark if insulin resistance. A common mnemonic acronym for the clinical association of hyperandrogenism, insulin resistance, and acanthosis nigricans is the HAIR-AN syndrome.

Staging acanthosis (neck severity) is as follows:³⁹

- Absent (0): Not detectable on close inspection
- Present (1): Clearly present on close visual inspection, not visible to the casual observer; extent not measurable



Figs 2A and B: (A) Acanthosis nigricans and; (B) Acrochordons (For color version see plate 14)

- Mild (2): Limited to the base of the skull, usually does not extend to the lateral margins of the neck
- Moderate (3): Extends to lateral margins of neck, but not visible anteriorly
- Severe (4): Visible anteriorly
- Severe (5): Circumferential

Premature Adrenarche

It may be present in some population of adolescent girls. In 30 percent of peripubertal daughters of mothers with PCOS may be exaggerated adrenarche accompanied by higher serum DHEAS and insulin concentrations than age-matched and BMI-matched girls born to women without PCOS may represent a precursor to polycystic ovarian syndrome.⁴⁰ Both hirsutism and obesity may be present in premenarchal adolescent girls with polycystic ovarian syndrome.

Menstrual Abnormalities

The spectrum of irregular menses, estimated to be present in about 66 percent of adolescents with PCOS,⁴¹ includes primary or secondary amenorrhea, oligomenorrhea, anovulatory regular menses, and dysfunctional uterine bleeding with oligomenorrhea or menorrhagia. Menstrual disturbance is due to impaired oocyte developmental competence or anovulation and results in subfertility/infertility and increased miscarriages. In young girls precocious puberty may be the first manifestation.⁴²

Breathing Problems

While sleeping (obstructive sleep apnea). This is linked to both obesity and insulin resistance.

Psychological Morbidity

Obesity, hirsutism and acne may lead to poor self image and psychological difficulties. Poor body image can lead to depression and suicidal tendencies. Women with PCOS have an increased prevalence of mood disorders, including depression (26–40%), anxiety (11.6%) and binge-eating (23.3%).⁴³

- High blood pressure
- Prediabetes or in some cases, diabetes
- Asymptomatic PCOS (usually lean).

Important Assessment from Pediatrician Perspective⁴²

- History of PCOS in mother
- Postnatal catch up growth as assessed by available growth charts
- Early assessment of obesity by BMI, waist hip ratio (WHR)
- Watch out for early adrenarche, menarche and puberarche
- Signs of hyperandrogenism as acne, hirsutism, acanthosis nigricans
- Eating habits and physical activity
- Television and computer watching hours

DIAGNOSTIC EVALUATION

Girls with possible PCOS and other androgen excess disorders should undergo a relatively straightforward evaluation. Comprehensive assessment should be done according to PCOS performa which includes physical evaluation, lab investigations and follow-up schedule. Principal disorders to exclude are steroid 21-hydroxylase (*CYP21A2*) deficient nonclassic adrenal hyperplasia (NCAH), hyperprolactinemia and thyroid dysfunction.⁴⁴

- Serum (blood) levels of androgens including androstenedione and testosterone may be elevated. Dehydroepiandrosterone sulfate levels above 700 mcg/dl are highly suggestive of adrenal dysfunction because DHEA-S is made exclusively by the adrenal glands. The free testosterone level is thought to be the best measure, with ~60 percent of PCOS patients demonstrating supranormal levels. The Free androgen index of the ratio of testosterone to sex hormone-binding globulin (SHBG) is high, is meant to be a predictor of free testosterone, but is a poor parameter for this and is no better than testosterone alone as a marker for PCOS, possibly because FAI is correlated with the degree of obesity (Table 1).
- Hyperprolactinemia, mild and present in ~20 percent of women with PCOS.
- Thyroid dysfunction (hypothyroidism) by TSH levels.
- LH hypersecretion—elevated LH levels and an LH:FSH ratio >2:1 (or 3:1) initially thought to be essential for a diagnosis of the syndrome. However, single hormone measurements are now thought to be unreliable. LH sampling every 20 minutes over 6 hours gives a variability of 38 percent in the follicular phase and 92 percent in the luteal phase. LH hypersecretion is found in 40 percent of women with PCOS and is associated with a reduced chance of conception and increased risk of miscarriage. Additional tests for assessing comorbidity:
- Fasting biochemical screen and lipid profile
- 2-hour oral glucose tolerance test (GTT) in patients with risk factors (obesity, family history, history of gestational diabetes) may indicate impaired glucose tolerance (insulin resistance) in 15 to 30 percent of women with PCOS. Frank diabetes can be seen in 65 to 68 percent of women with this condition. Insulin resistance can be observed in both normal weight and overweight patients.
- Fasting insulin level or GTT with insulin levels (also called IGT). Elevated insulin levels have been helpful to predict response to medication and may indicate as who will need higher dosages of metformin or the use of a second medication to significantly lower insulin levels. Elevated blood sugar and insulin values do not predict who responds to an insulin-lowering medication, low-glycemic diet, and exercise. A hypoglycemic response in which the two-hour insulin level is higher and the blood sugar lower than fasting is consistent

Table 1: Laboratory tests for the evaluation of patients with suspected PCOS⁴⁴

<i>Laboratory test</i>	<i>Usefulness</i>
TSH	To rule out thyroid dysfunction and hyperprolactinemia if present, reassess for PCOS once resolved
Prolactin	
17-OHP (measured in the follicular phase)	If 17-OHP >6 nmol/l, perform an ACTH stimulation test. An ACTH-stimulated 17-OHP >10 nmol/l is diagnosis of 21-OH deficient NCAH*
Total and free testosterone	To assess for hyperandrogenemia if no clinical evidence of hyperandrogenism (that is, hirsutism) is present. Total testosterone >7 nmol/l or DHEAS >16 µmol/l should prompt evaluation for an androgen-secreting neoplasm; however, clinical presentation is more useful than androgen levels for predicting the presence of an androgen-secreting neoplasm
Luteal phase (day 22-24) progesterone	To assess ovulation in patients with hirsutism who 'report regular menses'
1 mg DST or 24 h urinary free cortisol	To screen for Cushing syndrome if clinical stigmata are present
*The ACTH stimulation test is performed with 250 mg of corticotropin, followed by measurement of 17-hydroxyprogesterone 60 min later.	
Abbreviations: ACTH, adrenocorticotrophic hormone; DHEAS, dehydroepiandrosterone sulfate; DST, dexamethasone suppression test; 21-OH, 21-hydroxylase; 17-OHP, 17-hydroxyprogesterone; NCAH, nonclassic adrenal hyperplasia; PCOS, polycystic ovary syndrome.	

with insulin resistance. A mathematical derivation known as the HOMAI, calculated from the fasting values in glucose and insulin concentrations, allows a direct and moderately accurate measure of insulin sensitivity (glucose-level x insulin-level/22.5).

LONG-TERM SEQUEL OF PCOS

PCOS has long-term reproductive morbidity, metabolic morbidity and predisposition to cancers:

- Increased incidence of multiple pregnancy following ovulation induction with perinatal mortality and morbidity
- Increased incidence of gestational diabetes (13% vs 5-10% in controls). Women should be screened before 20 weeks gestation and referred if abnormalities are detected.
- Increased incidence of pregnancy induced hypertension independent of obesity and gestational diabetes
- Sleep apnea is an independent cardiovascular risk factor and has been found to be more common in PCOS even after controlling for BMI. The strongest predictors for sleep apnea were fasting plasma insulin levels and glucose-to-insulin ratios. Sleep apnea is an independent risk factor for cardiovascular disease.
- Cardiovascular disease—mortality is not significantly increased although women with PCOS have abnormal lipid profiles. Offer measurement of fasting lipids as early detection of abnormal levels might prompt dietary change and exercise. Hypertension should be treated but conventional methods for estimating risk of cardiovascular disease have not been validated in women with PCOS.

- Increased risk of adult onset diabetes mellitus ~ 40 per cent risk of NIDDM by the age of 40 years with truncal obesity and a strong family history of NIDDM being additional risk factors. Women should be offered regular screening in the form of fasting glucose or GTT if additional risk factors (BMI > 30 or strong family Hx)⁴⁵
- Increased risk of endometrial cancer (5-fold), especially if interval between menses is greater than 3 months
- Risk of ovarian cancer in women with PCOS remains controversial but no additional surveillance is needed. Risk of breast cancer is not increased.

TREATMENT APPROACH

Treatment in PCOS should be individualized to treat prevailing signs and symptoms and is rarely monotherapeutic. Indications for treating PCOS include correcting metabolic dysfunction (with increased risks of T2DM and CVD), dermatological manifestations (hirsutism, acne or alopecia), anovulatory uterine bleeding (with increased risks of endometrial hyperplasia or carcinoma and anemia and/or anovulatory infertility, maintaining psychological health.

Main goal is to screen and diagnose early and prevent progression of symptoms to reduce its long-term consequences. It includes multidimensional approach and long-term follow-up.

Principles of treatment: Primary prevention is the best and starts at the hands of pediatrician.

- Life style management for life style disease
- Avoid stress, smoking and alcohol consumption
- Reduce and maintain weight.
- Modify diet.
- Regular exercise.

Secondary Prevention

- Metformin
- Weight reducing drugs
- Ovulation induction drugs

Tertiary Prevention

- Laparoscopy ovarian drilling
- Bariatric Surgery

The clinical management of young women with PCOS should be focused on her individual problems. Obesity worsens both symptomatology and the endocrine profile and so obese girls (BMI >25 kg/m²) should be encouraged to lose weight, and they should also have a test of fasting glucose tolerance (e.g. 2h GTT) and fasting insulin to assess the glucose:insulin ratio.

Encourage low glycemic diet (GI), as it improves insulin resistance and many of its metabolic consequences while high GI diet has been shown to worsen postprandial resistance.⁴⁶ A recent meta-analysis published in the Cochrane Database of Systemic Reviews supports the use of a low GI diet in weight management as 6 RCT have shown significant reductions in body mass, fat mass, body mass index, total mass index, total cholesterol and LDL cholesterol with it.⁴⁷ Diets higher in monosaturated and unsaturated fats are associated with reduced risk of cardiovascular diseases and type 2 diabetes.⁴⁸

Practical Dietary Advice for Girls with PCOS

- Choose oat-based cereals such as porridge or muesli
- Choose wholegrain breads in place of white/brown varieties
- Aim to fill half of plate at lunch/dinner with variety of vegetables or salad vegetables
- Include low GI grains in meals including barley, cracked wheat, quinoa and buck wheat.
- Snack on fresh fruit, raw nuts, yogurt and whole grain crackers
- Replace butter on bread with avocado, tahini or pure nut spreads
- Use olive or canola oil in cooking and olive oil or flax-seed oil in dressings
- Replace salt in cooking with fresh or dried herbs and spices.

Role of Exercise

In a randomized control trial investigating the effect of a 3 month exercise program in young woman with PCOS, a significant improvement in insulin sensitivity was observed in those who undertook three 30 min exercise sessions a week compared to sedentary controls.⁴⁹

Exercise Recommendations Based on American Diabetes Association (ADA):⁵⁰

- At least 150 min per week of moderate to high intensity exercise.
- Distribute exercise over 3 days with no more than two consecutive days without activity.
- Reduce sedentary activities (watching television and playing computer games) as much as possible.

HIRSUTISM IN POLYCYSTIC OVARY SYNDROME

A primary treatment for hirsutism in PCOS has not been established, and treatment is often palliative rather than curative. Agents that have been used include oral contraceptives, antiandrogen drugs (spironolactone, flutamide, finasteride), insulin-sensitizing agents, and eflornithine. The FDA has labeled only topical eflornithine hydrochloride cream for the treatment of hirsutism; additional benefits or risks for the use of this agent in women with PCOS are unknown.

Optimally treatment combines cosmetic and medical therapies. Medical therapy is aimed at slowing the rate of hair growth and is effective only after 6 to 9 months of therapy due to time of hair growth cycle whilst cosmetic treatments attempt to remove existing hair immediately. Cosmetic therapy may be waxing, bleach, or epilation as temporary measures or electrolysis and laser as permanent. Laser therapy works best in women with dark hair on fair skin, but is expensive and not permanent (despite claims to the contrary). Electrolysis is the only permanent method of hair removal and should be delayed until androgens are effectively suppressed.

Hyperandrogenism can be treated by a combination of an estrogen and CPA 50 mg. Estrogens lower circulating androgens by a combination of a slight inhibition of gonadotrophin secretion and gonadotrophin-sensitive ovarian steroid production and by an increase in hepatic production of sex hormone-binding globulin resulting in lower free testosterone, the preparation Dianette[®] (Schering, UK) contains ethinylestradiol in combination with CPA, although at a lower dose (2 mg). CPA acts as a competitive inhibitor at the androgen receptor. CPA can rarely cause liver damage and liver function should be checked after 6 months and then annually.

Spironolactone, a potassium sparing diuretic, has antiandrogenic properties and is useful in women for whom the oral contraceptive pill is contraindicated (e.g. because of hypertension). Spironolactone, at a dose of 50 ± 200 mg daily, may result in erratic menstrual bleeding and should be combined with reliable contraception.⁵¹

A new COCP, Yasmin[®] (Schering UK), contains the progestogen, drospirenone, which is a derivative of

spironolactone, with potential antiandrogenic properties and benefits for women with PCOS and those with anovulatory DUB.⁵²

Metformin Therapy for PCOS

Insulin resistance is often the first step in a progression to DM and CAD. Metformin has been the mainstay of treatment for IR and IGT in PCOS women over the past decade.

Mechanism of Action

- Metformin is a biguanide that acts principally on the liver to inhibit hepatic gluconeogenesis.
- It inhibits acetyl-CoA carboxylase activity and suppresses fatty acid production.
- Acts on skeletal muscle to inhibit lipid production and acts peripherally on adipose tissue to stimulate glucose transport and uptake.
- Reduces insulin levels and promotes improved insulin receptor activity.
- Has direct and indirect effects on the ovary with respect to insulin action and steroidogenic enzymatic activity.
- In the endothelium, metformin seems to improve nitric oxide vasodilatory effects.⁵³
- It does not cause hypoglycaemia.
- The most important side effect is gastrointestinal side effects. Sometimes other side effects are abdominal discomfort, diarrhoea, nausea, vomiting and decreased appetite, so it is started in incremental manner depending on tolerance.
- The most serious side effect is lactic acidosis, which is rare and almost always occurs in populations at high risk with renal insufficiency, liver disease and congestive heart failure.
- Early metformin therapy was found to prevent or delay the development of hirsutism, androgen excess, oligomenorrhea, and PCOS more effectively than late metformin. The time window of late childhood and early puberty may be more critical for the development and thus for the prevention, of adolescent PCOS than the first years beyond menarche.⁵⁴
- Metformin decreases androgen level significantly in both lean and obese individuals and restores ovulation and fertility.⁵⁵

Ovulation induction drugs, laparoscopic ovarian drilling are beyond scope of this chapter and not the treatment for adolescents.

CONCLUSION

PCOS is a not only a life style disease but life time disease which threatens the womanhood on reproductive, metabolic and oncology fronts. Proactive measures to screen and treat are needed in early adolescents to prevent transgenerational progression. Early metformin

therapy can break the vicious cycle of hyperinsulinemia and hyperandrogenemia. Most important is follow up of these girls and treatin the co-morbidities timely.

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Diabetes Mellitus in Children: A Challenge Ahead

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Abstract

Diabetes mellitus (DM) is one of the ancient diseases. As early as 400 BC our Indian physician, Sushruta had described the disease as “Madhumeh”, the honey-urine disease. Type 1 diabetes is a continuing hormonal deficiency disorder that has significant short-term impacts on health and lifestyle and is associated with major long-term complications and reduced life expectancy. People with type 1 diabetes require insulin-replacement therapy from diagnosis to keep blood glucose concentrations as close as possible to the normal range to delay the long-term vascular complications of diabetes. Therefore, the complete treatment of diabetic patients not only includes meticulous attention to achievement of normoglycemia, but also correction of hypertension and dyslipidemia, correction of body weight and increase in physical activity. The goals of treating a child with DM are to achieve normal growth and development with prevention of acute and chronic complications of DM. These goals are achieved by coordinated care delivered by a multidisciplinary team focusing on insulin administration, glucose monitoring, meal planning, and screening for complications. Newer insulin analogues (“designer” insulin) and automated methods of delivery via programmable pumps have revolutionized the care of the child with diabetes. Systems of surveillance for the early detection of complications are important, as is effective management of complications when they occur.

INTRODUCTION

Diabetes mellitus is a metabolic syndrome characterized by chronic hyperglycemia with disturbance of carbohydrate, fat and protein metabolism resulting from improper insulin secretion and/or inefficient insulin action. This chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction and failure of various organs especially the eyes, kidneys, nerves, heart and blood vessels. Insulin is produced by the beta cells of the islets of Langerhans located in the pancreas, and the absence, destruction, or other loss of these cells results in type 1 diabetes (insulin-dependent diabetes mellitus [IDDM]). Most children with diabetes have type 1 diabetes mellitus (T1DM) and a lifetime dependence on exogenous insulin.^{1,2}

INCIDENCE

According to recent WHO report the worldwide prevalence of diabetes is 135 million in 1995, which will increase to 300 million by the year 2025.^{3,4} India had 33 million diabetics in 2000, which will become 57

million in 2025. About 1.6 million cases are diagnosed every year in India. It is affecting the children as young as six. India has thus become the “Diabetic Capital of the World” India has the distinction of having the largest number of diabetics in the world.⁵ It is expected that 200 children under the age of 14 will develop the disease every day.⁶

Every year 70,000 children under the age of 15 develop type 1 diabetes worldwide. Incidence of type 1 diabetes is growing by 3 to 5 percent each year.⁷ In 2007, the five countries with the highest diabetes prevalence in the adult population are Nauru (30.7%), United Arab Emirates (19.5%), Saudi Arabia (16.7%), Bahrain (15.2%), and Kuwait (14.4%).⁸

There is a dramatic rise of diabetes in Asians and Pacific islanders. It is projected that 300 million people will be affected by 2025. China is predicted to have the highest rise in prevalence rate (68%) followed closely by India (59%) and other Asian countries (41%).⁹

Both types 1 and 2 diabetes can occur in children and adolescents (Table 1). Type 1 diabetes is the

most common chronic disease in children in the developed countries. Generally, incidence rates increase with age until mid puberty then decline after puberty, but type 1 DM can occur at any age. Children aged 1 to 4 years are particularly at risk and may die due to diabetic ketoacidosis (DKA) at the time of diagnosis. Adolescents are also a high-risk group.

Most deaths result from delayed diagnosis or neglected treatment and subsequent cerebral edema during treatment for DKA, although untreated hypoglycemia also causes some deaths. Unexplained death during sleep may also occur. One of the most common diseases found in children and teens is diabetes. Ninety to ninety-five percent of children with diabetes have type 1 diabetes. The other 5 to 10 percent have type 2.

Most of the time when a child is diagnosed with diabetes it is assumed to be type 1 but in the last 20 years type 2 diabetes has been on the rise in children and teenagers. Thousands of children a year are diagnosed with diabetes and health care providers keep finding that more and more of these children have type 2 diabetes.¹⁰

CAUSES

The exact cause of type 1 diabetes is unknown. Scientists do know that in most people with type 1 diabetes, the body's own immune system, which normally fights harmful bacteria and viruses by mistake destroys the insulin-producing (islet) cells in the pancreas. It is an autoimmune disease directed at the insulin-producing cells of the pancreatic islets of Langerhans. These cells are progressively destroyed; with insulin deficiency. Type 1 diabetes is characterized by autoimmune destruction of insulin-producing β cells in the pancreas by CD4+ and CD8+ T cells and macrophages infiltrating the islets.

Genetics may play a role in this process, and exposure to certain viruses may trigger the disease. Monozygotic twins have a 60 percent life time concordance for developing type 1 diabetes mellitus. In contrast, dizygotic twins have only an 8 percent risk of concordance, which is similar to the risk among other siblings. The frequency of diabetes developing in children with a diabetic mother is 2 to 3 percent and 5 to 6 percent if the father has type 1 diabetes mellitus. The risk in children rises to almost 30 percent if both parents are diabetic.¹¹

Human leukocyte antigen (HLA) class II molecules DR3 and DR4 are associated strongly with type 1 diabetes mellitus.¹² Patients expressing DR3 are also at risk for developing other autoimmune endocrinopathies and celiac disease. These patients are more likely to develop diabetes at a later age. Patients expressing DR4 are usually younger at diagnosis and more likely to have positive insulin antibodies, yet they are unlikely to have other autoimmune endocrinopathies.

Two combinations of HLA genes (or haplotypes) are of particular importance: DR4-DQ8 and DR3-DQ2 are present in 90 percent of children with type 1 diabetes. A third haplotype, DR15-DQ6, is found in less than 1 percent of children with type 1 diabetes, compared with more than 20 percent of the general population, and is considered to be protective. The genotype combining the 2 susceptibility haplotypes (DR4-DQ8/DR3-DQ2) contributes the greatest risk of the disease and is most common in children in whom the disease develops very early in life. First-degree relatives of these children are themselves at greater risk of type 1 diabetes than are the relatives of children in whom the disease develops later.

Candidate gene studies also identified the insulin gene on chromosome 11 as the second most important genetic susceptibility factor, contributing 10 percent of genetic susceptibility to type 1 diabetes. Shorter forms of a variable number tandem repeat in the insulin promoter are associated with susceptibility to the disease, whereas longer forms are associated with protection. Demonstration of increased expression of insulin (mRNA) in the thymus of people with "long" or protective repeats—which suggests more efficient deletion of insulin-specific T cells during induction of central tolerance—provides an attractive potential mechanism for the role of the insulin gene in type 1 diabetes.

Over the last decade, whole genome screens have indicated that there are at least 15 other loci associated with type 1 diabetes, 16 to 18 and of those, another 2 genes intimately associated with T cell activation have been identified recently. An allele of the gene for a negative regulator of T cell activation, cytotoxic T lymphocyte antigen 4 (*CTLA-4*), found on chromosome 2q33, is considered to be the third susceptibility locus for type 1 diabetes and has been associated with increased levels of soluble *CTLA-4* and the frequency of regulatory T cells. A variant of *PTPN22*, the gene encoding LYP, also a suppressor of T cell activation, has been deemed the fourth susceptibility factor. The observation that the 4 most important susceptibility genes for type 1 diabetes can all be represented on a single diagram of antigen presentation to T cells (emphasizes the potential importance of current therapeutic strategies targeting this interaction). It is also worth noting that the HLA, *CTLA-4* and *PTPN22* have all been implicated in autoimmune thyroid disease and other autoimmune diseases, which supports the premise that similar or overlapping biological pathways contribute to different autoimmune diseases.¹²⁻¹⁴

No single factor has been identified, but infections and diet are considered the two most likely environmental candidates. Viral infections may be the most important environmental factor in the development of type 1 diabetes mellitus, probably by initiating or modifying an autoimmune process.¹⁵ Instances have been reported of a direct toxic effect of infection in congenital rubella.

Dietary factors are also relevant. Breastfed infants have a lower risk for IDDM, and a direct relationship is observed between per capita cow's milk consumption and the incidence of diabetes. Some cow's milk proteins (e.g. bovine serum albumin) have antigenic similarities to an islet cell antigen.

Nitrosamines, chemicals found in smoked foods and some water supplies, are known to cause type 1 diabetes mellitus in animal models; however, no definite link has been made with humans. Reduced exposure to UV light and lower vitamin D levels, both of which are more likely found in the higher latitudes, are associated with an increased risk of type 1 diabetes mellitus. Chemical causes: Streptozotocin and RH-787, a rat poison, selectively damage islet cells and can cause type 1 diabetes mellitus.^{16,17}

The cause of type 1 diabetes is different from the more common type 2 diabetes. In type 2, the islet cells are still functioning, but the body becomes resistant to insulin or the pancreas does not produce enough insulin. The environmental factors may interact with a genetically susceptible person.

Other causes are:

- Congenital absence of the pancreas or islet cells
- Pancreatectomy
- Type 1 diabetes mellitus secondary to pancreatic damage (i.e. cystic fibrosis, chronic pancreatitis, thalassemia major, hemochromatosis, hemolytic-uremic syndrome)
- Wolfram syndrome (diabetes insipidus, diabetes mellitus, optic atrophy, deafness [DIDMOAD])
- Chromosomal disorders such as down syndrome, turner syndrome, klinefelter syndrome, or Prader-Willi syndrome (The risk is said to be around 1 percent in down and turner syndromes).

CLINICAL MANIFESTATION

The American Diabetes Association's (ADAs) criteria for the diagnosis of DM were recently revised to include a new threshold for the diagnosis of impaired glucose tolerance (IGT) and impaired fasting glucose (IFG).

The diagnosis of DM is made on the basis of one of the following criteria:

- Symptoms of hyperglycemia including polyuria, polydipsia, weight loss plus random plasma glucose concentration >200 mg/dl (11 mm).
- Fasting (>8 hr fast) plasma glucose >126 mg/dl (7 mm).
- 2 hr postprandial glucose >200 mg/dl during an oral glucose tolerance test (OGTT).

Criteria for diagnosing IGT and IFG are two hours plasma glucose between 140 to 200 mg/dl or a fasting glucose between 100 to 125 mg/dl respectively.

The ADA classification of DM encompasses 4 groups: Type 1, Type 2, other specific types of diabetes, and

gestational diabetes. Type 1 DM is further subclassified into Type 1A which is associated with the presence of islet cell autoantibodies, and Type 1B characterized by the absence of such antibodies. Advances in our understanding of the physiology, and molecular and cellular basis for insulin secretion and action have prompted the continued evolution of alternate classifications.^{18,19}

- Diabetes with predominantly insulin deficiency including T1DM, neonatal diabetes, maturity onset diabetes of the young, and mitochondrial diabetes.
- Diabetes and other syndromes with predominantly insulin resistance, e.g. leprechaunism, lipodystrophic diabetes, and other entities where the resistance cannot usually be overcome by even supraphysiological insulin concentrations.
- Diabetes resulting from combined insulin deficiency and insulin resistance: T2DM. In normal physiology, the product of insulin secretion and insulin sensitivity is a constant, such that insulin resistance is compensated by increased insulin secretion and vice versa. Clinical diabetes only occurs when the product cannot be maintained within normal limits, usually because insulin secretion is inadequate to compensate for the prevailing degree of resistance to insulin action.²⁰

The most easily recognized symptoms of type 1 diabetes mellitus (T1DM) are secondary to hyperglycemia, glycosuria, and diabetic ketoacidosis (DKA). Their symptoms may include the following:

- Severe monilial diaper/napkin rash
- Unexplained malaise
- Poor weight gain or weight loss
- Increased thirst
- Vomiting and dehydration, with a constantly wet napkin/diaper

Hyperglycemia

Hyperglycemia alone may not cause obvious symptoms, although some children report general malaise, headache, and weakness.

They may also appear irritable and become ill-tempered. The main symptoms of hyperglycemia are secondary to osmotic diuresis and glycosuria.

Glycosuria

This condition leads to increased urinary frequency and volume (e.g. polyuria), which is particularly troublesome at night (e.g. nocturia) and often leads to enuresis in a previously continent child. These symptoms are easy to overlook in infants because of their naturally high fluid intake and diaper/napkin use.

Polydipsia

Increased thirst, which may be insatiable, is secondary to the osmotic diuresis causing dehydration.

Weight Loss

Insulin deficiency leads to uninhibited gluconeogenesis, causing breakdown of protein and fat. Weight loss may be dramatic, although the child's appetite usually remains good.

Failure to thrive and wasting may be the first symptoms noted in an infant or toddler and may precede frank hyperglycemia.

Nonspecific Malaise

Although this condition may be present before symptoms of hyperglycemia, or as a separate symptom of hyperglycemia, it is often only retrospectively recognized.

Symptoms of Ketoacidosis

Severe dehydration, smell of ketones, acidotic breathing (i.e. Kussmaul respiration), masquerading as respiratory distress, abdominal pain, vomiting drowsiness and coma.

Other nonspecific findings

Hyperglycemia impairs immunity and renders a child more susceptible to recurrent infection, particularly of the urinary tract, skin, and respiratory tract. Candidiasis may develop, especially in groin and flexural areas.

A physical examination may reveal findings associated with other autoimmune endocrinopathies, which have a higher incidence in children with type 1 diabetes mellitus (e.g. thyroid disease with symptoms of overactivity or underactivity and possibly a palpable goiter). Cataracts are rarely presenting problems and typically occur in girls with a long prodrome of mild hyperglycemia.

Necrobiosis lipoidica usually, but not exclusively, occurs in people with diabetes. Necrobiosis most often develops on the front of the lower leg as a well-demarcated, red atrophic area. The condition is associated with injury to dermal collagen, granulomatous inflammation, and ulceration. The cause of necrobiosis is unknown, and the condition is difficult to manage. It is also associated with poor metabolic control and a greater risk of developing other diabetes-related complications.^{21,22}

Dawn phenomenon

Blood glucose levels tend to rise in the early hours of the morning (usually after 0500 hours) prior to waking. This is called the dawn phenomenon. In nondiabetic individuals the mechanisms include increased nocturnal growth hormone secretion, increased resistance to insulin action and increased hepatic glucose production. These mechanisms are more potent in puberty.

Somogyi phenomenon is rebound hyperglycemia after hypoglycemia, which may be asymptomatic. This is caused by release of counter-regulatory hormones (e.g. catecholamines, cortisol, glucagon, growth hormone) in response to hypoglycemia.

SECONDARY DIABETES

This subclass contains a variety of types of diabetes, for some of which the etiologic relationship is known. Examples include diabetes secondary to exocrine pancreatic diseases, such as cystic fibrosis; endocrine diseases other than pancreatic diseases (e.g. Cushing syndrome); and ingestion of certain drugs or poisons (e.g. the rodenticide Vacor). Certain genetic syndromes, including those with abnormalities of the insulin receptor; also are included in this category. There are no associations with HLA's, autoimmunity, or islet cell antibodies among the entities in this subdivision.

Transient Diabetes Mellitus of the Newborn

Onset of persistent insulin-dependent diabetes before the age of 6 months is very unusual. The syndrome of transient diabetes mellitus in the newborn infant has its onset in the first weeks of life and persists only several weeks to months before resolving spontaneously. It occurs most often in infants who are small for gestational age and is characterized by hyperglycemia and pronounced glycosuria, resulting in severe dehydration and at times metabolic acidosis but with only minimal or no ketonemia or ketonuria. Insulin responses to glucose or tolbutamide are low to absent; basal plasma insulin concentrations, however, are normal. After spontaneous recovery, the insulin responses

Table 1: Characteristics of type 1 and type 2 diabetes in children and adolescents

Characteristic	Type 1	Type 2	Mody
Age at onset	Throughout childhood	Pubertal	Pubertal
Gender	Female = Male	Female > Male	Female = Male
Ethnicity	All (low incidence in Asians)	Native American African American	Caucasian Hispanic
Onset	Acute severe DKA common	Insidious ketosis less common	Gradual
Obesity	As in population	Common	Uncommon
Acanthosis nigricans	Absent	Present	Absent
Insulin secretion	Decreased/absent	Variable	Variably decreased

to these same stimuli are brisk and normal, implying a functional delay in β -cell maturation with spontaneous resolution. Occurrence of the syndrome in consecutive siblings has been reported. Permanent diabetes does not usually develop, although there are reports of patients with classic type I diabetes who formerly had transient diabetes of the newborn. It remains to be determined whether this association of transient diabetes in the newborn followed much later in life by classical IDDM is a chance occurrence or causally related. This syndrome should be distinguished from severe hyperglycemia that may occur in hypertonic dehydration, this occurs usually in infants past the newborn period, who respond promptly to rehydration and have a minimal requirement for insulin.

Administration of insulin is mandatory during the active phase of this syndrome. Intermediate-acting insulin in the dose of 1 to 2 U/kg/24 hr given in two divided doses, usually results in dramatic improvement and accelerated growth and gain in weight. Attempts at gradually reducing the dose of insulin may be made as soon as recurrent hypoglycemia becomes manifest or after 2 months of age. The parents should be assured of the transient nature of the disease and the excellent prognosis. Rarely, pancreatic agenesis may be associated with early but permanent diabetes mellitus as well as malabsorption.

The complications of type 1 diabetes mellitus ²²⁻²⁵

- Can be divided into three major categories:
 - Acute complications include: hypoglycemia, hyperglycemia, and DKA.²⁶
 - Long-term complications include the following:
 - Retinopathy
 - Cataracts
 - Hypertension
 - Progressive renal failure
 - Early coronary artery disease
 - Peripheral vascular disease
 - Neuropathy, both peripheral and autonomic
 - Increased risk of infection.
- Associated autoimmune diseases are common with type 1 diabetes mellitus, particularly in children who have the human leukocyte antigen DR3 (HLA-DR3). Some conditions may precede development of diabetes; others may develop later. As many as 20 percent of children with diabetes have thyroid autoantibodies.

LABORATORY STUDIES

Random Blood Sugar Test

A blood sample can be taken at a random time. Blood sugar values are expressed in milligrams per deciliter (mg/dl) or millimoles per liter (mmol/L). Regardless of when your child last ate, a random blood sugar level of 200 mg/dl (11.1 mmol/L) or higher suggests diabetes.

Fasting Blood Sugar Test

A blood sample can be taken after an overnight fast. A fasting blood sugar level less than 100 mg/dl (5.6 mmol/L) is normal. A fasting blood sugar level from 100 to 125 mg/dl (5.6–6.9 mmol/L) is considered prediabetes. If it is 126 mg/dl (7 mmol/L) or higher on two separate tests, your child will be diagnosed with diabetes.

Glycosylated Hemoglobin (A₁C) Test

This blood test indicates an average blood sugar level for the past two to three months. It works by measuring the percentage of blood sugar attached to hemoglobin, the oxygen-carrying protein in red blood cells. The higher the blood sugar levels, the more hemoglobin that has sugar attached. An A₁C level of 6.5 percent or higher on two separate tests indicates diabetes.

Glucose Tolerance Test

If the diagnosis is still unclear from these tests, a glucose tolerance test can be carried out. A glucose drink is given containing a standard amount of glucose (75g). Blood samples are taken before the drink is given and two hours later. The test is done after an overnight fast. A two-hour blood glucose level above 11.1 mmol/L is a diagnostic of diabetes. A level below 7.8 mmol/L is normal. If the level falls between these values, it suggests a decreased tolerance for glucose. This is known as impaired glucose tolerance (IGT).

Urine

A positive urine glucose test suggests, but is not diagnostic for, type 1 diabetes mellitus (T1DM). Diagnosis must be confirmed by test results showing elevated blood glucose levels. Test urine of ambulatory patients for ketones at the time of diagnosis. Ketones in the urine confirm lipolysis and gluconeogenesis, which are normal during periods of starvation. With hyperglycemia and heavy glycosuria, ketonuria is a marker of insulin deficiency and potential DKA.

Beginning at age 12 years, perform an annual urinalysis to test for a slightly increased AER, referred to as microalbuminuria, which is an indicator of risk for diabetic nephropathy.

Liver and Renal Function Tests

The liver helps maintain normal blood glucose concentration in the fasting and postprandial states. Loss of insulin effect on the liver leads to glycogenolysis and an increase in hepatic glucose production. Abnormalities of triglyceride storage and lipolysis in insulin-sensitive tissue's such as the liver are an early manifestation of conditions characterized by insulin resistance and are detectable earlier than fasting hyperglycemia. The precise genetic, environmental, and metabolic factors and sequence of events that

lead to the underlying insulin resistance, however, is not fully understood.

Diabetes is the leading cause of chronic kidney failure, or end-stage renal disease (ESRD). Uncontrolled high glucose levels can damage the nephrons. Measurement of serum creatinine is a screening test for diabetic nephropathy. All patients with diabetes should have their serum creatinine measured at diagnosis and at regular intervals thereafter, usually annually. Microalbuminuria rarely occurs with short duration of type 1 diabetes; therefore, screening in individuals with type 1 diabetes should begin after 5 years' disease duration.

Thyroid Function Tests

Because early hypothyroidism has few easily identifiable clinical signs in children, children with type 1 diabetes mellitus may have undiagnosed thyroid disease. Untreated thyroid disease may interfere with diabetes management. Check thyroid function regularly (every 2 to 5 years or annually if thyroid antibodies are present). Antithyroid antibody tests indicate the risk of present or potential thyroid disease.

Antigliadin Antibodies

Some children with type 1 diabetes mellitus may have or may develop celiac disease. Positive antigliadin antibodies, especially specific antibodies (e.g. antiendomysial, antitransglutaminase) are important risk markers. If antibody tests are positive, a jejunal biopsy is required to confirm or refute a diagnosis of celiac disease.

Lipid Profile

Lipid profiles are usually abnormal at diagnosis because of increased circulating triglycerides caused by gluconeogenesis. Apart from hypertriglyceridemia, primary lipid disorders rarely result in diabetes. Hyperlipidemia with poor metabolic control is common.

C-peptide Assay

Beta cells produce insulin and C-peptide in a 1:1 ratio. High blood sugar in the presence of C-peptide usually means a person is insulin resistant or type 2 diabetes. High blood sugar with a low or undetectable level of C-peptide means a person is insulin deficient or type 1. C-peptide actually causes insulin resistance by impairing the cells of the body from taking up more glucose. Physiologically this is because the blood sugar in the body is more than the body can handle. The idea is to prevent the insulin resistance from occurring in the first place. This can be done by increasing energy demands of the body through exercise or eating less refined and processed carbohydrates—resulting in less insulin secretion and less C-peptide.

The presence of anti-islet antibodies (to Glutamic Acid Decarboxylase, Insulinoma Associated Peptide-2 or

insulin)- American Diabetes Association expert committee has proposed an etiologic classification of diabetes with type 1A diabetes representing immune-mediated diabetes and type 1B a nonautoimmune idiopathic form of type 1 diabetes. Additional diseases with severe β -cell deficiency with known genetic or environmental etiologies are categorized individually. The best current markers to distinguish type 1A diabetes from other forms of diabetes are the presence of anti-islet autoantibodies. Typically, autoantibodies reacting with glutamic acid decarboxylase (GAD65), insulin, and insulinoma antigen-2 are measured. Assays can be set such that each assay has a false-positive rate of approximately 1 percent, and together one or more of these autoantibodies are present in approximately 90 percent of new onset patients with type 1A diabetes. There are undoubtedly additional autoantigens to be defined, and a subset of patients lacking the above three islet autoantibodies express cytoplasmic islet cell autoantibodies measured with indirect immunofluorescent staining of human pancreas. This latter assay has however a long history of poor standardization and although it detects a subset of GAD65 and insulinoma antigen-2 autoantibodies, it does not detect anti-insulin autoantibodies. Testing for GAD 65 antibodies has been proposed as an improved test for differentiating between Type 1 and Type 2 Diabetes. Islet cell antibodies may be present at diagnosis but are not needed to diagnose type 1 diabetes mellitus. Islet cell antibodies are nonspecific markers of autoimmune disease of the pancreas and have been found in as many as 5 percent of unaffected children. Other autoantibody markers of type 1 diabetes are known, including insulin antibodies. Additional antibodies against islet cells are recognized (e.g. those against glutamate decarboxylase [GAD antibodies]), but these are generally unavailable for routine testing.

TREATMENT

The initial step after the diagnosis is made is life-style modification. The patient is advised an appropriate diet and suitable exercise program. The response to diet and exercise should be assessed for two months in general.

DIET

The following are among the most recent consensus recommendations:

- Carbohydrates should provide 50 to 55 percent of daily energy intake (No more than 10 percent of carbohydrates should be from sucrose or other refined carbohydrates).
- Fat should provide 30 to 35 percent of daily energy intake.
- Protein should provide 10 to 15 percent of daily energy intake.
- View these recommendations in the patient's cultural context.

- Adequate intake of complex carbohydrates (e.g. cereals) is important before bedtime to avoid nocturnal hypoglycemia, especially for children having twice-daily injections of mixed insulin.
- The dietician should develop a diet plan for each child to suit individual needs and circumstances. Regularly review and adjust the plan to accommodate the patient's growth and lifestyle changes.
- Low-carbohydrate diets as a management option for diabetes control have regained popularity in recent years. Logic dictates that the lower the carbohydrate intake, the less insulin is required. No trials of low-carbohydrate diets in children with type 1 diabetes mellitus have been reported, and such diets cannot be recommended at the present.

Activity

- *Type 1 diabetes mellitus*: Exercise has real benefits for a child with diabetes. Most children can adjust their insulin dosage and diet to cope with all forms of exercise.
- *Role of yoga*: Several well-planned studies have demonstrated the beneficial effects of yogic practices in diabetics. Some of the asanas that were found to produce these benefits are *Dhanurasana*, *Ardhamatsayendrasana*, *Bhujangasana*, *Naukasana*, *Halasana*, *Paschimotasana*, and *Shavasana pranayam*.

Insulin

- Insulin is always required to treat type 1 diabetes mellitus. Originally, all insulin was derived from the highly purified pancreatic extracts of pigs and cattle, and this form of insulin is still available. Human insulin was later manufactured using recombinant DNA technology (Table 2).
- More recently, “designer” insulin's are produced based on the human molecule and are tailored to meet

specific pharmacological targets, particularly duration of action. Insulin must be given parenterally and this effectively means subcutaneous injection.

- Type 1 is treated with insulin replacement therapy—usually by insulin injection or insulin pump, along with attention to dietary management, typically including carbohydrate tracking, and careful monitoring of blood glucose levels using glucose meters.
- Insulin has four basic formulations—ultra short-acting (e.g. lispro, aspart, glulisine) traditional short-acting (e.g. regular, soluble), medium-acting or intermediate-acting (e.g. isophane, lente, detemir), and long-acting (e.g. ultralente, glargine).
- Regular or soluble insulin is bound to either protamine (e.g. isophane) or zinc (e.g. lente, ultralente) in order to prolong the duration of action. Combinations of isophane and regular, lispro or aspart insulins are also available in a limited number of concentrations that vary around the world, ranging from 25:75 mixtures to 50:50 mixtures.

Injection Regimens

- Twice-daily combinations of short-acting and intermediate-acting insulin.
- Multiple injection regimens, using once-daily or twice-daily injections of long-acting or intermediate-acting insulin and short-acting insulins given at each meal.
- A combination of the above two regimens, with a morning injection of mixed insulin, an afternoon pre-meal injection of short-acting insulin and an evening injection of intermediate-acting or long-acting insulin.
- Continuous subcutaneous insulin infusion (CSII) using an insulin pump.
- A wide variety of insulin-injection devices are available, including a simple syringe and needle, semiautomatic

Table 2: Timing of action of available insulins

	Insulin onset (hour) <i>Lispro 0.25</i>	Peak (hour) <i>0.5–1.0</i>	Duration (hour) <i>3</i>
<i>Regular</i>			
Human	0.5–1.0	2–3	3–6
Pork	0.5–2.0	3–4	4–6
<i>NPH/Lente</i>			
Human	2–4	4–10	10–16
Pork	4–6	8–14	16–20
<i>Ultralente</i>			
Human	6–10	Minimal (?)	18–20
Animal	8–14	Minimal	24–36
<i>Mixed (70% NPH, 30% regular)</i>			
Human	0.5	2–12	24

pen injector devices, and needle-free jet injectors. Increasing numbers of young people use insulin pumps to deliver continuous subcutaneous insulin, with bolus doses at meal times.

- When prescribing tailor the insulin dose to the individual child's needs. For instance, if using a twice-daily regimen, then, as a rule of thumb, prepubertal children require between 0.5 and 1 U/kg/d, with between 60 to 70 percent administered in the morning and 30 to 40 percent in the evening.
- Insulin resistance is a feature of puberty, and some adolescents may require as much as 2 U/kg/d. About one-third of the administered insulin is a short-acting formulation and the remainder is a medium-acting to long-acting formulation.
- Basal bolus regimens have a higher proportion of short-acting insulin. Typically, 50 percent of the total daily dose is given as long-acting or intermediate-acting insulin. CSII uses only short-acting insulin's, most often the analogues lispro or aspart. Typically, they also have around 50 percent of the insulin given at a basal rate; the remainder is given as food-related boluses.
- Alternatives to injecting insulin have been constantly sought; the most recent is an inhaled form of insulin. The search for alternatives continues, including oral sprays, sublingual lozenges, and delayed-absorption capsules.

Most children and adolescents require at least two injections per day of short and intermediate-acting insulin to achieve satisfactory metabolic control; the injections are administered shortly before breakfast and dinner. During the honeymoon period, when insulin requirements are at a minimum, one injection per day may be satisfactory for control. Except for this period, achieving control with a single daily injection is nearly impossible. Absorption may vary from different injection sites and is more rapid in exercised sites and at higher temperatures. Injection into hypertrophied sites may slow absorption.

Frequent blood glucose monitoring is necessary so that patients can respond to the levels by adjusting their insulin doses. For example, if an occasional fasting blood glucose level falls above the target range, the morning short-acting insulin dose should be increased. If the fasting blood glucose level is increased for several consecutive days, the evening NPH dose should be increased.

During the honeymoon period, dose requirements may drop to less than 0.5 U/kg/day. Except during this period, most preadolescent children need approximately 0.75 to 1.00 U/kg/day. Teenagers usually require approximately 1.0 to 1.2 U/kg/day after the first few years of the disease.

Patients on a twice-daily dosage regimen typically need approximately two-thirds of the total dose in the

morning and one-third before dinner. The doses usually are split between one-third short-acting (regular or lispro) and two-thirds NPH to one-half short-acting and one-half NPH. More short-acting insulin usually is required in the morning because of an early morning glucose rise. This early morning glucose increase (i.e. dawn phenomenon) may be caused by normal nocturnal increases in some counter-regulatory hormones.

Other insulin regimens may be needed to achieve adequate control. Often, the evening dose must be separated, with short-acting insulin given before dinner and NPH at bedtime to maintain adequate insulin levels throughout the entire night and to avoid hypoglycemia during the hours between 1:00 and 4:00 am. Sometimes additional short-acting insulin is needed before lunch, although this may be difficult to arrange in a school-aged child (without interfering with his or her school schedule), or before a mid afternoon snack.

Ultralente can be used to provide a continuous, fairly steady insulin level with a once or twice-daily dose, with short-acting insulin given before each meal. The use of continuous subcutaneous insulin infusion pumps can be considered in highly motivated and conscientious patients. Short-acting insulin is used for continuous subcutaneous infusion to achieve a continuous basal rate, with bolus doses given before meals. In other words, many different regimens are available. When insulin doses are more than 1.5 U/kg/day and especially when they are at or more than 2 U/kg/day, overtreatment must be considered. Excess insulin doses can worsen control and produce a clinical picture of widely variable blood glucose values.

New approaches for treatment:

- Pancreas transplantation
- Islet cell transplantation
- Stem cells approach
- Gene therapy approach

Alternatives to injecting insulin have been constantly sought; the most recent is an inhaled form of insulin. Several products were in development, and one (Exubera) was licensed for use but failed to generate sufficient market penetration to justify continued production. The search for alternatives continues, including oral sprays, sublingual lozenges, and delayed-absorption capsules.

Pancreas Transplantation

Pancreas transplants are generally performed together with or sometime after a kidney transplant. One reason for this is that introducing a new kidney requires taking immunosuppressive drugs such as cyclosporin. Nevertheless this allows the introduction of a new, functioning pancreas to a patient with diabetes without any additional immunosuppressive therapy. However, pancreas transplants alone can be wise in patients with extremely labile type 1 diabetes mellitus.

Scientists have found another alternative mode of pancreas transplantation through the use of xenografts especially from animals such as pigs. This alternative mode of transplantation from animals provides an alternative therapy for the treatment of type 1 diabetes.

Islet Cell Transplantation

Islet cell transplantation is expected to be less invasive than a pancreas transplant which is currently the most commonly used approach in humans.

Stem Cells Approach

Research is being done at several locations in which islet cells are developed from stem cells.

Gene Therapy Approach

Designing a viral vector to deliberately infect cells with DNA to carry on the viral production of insulin in response to the blood sugar level. Technology for gene therapy is advancing rapidly such that there are multiple pathways possible to support endocrine function, with potential to practically cure diabetes.

PREVENTION

New approaches are:

- Immunization approach
- DiaPep277
- Intranasal insulin
- Bacillus Calmette Guérin research
- Diamyd

Immunization Approach

If a biochemical mechanism can be found that prevents the immune system from attacking beta cells, it may be administered to prevent commencement of diabetes type 1. Several groups are trying to achieve this by causing the activation state of the immune system to change from Th1 state ("attack" by killer T Cells) to Th2 state (development of new antibodies). This Th1-Th2 shift occurs via a change in the type of cytokine signalling molecules being released by regulatory T cells. Instead of proinflammatory cytokines, the regulatory T cells begin to release cytokines that inhibit inflammation. This phenomenon is commonly known as "acquired immune tolerance".

DiaPep277

A substance designed to cause lymphocyte cells to cease attacking beta cells, DiaPep277 is a peptide fragment of a larger protein called HSP60. Given as a subcutaneous injection, its mechanism of action involves a Th1-Th2 shift. Clinical success has been demonstrated in prolonging the "honeymoon" period for people who already have

type 1 diabetes. The product is currently being tested in people with latent autoimmune diabetes of adults (LADA).

Intranasal Insulin

There is preclinical evidence that a Th1-Th2 shift can be induced by administration of insulin directly onto the immune tissue in the nasal cavity. This observation has led to a clinical trial, called INIT II, which began in late 2006, based in Australia and New Zealand.

Bacillus Calmette-Guérin Research

Bacillus Calmette-Guérin (BCG), an inexpensive generic drug, would have the same impact as injecting diabetic mice with Freund's Adjuvant, which stimulates TNF- α production. TNF- α kills the white blood cells responsible for destroying beta cells, and thus prevents, or reverses diabetes. She has reversed diabetes in laboratory mice with this technique, but was only able to receive funding for subsequent research from the Iacocca Foundation, founded by Lee Iacocca in honor of his late wife, who died from diabetes complications. Human trials have begun in 2008.

Diamyd

Diamyd is the name of a vaccine being developed by Diamyd Medical. Injections with GAD65, an autoantigen involved in type 1 diabetes, has in clinical trials delayed the destruction of beta cells for at least 30 months, without serious adverse effects. Patients treated with the substance showed higher levels of regulatory cytokines, thought to protect the beta cells. Phase III trials are under way in the USA and in Europe, with most sites actively pursuing participants. Two prevention studies, where the vaccine is given to persons who have not yet developed diabetes may be the next step.

Diabetes has correctly been labelled as the "silent epidemic"—its nondramatic, insidious and chronic nature often masks the menace inflicted by the disease through death, incapacitation, and negative impact on quality of life of patients as they spend years coping with their life-changing affliction.

Care of Children with Diabetes in the School and Day Care Setting

- Both parents and the health care team should work together.
- School and day care personnel must have an understanding of diabetes and must be trained in its management and in the treatment of diabetes emergencies.

WORLD DIABETES DAY

It is observed annually on November 14 to commemorate the birthday of Frederick Banting who, along with Charles Best, discovered insulin in 1921. Across 130 countries and cosponsored by the International Diabetes Federation

(IDF) and the World Health Organization (WHO), the day was first observed in 1991 in response to concern over the escalating incidence of diabetes around the world.

Diabetes is a silent killer and it is important that everyone in the country is screened for the disease. Government intends to do so in next five years. "Now with the growing cases of diabetes among children, there is a need to have a scheme for children."

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Management of Type 1 Diabetes Mellitus in Children and Adolescents Including Recent Advances

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INTRODUCTION

Type 1 diabetes mellitus (T1DM) is a common chronic disease of childhood. It is caused by deficiency of insulin resulting from the autoimmune destruction of insulin-producing pancreatic beta cells. Challenges in the management of pediatric diabetes are unique and different from those in adult diabetes. These include the obvious differences in the size of the patients, developmental issues such as the unpredictability of a child's dietary intake and activity level, and medical issues such as the increased risk of hypoglycemia and diabetic ketoacidosis. Because of these considerations, the management of a child with type 1 diabetes is more challenging and must take into account the age and developmental maturity of the child.

GOALS OF MANAGEMENT

The therapeutic plan and goals of therapy need to be individualized depending on the parents and the child's abilities, motivation, finances, age, educational status, daily schedule and access to a medical facility. The salient points include:

- Achieving a balance between strict glycemic control, which reduces the risk of long-term sequel and avoidance of severe hypoglycemia, which is more likely with stricter control.
- Setting realistic goals for each child and family. The patient's age and developmental status, and the level of family involvement are important factors that should be accounted for.
- Maintaining normal growth and development.
- Training the patient and family to provide appropriate daily diabetes care in order to attain glucose control within the range of predetermined goals.
- Prompt recognition and treatment of hypoglycemia.
- Increasing independence of the child in diabetes management and self-care as the child grows.

Overview

There are four therapeutic pillars for management of T1DM:

- Insulin therapy
- Meal planning
- Planned physical activity
- Self-monitoring of blood glucose (SMBG) and urinary/blood ketones.

Parental and family involvement is key to successful management. Parents or the child need to be educated regarding insulin therapy, SMBG, diet planning and sick day guidelines. Management of childhood diabetes is team work and needs to include a pediatric endocrinologist or a pediatrician with special interest in diabetes, a dietician, a psychologist, a social worker and a nurse educator.

The initial educational and care phase may occur either in the inpatient or ambulatory setting. Hospitalization for initial management is mandatory if the child is dehydrated, vomiting, breathless, or has features of ketosis. In patients who are not in ketosis at presentation, the indications for hospitalization include age below 5 years of age, parents not confident to administer insulin injections or residence in remote area. There is no single best way to manage diabetes, since the patients vary widely in terms of educational status, economic situation and availability of medical care at hand. On one hand there are intelligent, rich and motivated patients and parents who may opt for the insulin pump or a basal bolus insulin regimen using insulin analogs (3-5 injections a day), perform 5 to 8 blood glucose tests a day and use a meal plan based on carbohydrate counting. On the other end of the spectrum are the underprivileged, uneducated patients with little financial support to buy insulin and syringes, and poor motivation to understand the disease process and life style changes essential for its management. However, majority of patients would fall in between these two extremes; they can easily learn to mix

regular and NPH insulin, inject 2 to 4 times a day and test blood glucose at least 1 to 2 times daily.

INSULIN

Exogenous administration of insulin is needed to replace the deficient hormone and to attain normoglycemia, ideally mimicking the normal physiology. However, this goal remains elusive because of the difficulty in replicating the minute-to-minute variations of physiologic insulin secretion with exogenous insulin administration. There are many different insulin preparations and delivery systems. The selected regimen is individualized for the child and family to fit their lifestyle and optimize compliance while providing glycemic control that meets age-specific goals.

Insulin Preparations

In India, the available insulins include the conventional short acting regular insulin and intermediate acting NPH insulin. Lente and ultra-lente insulins are no longer available. The newer insulin analogs are also available, including rapid-acting analogs lispro, glulisine and aspart; and the long acting basal analogs glargine and detemir. Rapid-acting insulin analogs can be administered after the meal in younger children in whom intake is unpredictable and thus offer a significant advantage in management of younger children and toddlers with diabetes. The approximate time of onset, peak activity, and duration of action of the most commonly used insulins is shown in the Table 1.

Available premixed insulins include mixtures of regular with NPH (in the ratio 50:50 and 30:70) and of soluble rapid acting analogs with a protaminated suspension of the analog (in the ratio 30:70 in the case of aspart insulin and 25:75 or 50:50 in the case of lispro). Use of premixed insulins has the disadvantage that the individual components cannot be adjusted according to individual needs.

Insulin Storage

Insulin vials should be refrigerated at 2 to 8°C and should never be frozen. In households that do not have a refrigerator, insulin should be kept in a cool, dry place away from sunlight. It can be stored in an earthen pot. A vial in use (after the seal has been punctured) should not be used

beyond 3 months if refrigerated or 4 weeks if kept at room temperature.

Insulin Delivery Options and Sites

Insulin is usually injecting using insulin syringe or a pen device. In India, insulin vials are available in two concentrations (40 IU/ml and 100 IU/ml). It is extremely important to ensure that the insulin syringe has the same number of sub-divisions as the strength of insulin preparation in use (i.e. 40 IU syringe for 40 IU insulin vial). For most patients who mix their insulins, syringes are the only option. The pen is more suitable for those on a basal-bolus regimen, different pens being used for delivery of each type of insulin.

Insulin is injected subcutaneously in the upper arm, anterolateral thigh, the anterior abdominal wall (leaving out 2 inches from all sides of the navel) and the upper outer region of the buttocks. The injection area should preferably remain the same for a given time of the day as the rate of insulin absorption is different from each site. Systematic site rotation within the selected area is very important to prevent lipohypertrophy. Insulin requirement is based upon the body weight, age, and pubertal stage of the child. In general, the newly diagnosed child requires an initial total daily insulin dose of 0.5 to 1.0 u/kg. Prepubertal children usually require lower doses. Higher doses are needed in pubertal children, patients in ketoacidosis, or in patients receiving glucocorticoid therapy.

Insulin Regimes

Broadly, there are 2 regimens to give insulin using multiple daily subcutaneous injections: conventional *split-mix regimen* and *intensive basal-bolus regimen*. In recent times continuous subcutaneous insulin infusion is also finding wider use in pediatric practice.

- In the conventional split-mix regimen, which comprises of a mixture of short and intermediate acting insulin, one type of insulin covers one time period: the pre-breakfast short acting covers the period from breakfast to lunch while the intermediate acting works between lunch and dinner; the evening short acting covers the period from dinner to bedtime/midnight while the intermediate acting covers the period from

Table 1: The time action profile of various insulins available in India

Insulin	Onset of action (hr)	Peak action (hr)	Duration of action
Rapid acting analogs	0.25	1	3-4
Human regular	0.5-1	2-4	6-8
Human NPH	1-3	6-8	12-16
Glargine	1	Nil (peakless insulin)	11-24
Detemir	1	3-9	6-23

bedtime to pre-breakfast. The patient usually takes two injections, one pre-breakfast and the other pre-dinner. Generally 2/3rd of the total daily dose of insulin is given before breakfast and 1/3rd before dinner. Each injection is a mixture of rapid or short acting insulin and NPH in the ratio 1:3 for the morning dose and 1:1 or 1:2 for the evening dose. Variation of this regime includes giving evening NPH at bedtime instead of giving it along with evening short acting insulin to prevent pre-breakfast hyperglycemia due to waning of insulin action. In such a situation, stepping up of the pre-dinner intermediate acting insulin to control the pre-breakfast BG may cause nocturnal hypoglycemia.

- The intensive basal-bolus regimens are more physiological and if implemented correctly (with frequent SMBG, corrective supplemental doses of insulin) can give better control. These regimens use rapid or short acting insulin to cover meals and NPH or a basal analog to provide basal insulin (to cover hepatic glucose output in the fasting state). The common regimens in use are:

- *Regular insulin three times a day before each major meal and NPH insulin pre-breakfast plus bedtime*
- *Regular insulin three times a day before each major meal and glargine once a day or detemir twice a day*
- *Lispro, aspart or glulisine insulin before each major meal or large snack (3-5 doses a day) and either NPH/glargine/detemir for basal insulinemia.*

- *Continuous subcutaneous insulin infusion (CSII) or the open loop insulin pump:* It has the advantage that it uses only a rapid acting analog as a continuous infusion for both basal and bolus doses. The bolus can be delivered as a normal bolus, a square wave bolus (for a prolonged meal or a meal with high fat content) or a dual wave bolus (for meals with both rapidly and slowly absorbed carbohydrates and for correcting premeal hyperglycemia). Since there is no insulin depot in the body in pump users, mechanical failure of the pump can lead to rapid onset of DKA. Insulin pumps can give excellent control if all other aspects of diabetes self-management (in particular, meal planning, frequent home based blood glucose monitoring with corrective action) are intensified. A position statement of the ADA, European Society for Pediatric Endocrinology and others recommends that insulin pump therapy should be considered for patients with one or more of the following characteristics: recurrent severe hypoglycemia; wide fluctuations in blood glucose levels (regardless of A1C); suboptimal diabetes control (A1C exceeds target range for age); microvascular complications and/or risk factors for macrovascular complications; good metabolic control, but an insulin regimen that compromises lifestyle. Currently, the extremely high cost of insulin pump is a major limiting factor for wider use of CSII.

The choice of regimen would depend on multiple factors: the age of the child, stage of diabetes, financial condition of the family, school timings, motivation of child and parents, and feasibility of giving multiple shots. The split-mix regimens are the most commonly used in younger children as they are simple for the patient and require fewer daily injections. These regimens lack flexibility of lifestyle which may pose a problem in an infant or an adolescent age group. Basal-bolus regimens should be considered if good control with conventional regimen fails to occur. These can be started at the outset in patients who can afford the additional cost and are also motivated not only to take multiple shots and perform frequent SMBG and act on the results.

A few weeks after the diagnosis and initiation of insulin therapy, a period of decreasing exogenous insulin requirement occurs, commonly referred to as the “honeymoon” or remission phase of diabetes. During this period, the remaining functional beta cells secrete some endogenous insulin resulting in reduced exogenous requirement. Close monitoring of blood glucose is mandatory as hypoglycemic episodes are likely if the insulin dose is not appropriately adjusted. The duration of this phase is variable and may last several months to several years. Rising blood glucose levels, A1C, and increasing exogenous insulin need indicates the end of this phase.

MEAL PLANNING

Nutrition planning is an important component of optimum diabetes management. A dietician with special interest in pediatric diabetes must be part of the diabetes management team. Children and adolescents with T1DM do not need a special diet, unless the child has problems that require particular nutrition needs as in obesity, hypertension, hyperlipidemia, nephropathy and celiac disease. Caloric requirement is same as that for any nondiabetic child. The calorie intake should be adequate so that the child grows normally. What is important, especially in a patient on split-mix regime, is to ensure regular meal timings and consistent carbohydrate intake in each meal to prevent wide swings in blood sugar levels. A fine balance must be achieved between insulin administration, meals and exercise. It is important to prevent hypoglycemia especially in relation to exercise, during night hours and during intercurrent illnesses. Fixed timings (usually a six meal pattern with 3 small and 3 major meals) usually works well for patients on split-mix insulin regimen. The children on basal-bolus regimen can have considerable flexibility in their meal timings and content with the intelligent application of carbohydrate counting and insulin to carbohydrate ratio. This is however not practical in smaller children and infants. Carbohydrates should provide 50 to 60 percent of calories. Sucrose and other simple sugars are no longer forbidden, but their use is better minimized.

Complex carbohydrates and foods with low glycemic index give better postprandial control. A high fiber diet may confer some benefit by slowing absorption of sugar from the gut. Salt intake should be regulated to reduce risk of hypertension. Fats should constitute 30 percent of calories, with restriction of saturated fats to <10 percent and elimination of trans fatty acids. Protein intake should not be higher than the recommendation for healthy children. Protein restriction is needed if micro-albuminuria develops. Sweeteners may be used if necessary in older children but are best avoided. Diabetic snacks are not recommended. These children do not require routine vitamin and mineral supplementation.

Planned Physical Activity

Physical activity should be considered as an important aspect of management of T1DM. Regular physical activity has been demonstrated to improve glycemic control, fitness and muscle strength and psychological wellbeing. Children participating in sports should be supervised and should have access to sweetened drinks and snacks. Blood glucose levels should be monitored before, during and after physical activity. It is important to note that insulin should not be injected into a site that will be heavily involved in muscular activity. A general recommendation is that for every 30 minutes of moderate to intensive sport or physical activity, 15 g or an extra serving of carbohydrate should be consumed. Strenuous physical activity should be avoided if blood glucose concentration is >250 mg/dl, especially if ketones are present.

Sick Day Guidelines

Children whose diabetes is under good metabolic control should not experience more illness or infections than children without diabetes. The diabetes care team should provide clear guidance to patients and families on how to manage diabetes during intercurrent illnesses to avoid the complications of ketoacidosis, dehydration, uncontrolled or symptomatic hyperglycemia and hypoglycemia. Blood glucose and ketones must be checked every 2 to 4 hours. There is only one meter available in India that checks blood ketones and the cost of each ketone strip is very high (Rs 150/-approximately). In practice therefore most patients depend on the less reliable urine ketone tests. A blood glucose level above 180 mg/dl signifies insulin deficiency and the need for additional insulin. Presence of ketones in urine or blood would mean either carbohydrate deficiency due to poor intake (in which case the simultaneous blood glucose would be less than 100 mg/dl) or significant insulin deficiency (when associated with blood glucose over 180 mg/dl). Insulin should never be completely omitted even if child refuses to eat. Insulin dose can be reduced only when blood sugar is below 80 mg/dl and the child cannot eat. In this case, the short or rapid acting insulin dose is omitted

while the intermediate or long acting insulin is continued as usual. When BG is over 180 mg/dl the patient needs a supplement of short or rapid acting insulin immediately. This additional dose is calculated as a percentage of the total daily dose (TDD). The supplement may range from 5 to 20 percent of TDD depending on the BG and the ketone levels. It is always given as regular insulin or rapid acting analog. As a rough guide, when BG is over 180 mg/dl with absent or trace urinary ketones, a supplement of 5 to 10 percent of TDD may be taken; the supplement should be 10 to 20 percent if ketones are small or moderate and 20 percent if ketones are large. The patient who cannot eat his regular meals should be offered plenty of salty liquids (such as rice kanji, vegetable soup, dhal soup, buttermilk, milk without sugar or chicken soup) if BG is above 180 mg/dl and sweet liquids (non-diet soft drinks without fizz, fruit juices, milk with sugar, WHO-ORS or melted icecream) if BG is below 180 mg/dl.

Complications of T1DM

Multiple acute and long term complications may occur in children and adolescents with type 1 diabetes. The most common acute complications include hypoglycemia, hyperglycemia and diabetic ketoacidosis (DKA). The long term microvascular and macrovascular complications include retinopathy, nephropathy, neuropathy and cardiovascular disease. The time interval between onset of diabetes and appearance of complications is directly related to strictness of glycemic control. Poorer is the control; earlier is the onset of complications. Hypoglycemia is discussed here. The management of other complications are beyond the scope of this chapter.

HYPOGLYCEMIA

Hypoglycemia is the result of a mismatch between insulin dose, food consumed, and recent exercise and is rarely, if ever, a spontaneous event. A careful review of blood glucose (BG) records will yield a retrospective prediction of the hypoglycemic event for at least 50 percent of events. Non-modifiable predictors of severe hypoglycemia include age (infancy and adolescence) and longer duration of diabetes. Modifiable predictors are lower hemoglobin A1C (HbA1C) and higher insulin dose for stricter glycemic control.

There is no consistent or agreed upon numerical definition of hypoglycemia for the child with diabetes. Nevertheless, BG values below 60 to 70 mg/dl are generally agreed to place the individual at risk for severe hypoglycemia because values in this range are associated with alterations in the counter-regulatory hormones essential for the spontaneous reversal of hypoglycemia. For clinical use, the value of 65 mg/dl has been most often used as the level for defining hypoglycemia in the pediatric population. In an infant or toddler, BG should be maintained above 100 mg/dl to avoid hypoglycemia. Children on split-mix regimen

often have hypoglycemia if regular snacks or meals are missed especially during the overlap of the peak action of mixed NPH and regular insulin and at night time during prolonged period of fasting. Hypoglycemia can result in abnormal behavior (tantrums in a young child should not be ignored), drowsiness, convulsions, coma, or if prolonged, death. Recurrent hypoglycemia can lead to hypoglycemia unawareness, increasing the risk of later episodes. Parent should be counselled regarding the recognition and management of hypoglycemia. Mild or moderate hypoglycemia, symptomatic or asymptomatic (detected on SMBG), can be managed by patient/parents at home with oral carbohydrates. If the BG is more than 60 mg/dl and the sensorium is normal, the child should be given 5 to 15 g of carbohydrate orally. This should preferably be in the form of free sugars, because the presence of fat delays the absorption of the sugar. Thus the child can be given glucose, sugar, juice or honey. This is followed by a repeat blood sugar testing after 10 to 15 minutes and if still low, glucose should be given again. Severe hypoglycemia, when the patient has altered sensorium (coma or convulsions), requires glucagon or IV glucose and is best managed in hospital settings.

Monitoring of a Child with T1DM: Glycemic Control

Monitoring of glycemic control includes daily monitoring of glucose at home as well as periodic monitoring of overall glycemia over a specified period. The purpose of monitoring glycemic status is to assess level of glycemic control achieved by an individual so that treatment can be fine-tuned, and to help prevent both the acute and the chronic complications of diabetes.

Measurement of immediate glycemic control is best determined by self-monitoring of blood glucose (SMBG) as this provides immediate documentation of hyperglycemia and hypoglycemia, thus helping in finetuning insulin regime. Strict adherence to maintain optimal values of blood sugar by SMBG is seen to be associated with reduction in the levels of HbA1c, thereby reducing the incidence of long term microvascular and macrovascular complications. SMBG is a valuable tool to assess glycemic status during a 'sick day' and can prevent a hyperglycemic or hypoglycemic crisis. SMBG should be done many times every day – before breakfast (fasting), before lunch, before dinner and at bedtime. It should be done at around 2 to 3 AM at least once in a week. There are two types of adjustments in insulin dose based on blood glucose levels. If the premeal sugar is high, then the regular or rapid acting insulin dose to be taken for that meal is to be adjusted upwards. This adjustment is valid for any type of regimen. The second preventive type of adjustment is to be done if high or low reading is observed over a few days. The type of adjustment will differ with the regimen. Adjustments should be made not only in insulin, but also diet, and/or exercise, aimed at preventing the high blood sugar levels. Tables 2 and 3 show preventable insulin adjustments

in split-mix and basal-bolus regimens respectively. The target blood glucose varies based on the age of the child. Young children may suffer more from severe hypoglycemia, and therefore goals of blood glucose levels may be set higher than those for older children and adolescents. Table 4 highlights the 2011 recommendations of the American Diabetes Association on target blood glucose levels in children with diabetes.

Long-term glycemic control is best monitored by blood glycated hemoglobin (hemoglobin A1C). Another method to evaluate long term glycemic control is fructosamine and other glycyated products. Fructosamine measures the glycation of serum proteins such as albumin and reflects glycemia over the preceding 3 to 4 weeks. It is therefore used for the assessment of shorter periods of control than HbA1C. Fructosamine or glycated albumin may be useful in monitoring glucose control over time in individuals with abnormal red cell survival time or in children with thalassemia who concurrently have T1DM. However, fructosamine and other glycated products have not been evaluated in terms of later vascular risk.

Strict glycemic control has been shown to delay the onset of microvascular disease (retinopathy, nephropathy and neuropathy), slow progression of already-present microvascular disease, and decrease the incidence of cardiovascular disease. However, the DCCT (Diabetes control and complication trial) demonstrated that as A1C decreased, indicating a stricter glycemic control, the incidence of severe hypoglycemic episodes increased. Thus, the intensity of glycemic control needs to be balanced

Table 2: Preventive insulin adjustment in mixed split regimen

<i>Blood sugar value</i>	<i>Adjustment</i>	
Pre-breakfast	↑	↑ evening NPH*/ shift to bed- time
	↓	↓ evening NPH
Pre-lunch	↑	↑ morning regular
	↓	↓ morning regular
Pre-dinner	↑	↑ morning NPH
	↓	↓ morning NPH
Bed-time	↑	↑ evening regular
	↓	↓ evening regular

*Before increasing the night NPH check for somogyi phenomenon.

Table 3: Preventive adjustments in basal-bolus regimes using analogs

<i>SMBG reading</i>	<i>Insulin adjustment</i>
Fasting and premeals	Long acting analog
Postmeal	Regular or rapid acting analog

Table 4: Target blood glucose levels

<i>Time</i>	<i>Blood glucose levels age <6 years (mg/dl)</i>	<i>Blood glucose levels age 6-12 years (mg/dl)</i>	<i>Blood glucose levels age > 12 years (mg/dl)</i>
Fasting and premeal	100–180	90–180	90–130
Bedtime and midnight	110–200	100–180	90–150

against the increased risk of recurrent/severe hypoglycemia. Targeted goals for A1C and blood glucose have been defined by a committee of the American Diabetes Association (ADA) based upon the risk of hypoglycemia, with the highest target values set for young children and infants because they have the greatest risk for hypoglycemia. Age-specific goals for A1C are:

- <6 years of age: <8.5 percent
- 6 to 12 years of age: <8 percent
- 13 to 19 years of age: <7.5 percent
- Over 19 years of age: <7.0 percent

Before the emergence of blood glucose monitoring, urine sugar monitoring was used all over the world and diabetic children and their families were able to maintain reasonably good control. Blood glucose monitoring has now replaced urine monitoring in most developed countries, but it may not be feasible for many of our patients to perform 4 to 5 blood sugar tests per day due to the cost involved. Hence, using urine sugar testing in conjunction with blood sugar monitoring is an option when patients cannot do frequent blood glucose monitoring. The downside of this method is inability to detect hypoglycemia.

Urinary ketones should be monitored in a known case of T1DM in case of an infection or illness, stressful situation like surgery, inadequate insulin levels—due to missed dose and hypoglycemia. Parents should be informed regarding the monitoring of urinary ketones by means of a urinary ketostix in setting of fever with tiredness and loss of appetite, nausea and vomiting, rapid respiration, abdominal pain and drowsiness or loss of consciousness. If blood sugar is consistently >250 mg/dl, ketone body measurement is a must even if the child is asymptomatic.

Monitoring of a Child with T1DM: Long Term Complications

A child with diabetes should be under a regular follow-up. A complete physical examination should be performed at least twice a year and includes the following:

- Height and weight: Monitor for normal growth and weight gain. Poor growth may indicate poor glycemic control or presence of co-morbidities like hypothyroidism, celiac disease or an infection.
- Blood pressure: Screen for hypertension
- Pubertal assessment: Because puberty increases insulin resistance, increased insulin requirement can be anticipated by identifying early signs of puberty. Poor

glycemic control is often associated with delay in onset of puberty.

- Thyroid: Check for thyroid enlargement to screen for autoimmune hypothyroidism, a condition frequently associated with type 1 diabetes.
- Skin: Examination of injection sites for evidences of lipo-hypertrophy or atrophy that can alter insulin absorption rates.
- Eyes: All patients should have regularly scheduled dilated fundoscopic examinations. Examination without dilation of the pupils is of little value as a screen for retinopathy because diabetic retinopathy usually starts at the periphery of the retina. Annual ophthalmologic examination is needed for children ≥ 10 years of age and 3- to 5-year duration of diabetes to screen for retinopathy.
- Extremities: As the disease duration increases, extremity examination for evidence of limited joint mobility (sclerodactyly, joint or finger stiffness) or peripheral neuropathy (feet) especially the vibratory sense as it is a marker of early neuropathy. Annual foot examination should be done to evaluate foot health and screen for neuropathy in children ≥ 10 years of age.

Laboratory Parameters

- A1C, every three months
- Annual screening for microalbuminuria for children ≥ 10 years of age and five-year duration of diabetes — Screen for nephropathy
- Celiac disease screening (anti-TTG [tissue transglutaminase]) at diagnosis and every other year
- Lipid profile: Screen for dyslipidemia once puberty begins, and if normal, repeat the screen every five years. If abnormal, screen yearly as recommended in the ADA guidelines. However, children who are in poor glycemic control may manifest new lipid abnormalities. Therefore, it is important to rescreen at the time of a prolonged episode of poor glycemic control.
- Thyroid function testing: Screening for autoimmune hypothyroidism every one or two years or if features of hypothyroidism or if an enlarged thyroid are evident.

RECENT ADVANCES

Alternative Routes of Insulin Delivery

There is resistance to the use of insulin by patients because of its need to be injected subcutaneously and concerns

regarding potential effects on lifestyle, risk of hypoglycemia, and perception that people treated with insulin are “sicker”. Alternative, less invasive options for insulin therapy are therefore desirable. Oral administration has not been found to be effective as it results in loss of bio-potency due to breakdown in the stomach. Other routes of administration have been explored, including transdermal, buccal, nasal, and inhaled delivery. An inhaled form of rapid-acting insulin was available for a short time, offering the first new insulin delivery option (Exubera) since insulin’s discovery in the 1920s. However, it involved use of a bulky device to dispense insulin as a dry-powdered formulation with little dosing flexibility and a variable insulin delivery. Thus, it has been withdrawn since 2007. A different inhaled insulin formulation, which appears to have a more convenient delivery system and greater dosing flexibility, is in development. This formulation (Technosphere) contains recombinant human insulin dissolved with powder (fumaryl diketopiperazine). Once inhaled, the insulin is rapidly absorbed upon contact with the lung surface. Both the insulin and the powder are nearly completely cleared from the lungs of healthy individuals within 12 hours of inhalation; only 0.3 percent of the insulin and 0.4 percent of the powder concentration remain after 12 hours. In contrast, with the exubera formulation, about 8 to 9 percent of the inhaled dose remained in the lungs 12 hours later.

Continuous Glucose Monitoring

Subcutaneous glucose sensors that continuously measure interstitial fluid glucose levels are now available and approved for use in children. The currently available continuous monitoring systems are expensive and relatively inaccurate in the lower (<70 mg/dl) glucose range thus limiting their usefulness. The first generation of continuous glucose monitors provided blood glucose data only after downloading by the physician, and did not provide real-time feedback to the patient. This type of device did not appear to improve glycemic control in children, although there was some educational value in detecting patterns of blood glucose fluctuations and episodes of hypoglycemia during periods of sleep. The newer generation of continuous monitors report blood glucose levels to the patient in real time. Short-term studies indicate clinical benefits of these devices as compared to conventional methods of blood glucose monitoring, when used by motivated and well-informed patients. Studies are currently evaluating the efficacy of a fully automated closed loop system of insulin delivery based on continuous glucose sensing.

Immunomodulators

The increase in understanding of the pathogenesis of type 1 diabetes mellitus has made it possible to consider interventions to slow the autoimmune disease process in an attempt to delay or even prevent the onset of hyperglycemia. Multiple immunomodulators have been tried with variable

response. Azathioprine, mycophenolate mofetil alone or in combination with daclizumab failed to show significant remission beyond 1 to 2 years. Cyclosporine was studied in large-scale trials of recent diabetics in Canada and France. It was found that remissions were twice as common in the cyclosporine-treated patients, as compared with placebo. However, almost all patients required insulin again within three years. An analysis of subjects recruited into the Canadian-European cyclosporine trial showed that subjects who were IA-2 negative at entry to the trial were more likely to respond to cyclosporine (with a decrease in insulin requirements and an increase in C-peptide secretion) than IA-2 positive subjects. Immunotherapy with DAB486-IL-2, GAD65, Bacillus Calmette-Guerin (BCG), DiaPep277 have been tried with variable results. Anti-inflammatory drugs like TNF-alpha inhibitors, Etanercept and interferon alpha have all been tried with no results. Nicotinamide supplement was ineffective in the nicotinamide diabetes intervention trial (ENDIT) trial. A primary prevention trial of the effect of docosahexaenoic acid (an omega-3 fatty acid) on the natural history of type 1 diabetes is in progress. Another approach is based upon the possible immunogenicity of the complex dietary proteins found in cow’s milk and thereby avoiding cow’s milk.

SUMMARY

Optimal management of a child with diabetes is defined by the implementation of a care plan that maintains glucose control as near to normal as safely possible, balancing the risks of long-term sequelae and hypoglycemia. This requires comprehensive case management and intensive training of the parents. Diabetes education and self-management training by a pediatric diabetes multidisciplinary team provides the ideal setting to acquire the knowledge and skills needed for care. In the initial phase, the team teaches the family about the disease process and skills required for daily care (administering insulin, blood glucose monitoring, testing for urine ketones, and recognizing and treating hypoglycemia). The ability of the child to participate in self-management varies with the age, cognitive abilities, and emotional maturity of the child or adolescent. Intensive compared to conventional therapy improves glycemic control and decreases long-term complications of diabetes. Frequency of follow-up visits is tailored to the needs of the child and family. Follow-up visits monitor the child’s glycemic control and growth with appropriate readjustments to the management plan. On-going visits allow for continued family education and screening for complications of diabetes.

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Approach to Goiter in Children

Mohit Kehar

INTRODUCTION

A goiter is an enlargement of the thyroid gland. Persons with enlarged thyroids may have normal function of the gland (euthyroidism), thyroid deficiency (hypothyroidism), or overproduction of the hormones (hyperthyroidism).

Clinically goiter is defined as enlargement of the lobes greater than the terminal phalanx of the patient's thumb.

WHO CLASSIFICATION/GRADING

- 0: No goiter
- 1a: Palpable lobe
- 1b: Noticeable gland on neck hyperextension
- 2: Gland noticeable with neck in normal position
- 3: Visible gland at a distance of 10 m.

There have been various reports which showed the discrepancy of palpation and USG assessment in evaluation of goiter, palpation is relatively inaccurate for assessing the prevalence of goiter in mild iodine deficiency, thyroid volume measurement by ultrasound in children provides a useful tool for the assessment of goiter in mild iodine deficiency.

Formula for thyroid volume (formula of a rotation ellipsoid model): width \times length \times thickness \times 0.52 for each lobe. Table 1 gives the size of thyroid at various ages.

DIFFERENTIAL DIAGNOSIS OF GOITER

The enlargement of the thyroid is generally mediated by an increase in the pituitary-derived thyroid stimulating hormone (TSH) or in antibodies that bind to the TSH receptor, such as the thyroid stimulating immunoglobulin's (TSIs) found in Graves' disease. Inflammation or infiltration may cause diffuse, symmetrical enlargement, although the gland is usually asymmetric and nodular. The most common inflammatory process is autoimmune

thyroiditis.¹ More often following careful investigation no underlying cause can be identified for diffuse euthyroid enlargement often termed as simple colloid goiter. Table 2 gives the causes of thyroid enlargement.

Table 1: Thyroid volume according to age

Age (years)	Volume (ml) mean \pm SD
7	3.1 \pm 1.3
8	3.3 \pm 1.2
9	3.6 \pm 1.3
10	4.0 \pm 1.5
11	4.9 \pm 1.5
12	5.3 \pm 1.4
13	6.1 \pm 1.6
14	6.3 \pm 1.5

Table 2: Differential diagnosis

- Autoimmune thyroid disease
 - Chronic lymphocytic thyroiditis (Hashimoto's thyroiditis)
 - Graves' disease
- Colloid (simple) goiter
- Goitrogen exposure and drugs like lithium, etc.
- Dyshormonogenesis
- Infectious
 - Subacute (viral) thyroiditis
 - Chronic suppurative thyroiditis
- Anatomic abnormalities
 - Thyroglossal duct cyst
 - Hemigenesis of the thyroid
- Nodular goiter
 - Solitary nodule (adenoma, carcinoma, cyst)
 - Multinodular goiter secondary to autoimmune thyroid disease

CLINICAL AND INVESTIGATIVE EVALUATION OF PATIENT WITH GOITER

While evaluating a patient of goiter we should ask for family history of thyroid disease, consanguinity, geographical area of residence, exposure to irradiance, medication history, goitrogens, and in newborns history of maternal exposure to iodine or antithyroid drugs, symptoms suggestive of hyperthyroid or hypothyroid.

While examining a patient, general physical examination should be done, including vitals. We should look for features/signs suggestive of hypo/hyperthyroidism. The neck is then examined and thyroid is examined for nodularity, consistency, surface, and texture, signs of compression, lymphadenopathy, and bruits. A symmetric, diffuse enlarged gland needs an evaluation for hyperthyroidism and primary hypothyroidism. One should look for the scars, asymmetry and any neck swelling. Erythema overlying a tender swelling may be due to suppurative thyroiditis or infected thyroglossal cyst or brachial cleft cyst. Goiter due to dysmorphogenesis varies in size and tends to be softer in consistency with or without bruits. Disturbance in thyroid function and multinodularity usually excludes malignancy as opposed to a firm, irregular, painless single nodule.

In determining the cause of thyromegaly (Flow chart 1) the initial diagnostic evaluation should be limited to measurements of TSH and thyroid antibodies. The T4 level is required only if the TSH level is elevated. Free T4 measurement is preferred to the total T4 level because the former is not influenced by thyroid binding globulin levels and, therefore, better reflects the active thyroid hormone level. Thyroid antibody titers greater than 1:2000 or 10 mIU/L most likely indicate autoimmune thyroiditis.^{2,3}

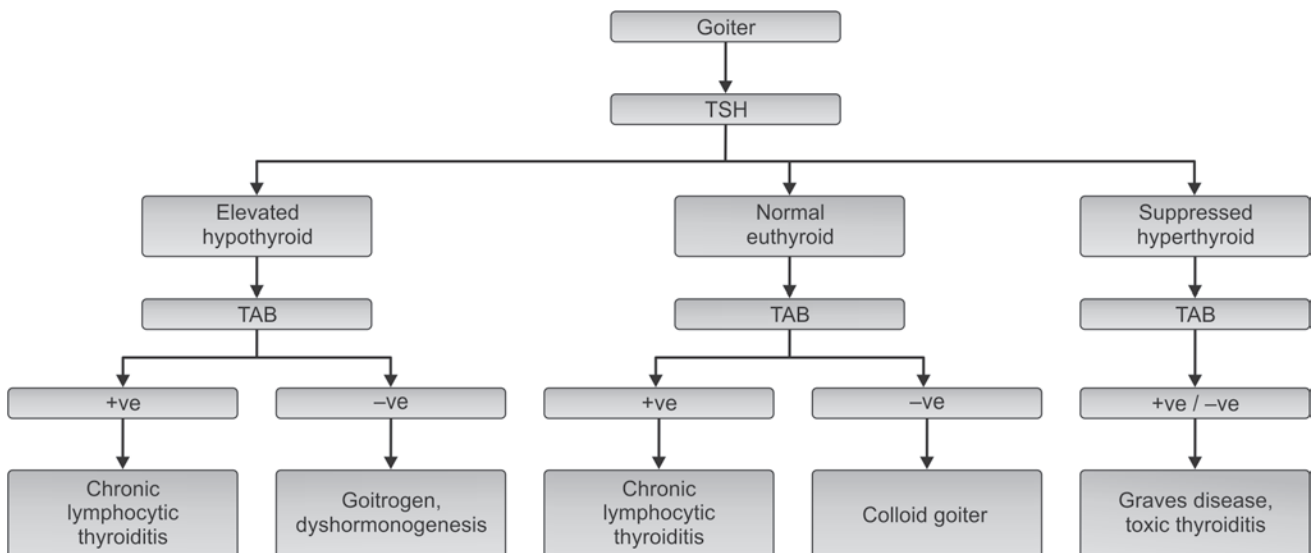
Lower levels may simply reflect a nonspecific inflammation of the thyroid gland. Imaging is only required if a solitary nodule is suspected.

GOITER AND HYPOTHYROIDISM

The most common cause of acquired hypothyroidism is chronic lymphocytic thyroiditis. Chronic lymphocytic thyroiditis (CLT), also known as Hashimoto's thyroiditis is uncommon in children younger than four years of age. The peak age of onset in the first-two decades of life is in early to midpuberty. The ratio is 2:1 in favor of females versus males; this ratio is less skewed than in adulthood when 90 percent of cases occur in females. Although there is no defined pattern of inheritance, a family history is reported in 30 percent of affected children. It is well established that the risk of CLT is higher in individuals with chromosomal abnormalities such as Turner syndrome, Klinefelter syndrome and Down syndrome. There is also an increase in association with other autoimmune diseases. The prevalence of thyroid autoantibodies in children and adolescents with type 1 diabetes has been reported to be as high as 20 to 40 percent, while abnormal thyroid function is reported in approximately 7 percent of these patients.

Autoimmune thyroid disease may be associated with a euthyroid state, hypothyroidism or hyperthyroidism. In the early stages, when examined the gland will be smooth and soft, progressing to a granular or pebbly texture, and then becoming firm and irregular. It has been seen that most children are euthyroid at diagnosis. Hypothyroidism will be present in 3 to 13 percent of patients, and they will show typical symptoms, 3 to 35 percent of patients have elevated TSH concentrations and normal T4 levels, a state termed subclinical or compensated hypothyroidism.

Flow chart 1: Most common causes of a goiter – negative (-ve); positive (+ve); thyroid antibodies (TAB); thyroid stimulating hormone (TSH)



Rarely, children may present with transient thyrotoxicosis with suppressed TSH, and elevated serum T3 and T4 levels, a condition known as toxic thyroiditis or hashitoxicosis.

An endemic goiter is the most common preventable cause of mental retardation. However, because of the routine addition of iodine to salt in the western world, it is not seen in that area. Goitrogen exposure should be considered in patients with a goitre and negative thyroid antibodies, and it will generally be evident from the patient's history. In addition to prescribed medications, it is important to ask about the use of over-the-counter preparations, such as iodide-containing expectorants and natural remedies. Dyshormonogenesis usually presents as congenital hypothyroidism, however, milder forms may present later as acquired hypothyroidism with goitre and negative thyroid antibodies. A family history should be sought because this is an autosomal recessive condition. While hypothyroidism may also occur if a patient has hypothalamic and pituitary lesions (i.e. tertiary and secondary hypothyroidism, respectively), a goitre is not a clinical feature of these cases.

Symptoms of Hypothyroidism

Deceleration of growth, goiter, which may be a presenting feature, typically is non tender and firm, with a rubbery consistency and a pebbly surface. Myxedematous changes of the skin, there will be constipation, cold intolerance, an increased need for sleep develop insidiously. Osseous maturation is delayed, adolescents typically have delayed puberty, whereas younger children may present with galactorrhea or pseudoprecocious puberty.

Treatment

The decision to treat with l-thyroxine is clear for overt hypothyroidism, but controversial for a euthyroid goiter or compensated hypothyroidism. In overt hypothyroid patients levothyroxine given orally is the treatment of choice, newborn require 10 µg/kg/24 hours and children with hypothyroidism require about 4 µg/kg/24 hours, and adults require only 2 µg/kg/24 hours.

For patients who are compensated the approach used is to monitor patients with mild elevations of TSH level (less than 10 mIU/L) six months after the diagnosis is confirmed and then annually. Repeat levels of TSH are often normal. In those patients with a confirmed TSH level that is greater than 10 mIU/L, treatment with thyroxine is usually continued until growth is complete. Thyroid status is then reassessed to determine the need for ongoing treatment. Patients with a TSH that is greater than 20 mIU/L have a high rate of progression to hypothyroidism, and are treated with thyroxine.⁴

SIMPLE GOITER (COLLOID GOITER)

The most common causes of euthyroid goiter in childhood are CLT and a colloid goiter. Thyroid enlargement that is not caused by inflammatory, infectious or neoplastic causes is termed a colloid goiter, also. Histological findings seen in cases of colloid goiter include enlarged thyroid follicles filled with abundant colloid. The cause remains controversial. Although TSH is the principal growth-stimulating factor for the thyroid, TSH levels are normal in patients with colloid goiter. The condition predominates in girls and has a peak incidence before and during the pubertal years. The goiter may be small or large. It is firm in half the patients and occasionally is asymmetric or nodular. Levels of TSH are normal or low, scintiscans are normal, and thyroid antibodies are absent. The natural history is for spontaneous reduction with time, and treatment with thyroxine is not indicated.

GOITER AND HYPERTHYROIDISM

Hyperthyroidism results from excessive secretion of thyroid hormone and during childhood is mainly due to Graves' disease. Other causes are rare and should be suspected only when there is an atypical presentation.⁵ As seen with other thyroid disorders females are predominantly affected and the ratio of affected females versus males is less pronounced than in adulthood. A family history of autoimmune thyroid disease is commonly present.

Other rare causes of hyperthyroidism that have been observed in children include toxic uninodular goiter (Plummer disease), hyperfunctioning thyroid carcinoma, thyrotoxicosis factitia, subacute thyroiditis, and acute suppurative thyroiditis. In infants who are born to mothers with Graves' disease, hyperthyroidism is almost always a transitory phenomenon; classic Graves' disease during the neonatal period is usually rare.

Graves' disease is an autoimmune disorder in which there is production of thyroid-stimulating immunoglobulin (TSI) which results in diffuse toxic goiter. About 5 percent of all patients with hyperthyroidism are younger than 15 years of age and the peak incidence in these children occurs during adolescence.

Manifestations of Hyperthyroidism

Symptoms include nervousness, irritability, heat intolerance, excessive sweating, palpitations, fatigue and weakness, weight loss with increased appetite, frequent bowel movements, and oligomenorrhea. Patients are anxious, restless, and fidgety. Skin is warm and moist, and fingernails may separate from the nailbed (Plummer's nails). Eyelid retraction and lid lag may be present. Cardiovascular findings include tachycardia, systolic hypertension, systolic murmur, and atrial fibrillation. A fine tremor,

hyperreflexia, and proximal muscle weakness may also be present. Long-standing thyrotoxicosis may lead to osteopenia. In Graves' disease, the thyroid is usually diffusely enlarged to two to three times its normal size, and a bruit or thrill may be present. Infiltrative ophthalmopathy (with variable degrees of proptosis, periorbital swelling, and ophthalmoplegia) and dermopathy (pretibial myxedema) may also be found. In subacute thyroiditis, the thyroid is exquisitely tender and enlarged with referred pain to the jaw or ear, and sometimes accompanied by fever and preceded by an upper respiratory tract infection.

Evaluation

The diagnosis of Graves' disease is made by finding a suppressed TSH level with elevated T4 and/or T3 levels. When the patient's clinical presentation is mild, free T4 levels may be high normal, with an inappropriately suppressed TSH, in which case T3 levels should be measured. Antithyroglobulin antibodies and thyroid peroxidase antibody levels may be positive but they are not pathogenic. TSI, if measured, will be positive.

Hashitoxicosis can present similar to Graves disease. However, hashitoxicosis is a self-limiting condition and lacks ophthalmopathy. It is caused by autoimmune damage to follicular cells, resulting in the release of preformed T4 and T3 into circulation. Transient or permanent hypothyroidism may follow a period of hyperthyroidism. If the hyperthyroidism lasts more than a few weeks, the diagnosis of hashitoxicosis is usually unlikely.

Subacute thyroiditis is generally caused by viral infections and is generally not seen in pediatric age group. Children with subacute thyroiditis have an enlarged, tender thyroid, malaise, fatigue and weakness that develop after an upper respiratory tract infection. There are two distinct phases in the progression. During the acute stage (two to six weeks), preformed T4 and T3 are released from the inflamed thyroid follicles, resulting in hyperthyroidism with or without clinical symptoms. For the next two to seven months, the damaged thyroid is less effective at synthesizing hormone, resulting in low to normal T3 and T4 concentrations with a compensatory elevation of TSH. Nearly all patients recover from hypothyroidism.

Autonomously hyperfunctioning adenomas secrete T3 and cause mild hyperthyroidism. The thyroid is usually of small or normal size with a palpable nodule. Symptoms of hyperthyroidism generally occur when the nodule is greater than 2.5 cm in diameter. The nodules are rarely malignant, and surgery is curative in such cases.

Treatment

Most centers recommend initial medical therapy using antithyroid drugs rather than radioiodine or subtotal

thyroidectomy, although radioiodine is gaining acceptance as initial treatment in children >10 years of age. The 2 antithyroid drugs in widest use are propylthiouracil (PTU) and methimazole, the initial dosage of PTU is 5 to 10 mg/kg/24 hours given 3 times daily, and that of methimazole is 0.25 to 1.0 mg/kg/24 hours given once or twice daily. A β -adrenergic blocking agent like propranolol (0.5–2.0 mg/kg/24 hours po, given 3 times daily) supplemented to antithyroid drugs in the management of severely toxic patients. Surgery or radioiodine treatment is indicated when adequate cooperation for medical management is not possible, when adequate trial of medical management has failed to result in permanent remission, or when severe side effects preclude further use of antithyroid drugs. The eye changes remit gradually; severe ophthalmopathy may require treatment with high-dose prednisone, orbital radiotherapy, or orbital decompression surgery.

NODULAR GOITER

Thyroid nodules are relatively common in adolescents these nodules are usually asymptomatic and often discovered incidentally, but they raise the fear of cancer. A multinodular goiter is almost invariably caused by Hashimoto's thyroiditis and it carries a good prognosis. The asymptomatic, solitary thyroid nodule is a thyroid adenoma, thyroid carcinoma or a thyroid cyst. Thyroid carcinoma occurs in approximately one per one million persons/year in the first-two decades of life.⁶

A large-sized nodule (more than 4 cm) which is rapidly growing has a hard texture with fixation to adjacent structures, associated with regional lymphadenopathy and hoarseness or dysphagia are suspicious clinical features, increasing the probability of malignancy.

Investigation of a solitary nodule should begin with thyroid function tests and thyroid antibodies. Thyroid cancer is unlikely in the presence of hypothyroidism, hyperthyroidism or autoimmune thyroiditis.⁷ The first line investigation is thyroid ultrasound. It will identify other cervical masses that can be confused with a thyroid nodule, such as a thyroglossal duct cyst, and determine whether the nodule is cystic, solid or mixed. If a purely cystic thyroid nodule is identified, no further investigations are required and the patient may be followed conservatively. If, however, the lesion is solid or of mixed density, then radionuclide scanning (^{99m}Tc-pertechnetate, ¹²³I or ¹³¹I) is indicated to differentiate a hyperfunctioning (hot) from a hypofunctioning (cold) nodule. A hyperfunctioning nodule is, most likely, a benign hyperfunctioning adenoma. A cold nodule in a pediatric patient has a more likelihood of malignancy than in adults with cold nodule.

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Menstrual Problems in Adolescents

Harsha Khullar

Menarche is the first menstrual period in life. Average age in western world is 12.8 years for white and 12.6 years for black adolescents (Mac Mohan B). It may occur anywhere between 10 and 16 years. The peak age is 13 years in India with mean age of 14 years.

Menstruation is the cyclic physiologic shedding of the endometrium due to action of hormones in the presence of intact hypothalamus-pituitary-ovarian axis.

Three very important components for it to occur are:-

- Endometrium must respond to the hormones, i.e. estrogen and progesterone.
- Outflow tract, i.e. passage should be patent.
- Normal genetic karyotype, i.e. 46 XX.

Any problem with the above stated can lead to menstrual problems.

Normal menstrual cycle is the cyclic bleeding with an average rhythm of 28 ± 7 days with 4 to 6 days of bleeding.

Normal interval for menstruation is 21 to 45 days with little cycle to cycle variation in adults (Beach et al). Adolescents show more variations in cycle length than do adults and have a normal duration of flow of 3 to 7 days.

Abnormal bleeding in adolescents is a common problem and a difficult situation for a gynecologist to deal with. Almost 50% of adolescent girls visit to gynecologist with abnormal bleeding.

Various menstrual disturbances terminology is as follows:

- Amenorrhea
- Oligomenorrhea
- Polymenorrhea
- Menorrhagia
- Menometrorrhagia
- Hypomenorrhea
- Intermenstrual bleeding

Amenorrhea is the absence of menstruation. It may be:

- Physiological or
- Pathological

PHYSIOLOGICAL AMENORRHEA

Prevails prior to puberty, during pregnancy and lactation and post menopause.

Pathological amenorrhea may be due to:

- Systemic disease
- Endocrinopathies
- Hypothalamo-pituitary-ovarian-uterine axis disturbance
- Psychological factors
- Drug usage
- Genetic factors

Amenorrhea may be:

- Primary
- Secondary

Primary amenorrhea is the failure of onset of menses beyond 16 years of age in the presence of secondary sexual characteristics development.

Various causes of primary amenorrhea can be grouped into 5 levels: (Speroff)

Level I—Extrinsic to hypothalamo-ovarian axis. These include:

- Systemic diseases
- Thyroid and adrenal disorders
- Physiological
- Pregnancy and lactation

Level II—Hypothalamic

- Congenital: Kallman's syndrome
- Acquired:
 - Pituitary stalk disconnection syndrome
 - Excessive weight loss
 - Excessive weight gain
 - Craniopharyngioma
 - Cranial radiotherapy

Level III—Pituitary:

- Tumors

- Prolactinomas
- Non-functional tumors
- Infection: Tuberculosis
- Radiotherapy, surgery

Level IV–Ovarian

- Polycystic ovarian syndrome
- Premature menopause (ovarian failure)
- Ovarian agenesis, dysgenesis (Turner syndrome)
- Chemotherapy/Radiotherapy/Surgery

Level V–Uterovaginal

- Uterus agenesis
- Testicular feminisation
- Imperforate hymen
- Radiotherapy

Secondary Amenorrhea: is the absence of a period for more than 6 months.

To evaluate a case of amenorrhea:

- Establish presence of secondary sex characters
- Exclude anatomical causes and chromosomal cause
- Look for signs of virilization and hirsutism
- Calculate BMI
- Local examination to see for imperforate hymen.
- Ultrasound to establish the presence or absence of uterus

In the absence of secondary sex characters development the clinician should start investigating the patient after the mean age of menarche, i.e. 14 years but the investigations may be delayed to 16 years in their presence in case of primary amenorrhea.

Baseline investigations include:

- FSH, LH,
 - Thyroid function test and
 - Serum prolactin,
 - Antimüllerian hormone for ovarian reserve.
- Progesterone challenge test to evaluate the level of endogenous estrogen and the integrity of outflow tract.
- Positive bleed: confirms a functional outflow tract
- No bleed suggests either outflow obstruction or absent estrogen effect on the endometrium.
- Serum prolactin: If high, MRI brain should be done to rule out pituitary tumor.
 - Gonadotropic hormones, if normal or low- hypothalamus amenorrhea.
 - High levels of gonadotropin indicate primary ovarian failure.

MANAGEMENT OF PRIMARY AMENORRHEA**Imperforate Hymen**

Patient may present with cyclical abdominal pain, sometimes urinary retention due to vaginal distension (hematocolpos).

Examination reveals a palpable suprapubic mass. Vulval examination reveals a blue colored membrane at vaginal opening.

It can be managed by a cruciate incision of the membrane under general anesthesia.

It should be a slow decompression.

Absence of Uterus and Vagina

Complete androgen-insensitivity syndrome is an X linked disorder where it is a phenotypically female with well developed breasts and external genitalia with genetically male XY karyotype. In such cases testes are found in the inguinal canal or abdomen. The testes should be removed because of the risks of malignancy.

Tuberculosis has to be ruled out. The incidence of tuberculosis with primary amenorrhoea is 3 to 4 percent.

Oligomenorrhea/Hypomenorrhea

In this the pattern of menstrual cycle extends to cycle length exceeding 35 days. It is compatible with normal reproductive capacity. The causes are similar to that of amenorrhea, genital tuberculosis and polycystic ovarian disease.

Hypomenorrhea means scanty menses with regular cycles. The main causes include causes of oligomenorrhea, genital tuberculosis, Asherman's syndrome (uterine synechiae)

Polymenorrhea/Epimenorrhea

In this the cycles are short (21 days or less) with heavy bleeding. The cause of the ovarian overactivity seems to be the result of disturbed endocrine axis.

Menorrhagia

It is the excessive bleeding with regular cycles.

Metrorrhagia

Irregularly timed episodes of bleeding superimposed on normal cyclical bleeding.

Menometrorrhagia

Excessive prolonged bleeding that occurs at irregularly timed and frequent intervals.

Intermenstrual Bleeding

It is the bleeding occurring in between otherwise normal menstrual cycles.

Menstrual disturbances in adolescents whether actual or perceived are mainly:

- Dysmenorrhea
- Irregular menses
- Excessive menstrual bleeding

Dysmenorrhea

The most frequent complaint in adolescent girls is dysmenorrhea. It is classified as:

- Primary or
- Secondary.

Primary Dysmenorrhea

It starts on the first day of the period and lasts for 12 to 24 hours. It only occurs in ovulatory cycles. The first menses are usually anovulatory. It usually does not present until ovulation has been established.

Secondary Dysmenorrhea

It usually starts before menses and lasts till the bleeding lasts. It is predictive of uterine or pelvic pathology like uterine fibroids, endometriosis, or pelvic adhesions.

Adolescents Usually have Primary Dysmenorrhea

Cause of dysmenorrhea in adolescents:

- Five to ten percent of adolescents miss school due to this
- It is thought to be caused by increased prostaglandin synthesis
- Usually there is family history, i.e. her mother or sister might have suffered from it. More than 20 percent of patients with dysmenorrhea report that their mothers or sisters also had similar problems.

MANAGEMENT

- Complete history
- Differentiate primary from secondary dysmenorrhea
- Prostaglandin synthetase inhibitors are used as pain killers.
- Symptomatic relief is reported by 70 percent of patients with PG synthetase inhibitors (mefenemic acid, naproxen sodium when started premenstrually).
- In girls who need contraception or those not responding to analgesics combined oral contraceptive pills provide effective pain relief.
- Study by Robinson shows that adolescents who improve symptomatically with OCs are eight times more likely to continue treatment.
- If there is no improvement further investigations in the form of ultrasound, laparoscopy/hysteroscopy are performed to rule out any pathology.

Irregular Menstrual Cycles

- Forty-five percent of adolescents do not ovulate for 1 to 2 years after menarche. Hence, it is not surprising that irregular or infrequent cycles are a common occurrence in this age group.
- Lack of regular menstruation is a common cause of concern especially for the mothers of girls at this age.
- It is very important to reassure the patient and her mother, that this is a self-limiting problem.
- If previous cycles were regular with infrequent cycles now, further assessment is necessary.

In patients with regular periods, with polymenorrhea, the most common reason is suppression of hypothalamic or pituitary function caused by emotional stress. Acute

weight loss and excessive exercise can also lead to polymenorrhea, oligomenorrhea or amenorrhea. Anorexia nervosa is another cause for the same.

- Polycystic ovaries can cause oligomenorrhea. It can be diagnosed by LH/FSH ratio, androgen levels and classic ovarian ultrasound picture.
- Androgen producing ovarian tumor can cause amenorrhea with virilizing changes.
- Rarely adrenal tumors can cause amenorrhea.

Clinical assessment and investigation approach to these patients depend on the most likely underlying problem.

Cycle regularity can be restored with combined estrogen-progesterone preparations.

Polymenorrhea in adolescents is usually caused by luteal phase dysfunction. These patients respond well to either progestogen treatment in the luteal phase or combined estrogen progestogen preparation.

Assessment of any coagulation disorder or blood dyscrasias should also be included in the management of patients with polymenorrhea.

Puberty Menorrhagia

Puberty menorrhagia is defined as bleeding occurring between menarche and 19 years.

There is immaturity of the hypothalamus and inadequate positive feedback resulting in excess levels of estrogen. Approximately 20 percent of adolescents have an underlying endocrine or some other disorder which needs further investigations.

During puberty, maturation of the hypothalamus-pituitary-ovarian-axis is characterized by an increase in the frequency and amplitude of pulsatile GnRH, which initiates and regulates secretions of pituitary gonadotropins.

During pre pubertal years, LH is secreted primarily at night in an episodic fashion. With progression to puberty, LH peaks increase in pattern similar to that seen at night. The timing of these LH pulses is crucial in establishing normal ovulatory cycles. Increase in basal LH as well as immature timing of pulses result in anovulatory cycles. These cycles are characterized by levels of LH and FSH secretion that are sufficient to induce follicular development and estrogen production but inadequate to induce follicular maturation and ovulation. Thus unopposed estrogen stimulates endometrial growth. This ultimately outgrows the blood supply and architectural support, resulting in partial breakdown and shedding in an irregular manner.

Equal amounts of PGF2 α (vasoconstrictor and weak platelet aggregator) and PGE2 (vasodilator with weak platelet antiaggregatory effect) are synthesized in the endometrium in proliferative phase whereas levels of PGF2 α progressively increase during luteal phase under the influence of estradiol and progesterone. During normal menstruation, ratio of PGF2 α : PGE2 is 2:1, i.e. the vasoconstrictor effect is more than vasodilator effect.

During anovulatory cycle there is lack of progesterone resulting in decreased PGF 2α and PGE 2 ratio, i.e. vasodilator effect is more than vasoconstrictor effect. This results in increased blood loss and painless periods.

In a study by Sanjay Rao et al 80 percent of cases of puberty menorrhagia, the cause was anovulatory.

Simultaneously the patient with puberty menorrhagia should be evaluated for hematological status to rule out blood dyscrasias. Classens and coworkers have reported that 19 percent of adolescents with menorrhagia requiring hospital admission suffered from coagulation disorder. Various hematological disorders leading to heavy periods are:

- Idiopathic thrombocytopenia purpura
- Von Willebrand's disease
- Leukemia
- Platelet dysfunction like Glanzmann's thrombasthenia.

Investigations

- Rule out pregnancy by urine pregnancy test
- Complete blood count with peripheral smear
- Coagulation profile
- Blood group and Rh
- Thyroid function tests
- Hormonal assays (LH, FSH, Prolactin)
- Ultrasound whole abdomen and pelvis
- X-ray chest

Management of Puberty Menorrhagia

- Good history
- Physical examination
- Rule out pregnancy, thyroid disease, hypoprolactinemia and coagulation defects
- Young girls should be advised to maintain menstrual diary referring to frequency and heaviness of her periods.
- If the periods do fall within normal limits, reassure the patient.
- If periods are heavy with regular cycles PG synthetase inhibitors such as mefenamic acid or tranexamic acid can be advised during the days of heavy flow.
- If periods are irregular, hormone treatment is advised. Norethisterone or dydrogesterone 5 mg thrice daily from 15th to 25th day of period may be advised.
- In case of heavy bleeding intravenous conjugated equine estrogen is effective. It stimulates fibrinogen production factors V and IX and platelet aggregation is also stimulated.

Estrogen therapy yields very good results and brings heavy bleeding under prompt control but it is not recommended due to its high dosage and associated side effects.

- The choice of treatment is progestogens and oral contraceptives. OC pills are of use due to its ease of use and ability to regulate the cycle.
- Oral medroxyprogesterone acetate 60 to 120 mg oral followed by 20 mg/day for 10 days
- Mirena (progesterone intrauterine device) controls bleeding in resistant cases by thinning endometrium. It cannot be used in virgin girls.
- Desmopressin (synthetic analog of arginine vasopressin, IV or nasal spray 1.5 mg/ml is administered in von Willebrand's disease)
- In rare cases of arteriovenous aneurysms uterine artery embolization has been reported.
- The use of GnRh analog is controversial. These may be used in patients with hematological disorders and when coagulopathy is predictable as in patients undergoing chemotherapy and bone marrow transplantation.
- Danazol is contraindicated in young girls as it may cause hirsutism.
- If young girl fails to respond to medical therapy endometrial curettage is done to rule out genital tuberculosis.
- Simultaneously oral iron should be prescribed to control anemia.

CONCLUSION

- The management of menstrual disorders in adolescents begins with the explanation of the nature of the problem and reassurance to patient and her family.
- Hormonal treatment is helpful in patients with recurrent problem or if patient is anemic. Progestogens are usually effective but estrogens can be added in cases with breakthrough bleeding.
- Progestogens therapy alone can be used as it prevents endometrial hyperplasia. Combined estrogen progestogen therapy can also be used. Estrogen alone should not be used as it stimulates endometrial stimulation.
- In adolescents who do not respond to medical therapy occasional diagnostic curettage may be needed to rule out endometrial hyperplasia. In patients who become anemic and have repeated problem, regular hematological investigations should be done to rule out blood dyscrasias.

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Section 9

Nutrition

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Fetal Origin of Adult Disease

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Recent research has suggested that impaired intrauterine growth and development are responsible for several of the major diseases of later life, including coronary heart disease, hypertension, and type 2 diabetes. It has been proposed that alterations in fetal nutrition and endocrine status result in developmental adaptations with consequent changes, sometimes permanent, in the structure, physiology, and metabolism of the individual leading to cardiovascular, metabolic, and endocrine disease in adult life.¹ The process whereby a stimulus or insult at a sensitive or critical period of development has long-term effects is termed programming.²

The initial evidence of the existence of this phenomenon of fetal programming came from animal studies, which showed that alterations in maternal nutrition can have long-term effects on the offspring that are relevant to human cardiovascular disease. For example, feeding pregnant rats a low-protein diet results in lifelong elevation of blood pressure in the offspring.³ Other similar experiments showed notable long-term effects of alterations in maternal nutrition, which included changes in cholesterol metabolism, insulin secretion, and renal development.⁴ The fetal hypothalamus has been implicated as the key site that is programmed by transient changes in prenatal endocrine status.⁴

Fetal Growth and Coronary Heart Disease

At the start of the twentieth century, coronary heart disease became the leading cause of mortality in the Western countries. In some of these countries, the steep rise was followed by an unexplained fall over recent decades that could not be accounted for by changes in adult lifestyle. Simultaneously, the incidence of coronary heart disease has started rising in other parts of the world like China, India, and Eastern Europe, which are not as prosperous and have lower incomes and different lifestyles as

compared to the Western countries. Combined with the limited ability of adult lifestyle risk factors to predict coronary heart disease, this paradox led to the hypothesis that adverse influences in early life might play an important role.

Supportive evidence came from the study by Rose et al⁵ which showed that siblings of patients with coronary heart disease had stillbirth and infant mortality rates that were twice as high as those of control subjects. This led him to conclude that “ischemic heart disease tends to occur in individuals who come from a constitutionally weaker stock”.⁵ Epidemiologic evidence was provided by Forsdahl,⁶ showing that past infant mortality correlated with later arteriosclerotic heart disease in the 20 counties of Norway. These studies seemed to suggest that a poor standard of living in childhood and adolescence was a risk factor for heart disease. Geographic comparisons in England and Wales led to an association between low birth-weight and markedly elevated coronary heart disease death rates.⁷ This led to the postulation of the hypothesis that low-birth-weight babies who survived infancy and childhood might be at increased risk of coronary heart disease as adults.

This hypothesis was then supported by a number of studies. A follow-up study of 15726 men and women born in Hertfordshire, United Kingdom, showed for the first time that those who had low birth weights had relatively high death rates from coronary heart disease in adult life.⁸ Another study, of 1586 men born in Sheffield during 1907–1925, showed the importance of intrauterine growth retardation in comparison to prematurity in determining the increased risk of the disease.⁹ Findings from UK have been replicated in a number of trials all over the world including India.¹⁰ This has led to wide acceptance that low rates of fetal growth are associated with coronary heart disease in later life.

Subsequent studies have found that a wide range of organs and systems may be programmed by the intrauterine environment. These findings are in keeping with the results of experimental studies in animals and suggest that programming reflects a general principle of developmental biology.

High Blood Pressure and Hypertension

A systematic review of 34 studies found a strong association between low birth weight and high blood pressure in prepubertal children and adults.¹¹ Similarly to coronary heart disease, high blood pressure is found in people who were small for gestational age rather than those born prematurely.⁴ Also individuals who were disproportionate (thin or short) at birth also tended to have high blood pressure and a greater risk of hypertension in adult life.⁴

Critics of the hypothesis of 'fetal programming' have often argued that it is the persistence of adverse environmental influences that produces the effects attributed to programming *in utero*. There is, however, little evidence to support this argument. Rather, associations between birth weight and adult blood pressure, for example, were found in each social group and are independent of influences such as smoking, alcohol intake, and obesity in adult life.^{1,4}

Type 2 Diabetes and Insulin Resistance

An association between low birth weight and altered glucose metabolism has been reported in a number of studies.^{4,12-18} The prevalence of type 2 diabetes and impaired glucose tolerance was found to fall progressively between those who were small and those who were large at birth. As for high blood pressure, the associations between birth weight and later glucose tolerance are independent of adult lifestyle influences.¹ Adult obesity does, however, add to the intrauterine effects, such that the highest prevalence of type 2 diabetes and impaired glucose tolerance is seen in people who were small at birth but obese as adults.¹⁸

The mechanism of association between poor intrauterine growth and impaired glucose tolerance may be due to reduction in the number of pancreatic B-cells and a diminished capacity to make insulin.¹⁹ There is stronger evidence that people who were thin at birth tend to be insulin resistant in adulthood and to have metabolic changes suggestive of a bias toward fuel conservation.^{12,20,21} The glucose–insulin–insulin-like growth factor I axis has a key role in stimulating cell division in fetal life.²² Presence of adverse intrauterine environment leads to an adaptive conservation of glucose by reducing growth by inducing insulin resistance in specific tissues, including skeletal muscle. This results in diminished muscle mass and thinness at birth. In adult life, persistence of insulin resistance in skeletal muscle leads to a range of metabolic abnormalities and could underlie the strong association between low

birth weight and thinness at birth and the insulin resistance syndrome in adult life.

Cholesterol Metabolism and Blood Coagulation

Adult men and women whose fetal growth was restricted tended to have high serum concentrations of total cholesterol, LDL cholesterol, apolipoprotein B, fibrinogen, and factor VII.^{4,23} These abnormalities were more pronounced in those who had abnormal body proportions at birth and a short body in relation to their head size, i.e. asymmetric growth retardation. The abdominal circumference at birth seems to be highly predictive of high serum LDL-cholesterol and plasma fibrinogen concentrations in adult life.²³ It has been postulated that poor fetal nutrition and oxygenation leads to cranial redistribution of oxygenated blood away from the trunk to sustain brain metabolism. This impairs the growth of the liver and may underlie permanent abnormalities in the regulation of cholesterol and clotting factors.

The other tissues and organ systems for which there is evidence of programming in humans is summarized in Table 1.²⁴

The evidence cited so far has demonstrated that low birth weight is associated with subsequent development of adult diseases. However, it must be remembered that there are critical specific windows during development, often coincident with periods of rapid cell division, during which a stimulus or insult may have long-lasting consequences on tissue or organ function after birth. Birth

Table 1: Tissues and systems for which there is evidence of programming in humans²⁴

<i>Tissue or system</i>	<i>Examples of programming</i>
Cardiovascular system	Vascular compliance, endothelial function
Respiratory system	Lung volume
Endocrine system	Hypothalamic-pituitary-adrenal axis Glucose-insulin metabolism, growth hormone-IGF-1 axis
Reproductive system	Age at menarche, polycystic ovary syndrome
Central nervous system	Schizophrenia
Skeletal muscle	Insulin resistance, glycolysis during exercise
Bone	Bone mineral content
Kidney	Renin-angiotensin system
Liver	Cholesterol metabolism, fibrinogen and factor VII synthesis
Immune system	Thyroid autoantibodies, IgE concentrations

IGF-1: insulin-like growth factor 1; Ig: immunoglobulin.

weight is only one marker of an adverse fetal environment, and confining studies to this population only may lead to erroneous conclusions. There is emerging evidence that mitochondrial dysfunction and oxidative stress play an important role in the pathogenesis of the fetal origins of adult disease.

Low Birth Weight

It is apparent that the *in utero* environment in which a fetus grows and develops may have long-term effects on subsequent health and survival. Ravelli and colleagues²⁵ in their landmark study of 300,000 men showed that exposure to the Dutch famine of 1944 through 1945 during the first half of pregnancy resulted in significantly higher obesity rates at the age of 19 years. In the previous section we have cited subsequent studies which have demonstrated a relation between low birth weight and the later development of cardiovascular disease, impaired glucose tolerance and other diseases even after adjusting for lifestyle factors, such as smoking, physical activity, occupation, income, dietary habits, and childhood socioeconomic status, and occur independent of the current level of obesity or exercise.²⁶

High Birth Weight

Higher birth weight is associated with higher body mass index (BMI) and increased prevalence of obesity in adult life.²⁷ It is difficult to discern whether it is metabolic programming or establishment of lifestyle behaviors which is responsible for 'tracking' of weight through life. Recent data also suggest that rapid weight gain during infancy is associated with obesity later in childhood, perhaps reflecting a combination of genetically determined catch-up growth and postnatal environmental factors.²⁷

ROLE OF CATCH-UP GROWTH

Catch-up growth can refer to the first 6 to 12 months of life to as late as 2 years after birth and usually refers to realignment of one's genetic growth potential after intrauterine growth retardation (IUGR). The effects of impaired fetal growth are modified by subsequent growth. This led to the second part of the hypothesis proposed by Barker and Hales: the idea of the "thrifty phenotype." As an adaptation to undernutrition in fetal life permanent metabolic and endocrine changes occur which would be beneficial if nutrition remained scarce after birth. If nutrition becomes plentiful, however, these changes predispose to obesity and impaired glucose tolerance. The highest risk for the development of type 2 diabetes is among adults who were born small and became overweight during childhood.²⁸⁻³⁰ Insulin resistance is most prominent in Indian children and in Indian men and women who were born small for gestational age (SGA) but had a high fat mass between the ages of 2 and 12 years.^{28,29} Similar findings were reported

in 10-year-old children in the United Kingdom.³¹ It is likely that accelerated growth confers an additional risk to the growth-retarded fetus.

New Findings from Mechanistic Studies

The 'Barker hypothesis' is increasingly being accepted and has been expanded to other diseases like cognitive functional development, osteoporosis and allergies. The impact of environmental influences on adult disease risk has become more acceptable with elucidation of sound theoretical frameworks of evolutionary biology and epigenetic data that provides molecular mechanisms for the same.³² For instance, epigenetic studies in individuals exposed to the Dutch famine have found decreased methylation in of IGF2 gene.³³ Other investigators have similarly identified six more genes in growth, metabolic and cardiovascular disorders with altered methylation status in fetus exposed to *in utero* deprivation.³⁴ Other mechanisms attributable to nutritional programming of disease include alteration in the cell number/type, impaired HPA axis, impaired mitochondrial activity, free radical damage and altered endocrine and corticoid sensitivity.³⁵ The basic objective of fetal programming is to adjust to an adverse environment. However, if the environment differs in the postnatal period differs from that in the prenatal and early postnatal period it brings various diseases in its wake.

Caveats

These data suggest that low birth weight is associated with glucose intolerance, type 2 diabetes, and cardiovascular disease. The question remains as to whether these associations reflect fetal nutrition or other factors that contribute to birth weight and the observed glucose intolerance. Because of the retrospective nature of the cohort identification, many confounding variables were not always recorded, such as lifestyle, socioeconomic status, education, maternal age, parental build, birth order, obstetric complications, smoking, and maternal health. Maternal nutritional status, directly in the form of diet history or indirectly in the form of BMI, height, and pregnancy weight gain, were usually not recorded. Instead, birth anthropometric measures were used as proxies for presumed under nutrition in pregnancy.

To conclude, childhood onset of adult cardiovascular disease has become a significant public health problem that needs to be addressed globally and individually. Genetic-environment interactions are ubiquitous in human development. It remains to be seen whether better maternal nutrition decreases the incidence of cardiovascular disease in offspring. The final link, of course, will be at the molecular level. Although much progress has been made in the identification and treatment of adult cardiovascular disease, the mechanisms of obesity, hypertension,

atherosclerosis, and diabetes remain to be elucidated, and the changes that take place in an abnormal fetal environment remain poorly understood. The thrifty phenotype also is a paradigm that has stimulated animal as well as human research on fetal growth retardation; its neuroendocrine and metabolic effects; and the possible mechanism by which metabolism, body composition, and growth may be permanently affected. It was widely if not universally accepted by the congress as a model to explain the link between fetal growth retardation and later diseases. Of the existence of that link there is no doubt, and in the 21st century it may matter most in the Indian subcontinent. A recent review has dealt in depth the intrauterine environment that is dramatically impacted by the overall maternal health and the so called "fetal programming" that includes developmental disruption, immediate adaptation, or predictive adaptation which can lead to epigenetic changes affecting a specific organ or overall health.³⁶ Better understanding of the etiology of these disease states will bring with it enhanced preventive and targeted therapies.

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An Approach to Management of Rickets

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AN APPROACH TO MANAGEMENT OF RICKETS

Rickets is generally regarded as the vitamin D deficiency disease. The term rickets evolved from the old English word—wreck, meaning to twist. This twisting or bending of bones was known to physicians since centuries ago and it was gradually found to have more than one cause.¹

Rickets was rampant in north Europe and USA during the early years of the 20th century. Although public health measures have largely corrected this problem, many cases are still reported secondary to preventable nutritional vitamin D deficiency. It is currently a significant problem in developing countries with prevalence of >10 percent among children in Africa. UNICEF has estimated that up to 25 percent of children in China have some evidence of rickets.²

Normal bone growth and mineralization require adequate amount of calcium and phosphate, the two major constituents of the crystalline component of bone. Deficient mineralization can result in rickets and/or osteomalacia. Deficient mineralization at the growth plate causes rickets, whereas impaired mineralization of the bone matrix leads to osteomalacia. They both usually occur together as long as the growth plates are open; only osteomalacia occurs after the growth plates have fused.³

Mineralization defects are classified according to the predominant mineral deficiency. Calcipenic (hypocalcemic) rickets is primarily caused by the calcium deficiency and phosphopenic (hypophosphatemic) rickets is primarily caused by phosphate deficiency.

STAGES OF RICKETS

Clinical manifestations of rickets in children usually occur in the latter half of the first year or in the second year. Rickets is uncommon before the age of three months. It may occur in older children with malabsorption or other systemic disorders. The disease can be divided into three stages:⁴

Stage 1: Osteopenia and subclinical or overt hypocalcemia (usually transitory, and undocumented).

Stage 2: Rising levels of parathyroid hormone (PTH) causes calcium re-absorption from the bones and correction of hypocalcemia. Demineralization of collagen matrix leads to various bone changes and bone pain (mediated by the periosteal sensory pain fibers).

Stage 3: Bone changes becomes more severe and hypocalcemia once again becomes evident.

CLINICAL FEATURES

Rickets can be asymptomatic and is often detected as a chance clinical finding. Its symptoms can range from none to varying degrees of irritability, delay in gross motor development, and bone pain. Clinical findings are related to the involved skeletal sites (Fig. 1).

Head

- Anterior fontanel closure is delayed and may remain open after 18 months.
- Craniotabes (soft skull bones) and flattening of the posterior skull can be seen. Prominence of frontal bones and the major foramen can result in frontal bossing and a prominent sometimes square, forehead (caput quadratum).

Thorax

- *Rachitic rosary:* This consists of enlarged ends of the ribs, resembling beads. These are palpable and visible at the costochondral junction. As a result the sternum can become more prominent, leading to a pigeon breast or pectus carinatum appearance.
- *Harrison groove:* This is a semicircular linear depression in chest wall over the abdomen at the level of the insertion of the diaphragm. This occurs because pliability of ribs increases due to softening.

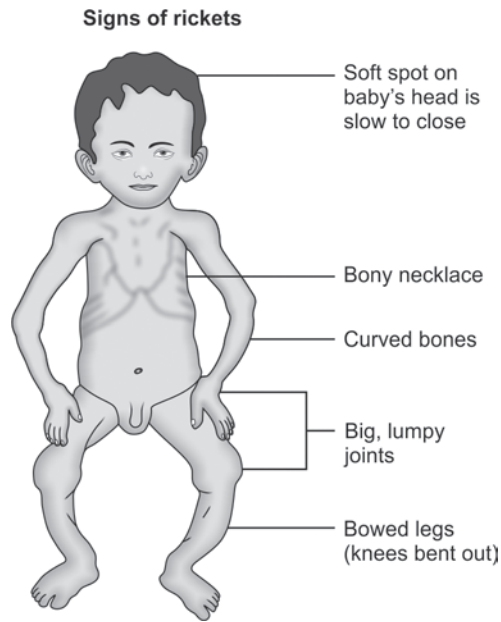


Fig. 1: Clinical features of rickets



Fig. 2: Radiological features of rickets

Spine

A mild to more pronounced scoliosis can be found.

Pelvis

A prominent promontary can be found and the antero-posterior diameter of the pelvis can shrink as a result of scoliosis. This may cause difficulty during child birth as it persists in girls.

Extremities

Arms

- Greenstick fractures due to concurrent osteomalacia.
- Thickening of wrist at the level of epiphysis if found clinically. However, this is not visible in X-ray, since the lesion consists of cartilage.

Legs

- Bowing of long bones (genu varum) is typical due to weight bearing.
- Anterior bowing of tibia (Saber-shin deformity) may occur.
- Development of knock-knees may occur due to displacement of growth plate due to active disease.
- Identical to the process in wrist, thickening at the level of ankle occurs leading to appearance like double malleoli.

Diagnose of Rickets

The diagnosis of rickets is based on clinical manifestation, characteristic radiological picture and biochemical findings. Biochemical findings are often positive early in course of rickets when radiological feature are not present.

Radiological Findings⁵ (Fig. 2)

The findings are due to, increased uncalcified osteoid in the immature skeleton. The changes of rickets are best visualized at the growth plate of rapidly growing bones. Thus, in the upper limb, the distal ulna is the site that best demonstrates the early signs of impaired mineralization. The metaphysis above and below the knees are the most useful sites in the lower extremities.

A 10 point radiographic scoring system was developed to aid in assessment of the severity of rickets on the basis of knee and wrist findings⁶ (Table 1).

Table 1: Radiological scoring of nutritional rickets⁶		
<i>Wrist</i>	<i>Score both radius and ulna separately</i>	<i>Score</i>
Grade-1	Widened growth plate. Irregular metaphyseal margins, but without concave cupping	1
Grade-2	Metaphyseal concavity with fraying of margins	2
	2 bones × 2 points = 4 points possible	
Knee	Score both femur and tibia separately. Multiply the scores in A by the multiplier in B to get the final score.	
A	Grading based on degree of lucency and widening of zone of provisional calcification.	
Grade-1	Grading based on degree of lucency and widening of zone of provisional calcification.	1
Grade-2	Partial lucency, smooth margin of metaphysis not visible.	2

Cont...

Grade-3	Complete lucency, epiphysis appears widely separated from distal metaphysic.	3
B	Multiplier	
	0.5 = <1 condyle or plateau; 1 = 2 condyle or plateau	
	2 bones × 1 point × 3 points = 6 points possible	
	Maximum 10 points are possible.	

Score the worst affected knee and wrist. See Figure 3. Adapted from reference.⁶

Types of Rickets

The most commonly encountered rickets is the one due to vitamin D deficiency. There may be various causes of vitamin D deficiency and rickets may not be due to vitamin D deficiency alone (Table 2).

Though this list is long, not all the causes are clinically important. Clinically useful causes are:

1. Vitamin D deficiency
2. Vitamin D dependent rickets type 1 (due to decreased 1 α hydroxylase)
3. Vitamin D dependent rickets type 2 (due to end organ resistance)

Table 2: The causes of rickets

S.No.	Category	Causes
1.	Vitamin D deficiency	Dietary deficiency Deficient endogenous synthesis
2.	Mal absorption of vitamin D	Small intestine disease Partial or total gastrectomy Hepatobiliary disease Chronic pancreatic insufficiency
3.	Disorders of vitamin D metabolism	Vitamin D dependent rickets types 1 and 2 Use of anticonvulsants Chronic renal failure
4.	Acidosis	Distal renal tubular acidosis (RTA) Chronic acetazolamide ingestion Chronic ammonium chloride ingestion
5.	Chronic renal failure	
6.	Phosphate depletion	Dietary-low phosphate ingestion Use of nonabsorbable antacids Tumor associated (oncogenic rickets)
7.	Generalized renal tubule disorders	Primary renal Associated with systemic metabolic disorders – Cystinosis – Glycogenosis – Lowe syndrome Systemic disorders with associated renal disease – Inborn errors (Wilson's disease, tyrosinemia) – Acquired-multiple myeloma – Intoxication-cadmium, lead
8.	Primary mineralization defects	Di-phosphonate treatment Fluoride treatment

Table 3: Biochemical parameters in different conditions causing rickets

Type	Vit. D deficient	Vit. D dependent Type-1	Vit. D dependent Type-2	X-linked hypophosphatemia	Hereditary hypophosphatemic rickets with hypercalciurea
Calcium	↓ or N	↓	↓	N	N
Phosphate	↓ or N	↓ or N	↓ or N	↓↓	↓↓
Alkaline phosphatase	↑	↑↑	↑↑	↑	↑
PTH	↑	↑	↑	N	↓ or N
25-(OH)D ₃	↓	N	N	N	N
1,25(OH) ₂ D ₃	↓ or N	↓↓	↑↑	↓ or N	↓
Urine calcium	↓ or N	↓	↓	↓	↑

↑, increased; ↓, decreased; N, normal. Adapted from Reference⁷

4. Vitamin D resistant rickets (X-linked hypophosphatemic rickets)
5. Renal rickets (Rickets with hyperphosphatemia).

Various conditions causing rickets have different combination of abnormalities in biochemical parameters as given in Table 3.

Management of Vitamin D Deficiency Rickets

Treatment of vitamin D deficiency rickets consists of the replacement of deficit plus adequate mineral intake. Two approaches have been used. One is Stross therapy, a method first devised in Europe in the 1930's to prevent rickets in infants and the others, consists of daily administration of high dose vitamin D. Stross therapy involves the single day administration of a large dose of vitamin D 3 lakh to 6 lakh IU given once or in two divided doses over 24 hours either orally or intramuscularly.⁸ Serum levels of 25(OH) D₃ and calcitriol begin to increase within hours. Radiological evidence of healing is visible in one week. If healing is not seen on X-ray plates of bones within 3-4 week, then the above dose is repeated. Cases who respond are further put on 400 units or 10 micrograms of vitamin D per day after the process of healing has started. Biochemically Ca and iP levels increase in serum by day 5 and PTH levels begin to decline. Alkaline phosphatase concentrations remain high for months. Rarely Stross therapy fails or the reaction is delayed, this appears to be related to the presence of intercurrent illness at the time

of administration. Hypercalcemia can occur if the treatment is repeated more than twice a year and has been reported in 34 percent of such case.^{9,10}

The alternative of Stross therapy is daily administration of oral vitamin D at a dose of 2000 to 4000 IU for 2 to 4 weeks followed by 400 IU daily. Radiological and biochemical response are slower by this method and care must be taken to monitor 25(OH) D₃ levels to prevent hypervitaminosis D. Daily therapy needs strict vigil on compliance and follow up for 2-4 months. This makes Stross therapy a preferred mode of treatment. It provides sufficient vitamin D to maintain 25-hydroxy D₃ levels for approximately 3 months.

Approach to a Case of Resistance to Vitamin D

Till the 2nd dose of vitamin D the management of rickets is straightforward, the problem arises when there is no response to the 2nd dose. Now, the cause of vitamin D resistance has to be searched. A basic approach is outlined in Flow chart 1.

Characteristic Features and Management of Vitamin D Resistant Variants of Rickets

Vitamin D Malabsorption

Vitamin D absorption is chylomicron dependent.¹¹ Children with gastrointestinal diseases that interfere with fat absorption and enterohepatic recirculation are at risk for

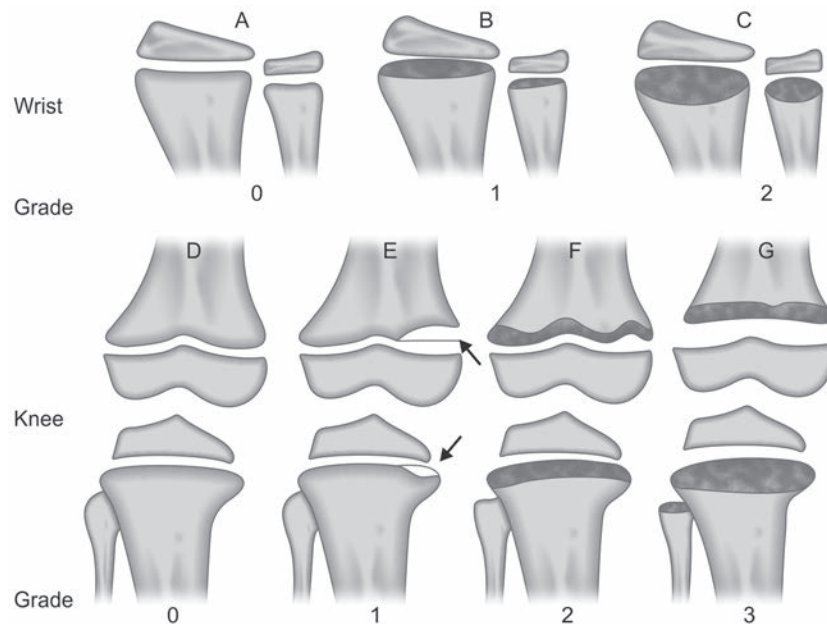
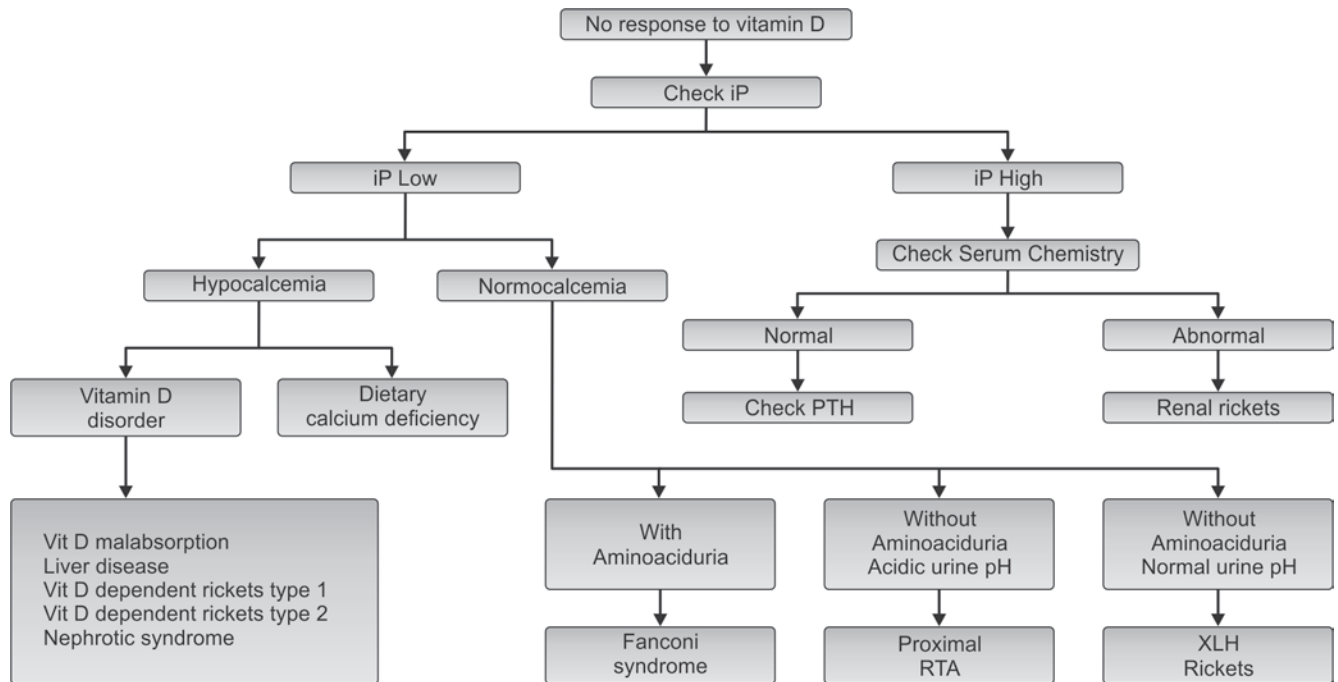


Fig. 3: Radiological scoring for nutritional rickets. A = Normal wrist; B = Irregularity and widening of the growth plate, but without concave cupping; C = Concave metaphyseal cupping and frayed margins; D = A normal knee; E = Only the medial portion of the femoral and tibia metaphyses are affected; F = There is partial lucency of the metaphyses, but the margins are not sharply defined. However, the zone of provisional calcification is not completely lucent and displays some calcification; G = Complete lucency of provisional zone of calcification. The epiphyses appear widely separated from the distal epiphyses. Reproduced with permission from Oxford University Press; reference⁶

Flow chart 1: Outline of diagnosis of vitamin D resistant rickets



developing vitamin D deficiency. These disorders include cholestatic hepatopathies, chronic disease, cystic fibrosis and celiac disease. Parental Stross therapy is indicated.²⁰

Liver Failure

Liver parenchymal cells have a large capacity to produce 25-hydroxy vitamin D and significant hepatic destruction must occur before a deficiency state is reached. Administration of anticonvulsants (phenobarbitone, phenytoin) may cause vitamin D to be shunted to other enzymatic pathways in liver that results in production of polar metabolites that are rapidly excreted. Inborn errors of metabolism causing defective 25-hydroxylation are very rare.¹²

In drug induced rickets correction of vitamin D deficiency is done by Stross therapy and 1000 IU daily of vitamin D supplementation should be given to prevent recurrence of the disorder.¹²

Vitamin D Dependent Rickets Type 1

It is an autosomal recessive disorder manifesting at around 3 to 6 months of age. Enzyme activity of 25(OH)-1 α -hydroxylase is deficient resulting in low levels of 1, 25(OH) D₃, even in presence of hypocalcemia, hypophosphatemia and high parathormone levels. These children develop dental enamel hypoplasia.¹³

For treatment either massive dose of D₃ (2 lakh to 1 million) or low dose of calcitriol 1 to 2 microgram/day are recommended. The treatment has to be continued indefinitely.

Vitamin D Dependent Rickets Type 2

Some cases of vitamin D dependent rickets fail to reverse after treatment with either high dose of vitamin D₃ or calcitriol at 1 to 2 microgram/day. They are labeled as having vitamin D dependent rickets type 2. They have either:¹⁴

1. Reduced or absent 1,25(OH)₂ D₃ binding to the human vitamin D nuclear receptor.
2. Decreased affinity of this receptor for DNA so that transcription does not occur.
3. Defective nuclear translocation or retention.

This condition is particularly common among children of first cousin marriages. Some patients have short stature and alopecia totalis and ectodermal defects (oligodontia, milia and epidermal cyst).¹⁵ This condition may be reversed by administration of 15 to 30 micrograms/day of 1, 25(OH)₂ D.

X-Linked Hypophosphatemic Rickets (Vitamin D Resistant Rickets)

It is the most common form of non-nutritional form of rickets.¹³ Usual mode of inheritance is X-linked dominant, so mothers of affected sons are also affected though with milder manifestations. The defects involve in proximal tubular reabsorption of phosphate and in conversion of 25(OH) D to 1, 25(OH) D. So oral phosphate supplementation alone cannot correct bone disease, the correction requires 1, 25(OH)₂ D therapy.

Clinical features: Age of onset is usually after 6 to 12 months of age. Children present with bowing of lower extremities.

Tetany is not present and the profound myopathy, rachitic rosary and Harrison groove characteristic of calcium deficient rickets are not present. Maximum manifestations are in lower extremities and short stature. Genu varum is more common than genu valgum.¹⁵ Pulp deformities and lesions of intraglobular dentin are characteristic tooth anomalies. Enamel defects are found only occasionally (calcium deficient rickets usually results in enamel defects).

Lab findings: Radiological findings are similar to calcopenic rickets. Biochemically patients have normal or slightly reduced calcium level, a moderately reduced serum phosphate (1.5-3 mg/dl) elevated alkaline phosphatase and no evidence of secondary hyperparathyroidism. Urinary phosphate excretion despite hypophosphatemia is large indicating a defect in tubule phosphate absorption. Aminoaciduria, bicarbonaturia, glycosuria and kaliurea are not found differentiating the condition from generalized tubular disorders.¹⁴

Treatment: Oral phosphate supplements coupled with vitamin D analogs.¹⁴

Phosphate: Young children need 0.5 to 1 gm/day and older children need 1 to 4 g/day. Phosphate is given as Joulie's solution (30.5 mg of phosphate/ml). It has to be given every 4 hours as urinary excretion of phosphate is constant. The main side effect of oral phosphate is diarrheas.

Calcitriol: 50 to 65 ng/kg/day or vitamin D₂ at 2000 IU/kg/day. The side effect is hypercalciurea and nephrocalcinosis, which can be reduced by hydrochlorthiazide.

Renal Rickets

Many factors contribute to osteodystrophy in chronic renal failure including:¹⁵

- Decreased synthesis of 1,25 (OH)₂ D₃.
- Hyperphosphatemia—which causes a reciprocal decrease in serum calcium, which stimulates parathyroids. Hyperparathyroidism causes osteitis fibrosa cystica.
- Metabolic acidosis.

Clinical features depend on age of patient and duration of disease. Infants show features of rickets with delayed development. In older child genu valgum and ulnar deviation of wrist, scoliosis, compression fractures of vertebrae. Pathological fractures of long bones, etc.

Treatment

- Restrict high phosphate foods such as dairy products, chocolate, dark colored sodas.
- Calcium containing phosphate binders as calcium carbonate and acetate. Usual starting dose is 500 to 1250 mg of calcium carbonate or acetate with each meal.
- 1, 25 (OH)₂ D₃ at 0.25 to 1 microgram/day.

Preparations of Vitamin D Available in India

The available preparations are:¹⁶

1. *Calciferol (ergocalciferol, vitamin D₂)*: As solution in oil, filled in gelatin capsules 25,000 and 50,000 IU caps.
2. *Cholecalciferol (vitamin D₃)*: As granules for oral ingestion and oily solution for IM injection. Arachitol 3 lakh IU (7.5 mg) and 6 lakh IU (15 mg) per ml. Calcirol 60,000 IU in 1 gm granules.
3. *Calcitriol (1, 25 (OH)₂ D₃)*: 0.25 to 1 microgram sachets.
4. *Alfacalcidol*: By passes the renal activation step. Useful in renal rickets 0.25 to 1 microgram sachets.
5. *Dihydrotachysterol (DHT)*: Synthetic analog of vitamin D₂. Directly mobilizes calcium from bones. Does not require PTH dependent activation in kidneys-useful in hypoparathyroidism and renal bone disease. Dose 0.25 to 0.5 mg/day.

ANNEXURE

Reference Values¹⁷

S.No	Entity	Group	Value
1.	Serum iP	0-5 days	4.8-8.2 mg/dl
		1-3 yrs	3.8-6.5 mg/dl
		4-11 yrs	3.7-5.6 mg/dl
		12-15 yrs	2.9-5.4 mg/dl
		16-19 yrs	2.7-4.7 mg/dl
2.	Ionized calcium	Cord blood	5.0-6.0 mg/dl
		Newborn (3-24 hrs)	4.3-5.1 mg/dl
		24-48 hrs	4.0-4.7 mg/dl
		thereafter	4.8-4.92 mg/dl
3.	Total calcium	Cord blood	9.0-11.5 mg/dl
		Newborn	9.0 -10.6 mg/dl
		24-48 hrs	7.0-12.0 mg/dl
		2-7 days	9.0-10.9 mg/dl
		Child thereafter	8.8-10.8 mg/dl 8.4-10.2 mg/dl
4.	Alkaline phosphatase	1-9 yrs	145-420 U/L
		10-11 yrs	130-560 U/L
		12-13 yrs-male	200-495 U/L
		12-13 yrs-female	105-420 U/L
		14-15 yrs -male	130-525 U/L
		14-15 yrs-female	70-230 U/L
		16-19 yrs-male	65-260 U/L
5.	25 (OH) D ₃	1-30 days	1.9-33.4 ng/ml
		31 day-1 year	7.4-53.3 ng/ml
6.	1,25(OH) D ₃		25-45 pg/ml
7.	Urinary calcium	Cal free diet	5-40 mg/day
		Low to average Ca in diet	50-150 mg/day
		Average Ca in diet	100-300 mg/day

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INTRODUCTION

Zinc is a trace element of vital importance for the normal functioning of the reproductive, neurologic, immune, dermatologic and gastrointestinal systems. It is a constituent of various metalloenzymes including transferases, hydrolases, ligases, lyases, isomerases and oxidoreductases which help in nucleic acid and protein synthesis and degradation. Zinc chelates with the amino acids cysteine and histidine, forming 'zinc fingers' that are important for protein transcription. Processes that are regulated by zinc include expression of the metallothionein gene, apoptosis and synaptic signaling. Zinc deficiency is one of the ten biggest factors contributing to burden of disease in developing countries with high mortality.¹ With the emerging evidence of the anti-infective potential of zinc in preventing and shortening diarrhea, in combating respiratory infections, and even in reducing mortality in malaria, this trace element is currently the center of enormous interest.

ZINC REQUIREMENT AND DEFICIENCY

The current recommended dietary allowance (RDA) for zinc is listed in Table 1.² For infants aged 0 to 6 months, the values reflect adequate intake (AI) for zinc that is equivalent to the mean intake of zinc in healthy breast fed infants. The optimal source of zinc is from animal sources, such as beef, lamb and oysters. Exclusively breast-fed infants are usually able to get an adequate amount of zinc from breastfeeding during the first six months of life. However, infants who are small for their gestational age and premature infants may benefit from zinc supplementation in addition to the zinc they receive from breastfeeding. During the second six months of life when complementary foods are introduced, the risk for zinc deficiency increases because zinc is commonly the most deficient nutrient in complementary food mixtures fed to infants

during weaning.³ As more and more single-nutrient intervention research is conducted, it is becoming clear that zinc-responsive deficits in body composition are widespread in developing countries. Populations in South East Asia and sub-Saharan Africa are at greatest risk of zinc deficiency; zinc intakes are inadequate for about a third of the population and stunting affects 40 percent of preschool children.⁴ The deficiency has been attributed to a low dietary intake of zinc-rich foods, high consumption of cereal grains and legumes, which contain inhibitors

Table 1: Recommended dietary allowances (RDAs) for zinc

Age	Recommended dietary allowance
0–6 months	2 mg*
7–12 months	3 mg
1–3 years	3 mg
4–8 years	5 mg
9–13 years	8 mg
14–18 years	
Male	11 mg
Female	9 mg
19+ years	
Male	11 mg
Female	8 mg
Pregnancy	
<18 years	12 mg
≥19 years	11 mg
Lactation	
<18 years	13 mg
≥19 years	12 mg

* Adequate intake (AI)

of zinc absorption and excess fecal losses of zinc due to recurrent episodes of diarrhea.

Serum or plasma zinc is the best available biomarker of the risk of zinc deficiency in populations. As serum zinc does not necessarily reflect individual zinc status, presently the use of this indicator for diagnosis and treatment of individuals is not recommended. A joint WHO/UNICEF/IAEA/IZiNCG expert group recommended a serum zinc cutoff of 65 µg/dl (9.9 µmol/L) for identifying zinc deficiency in populations for children aged between two to ten years.^{5,6} Further, the group concluded that the risk of zinc deficiency is considered to be of public health concern when the prevalence of low serum zinc concentrations is greater than 20 percent. Amongst the functional outcomes, height- or length-for-age is the parameter of choice for estimating zinc deficiency in populations.

A recent cross sectional study from five states of India reported an overall prevalence of zinc deficiency amongst children 6 to 60 months of age as 43.8 percent.⁷ The prevalence of zinc deficiency was highest in Orissa (51.3%), followed by Uttar Pradesh (48.1%), Gujarat (44.2%), Madhya Pradesh (38.9%) and Karnataka (36.2%).⁷ Studies from other regions of India and other developing countries also report zinc deficiency of sufficient magnitude to be a significant public health problem.

ROLE OF ZINC IN INFECTIONS

Zinc is essential for the formation and function of immune system. Zinc deprivation results in impairment of macrophage and T cell activity as well as thymic atrophy and reduced viability of thymocytes, thus compromising the cell mediated immunity. The potential anti-infective benefit of zinc is also mediated via stabilization of the epithelial barrier as well as alterations in the balance of T helper cell and TH1 and TH2 cytokines.

Childhood Diarrhea

A large number of randomized controlled trials (RCTs) have established the importance of zinc in the treatment of acute and persistent diarrhea in under-five children. Zinc supplementation in children in developing countries is associated with a substantial reduction in the rates of diarrhea, according to a pooled analysis by the Zinc Investigators' Collaborative Group.⁸ The group analyzed ten RCTs from nine developing countries. The studies assessed the effects of oral zinc in apparently healthy children younger than 5 years. There were seven continuous trials (in which 1-2 times the RDA of zinc was given 5-7 times per week), and three short-course trials (2-4 times the RDA daily for 2 weeks). For the zinc-supplemented children compared with the control group in the continuous trials, the pooled ORs for diarrheal incidence and prevalence were 0.82 (95% CI 0.72 to 0.93) and 0.75 (95% CI 0.63 to 0.88), respectively. In the short-course trials the

OR for the effects of zinc on diarrheal incidence (OR 0.89, 95% CI 0.62 to 1.28) and prevalence (OR 0.66, 95% CI 0.52 to 0.83) were similar to those in the continuous trials. No significant differences were seen between short and continuous courses.

In a pooled analyses of RCTs of the effects of supplementary oral zinc in children aged <5 y with acute or persistent diarrhea,⁹ zinc-supplemented children had a 15 percent lower probability of continuing diarrhea on a given day (95% CI: 5%, 24%) in the acute-diarrhea trials and a 24 percent lower probability of continuing diarrhea (95% CI: 9%, 37%) and a 42 percent lower rate of treatment failure or death (95% CI: 10%, 63%) in the persistent-diarrhea trials.⁹ In none of the subgroup analyses were the 2 subgroups of each pair significantly different from each other; however, in persistent diarrhea there tended to be a greater effect in subjects aged <12 mo, who were male, or who had wasting or lower baseline plasma zinc concentrations.

In the most exhaustive systematic review from the Cochrane group¹⁰ (Table 2) examining eighteen trials enrolling 6165 participants, zinc resulted in a shorter diarrhea duration (MD -12.27 h, 95% CI -23.02 to -1.52 h; 2741 children, 9 trials), and less diarrhea at day three (RR 0.69, 95% CI 0.59 to 0.81; 1073 children, 2 trials), day five (RR 0.55, 95% CI 0.32 to 0.95; 346 children, 2 trials), and day seven (RR 0.71, 95% CI 0.52 to 0.98; 4087 children, 7 trials). Zinc also reduced the duration of persistent diarrhea (MD -15.84 h, 95% CI -25.43 to -6.24 h; 529 children, 5 trials). No trial reported serious adverse events, but vomiting was more common in zinc-treated children with acute diarrhea (RR 1.71, 95% CI 1.27 to 2.30; 4727 children, 8 trials).

Acute Respiratory Infections

Owing to its benefit in treating childhood diarrhea, some recent trials tried to evaluate the role of zinc in treatment and prevention of pneumonia. A Cochrane review¹¹ of four randomized controlled trials (3267 children aged 2-35 months) showed that zinc supplementation in addition to standard antibiotic therapy in children with severe and nonsevere pneumonia failed to show a statistically significant effect on clinical recovery (risk ratio (RR) 1.02; 95 percent confidence interval (CI) 0.93 to 1.11). Similarly, zinc supplementation in children with severe pneumonia did not show a statistically significant effect on clinical recovery measured as resolution of tachypnea (respiratory rate >50 breaths per minute) (RR 1.13; 95% CI 0.82 to 1.57) and cessation of chest in-drawing (RR 1.08; 95% CI 0.88 to 1.31) as compared to the control group. Zinc supplementation in children with severe pneumonia also showed a nonsignificant effect on the duration of hospitalization stay as compared to the control (RR 1.04; 95% CI 0.89 to 1.22). The review concluded that there is no sufficient evidence to recommend the use of zinc as an

Table 2: Systematic reviews of zinc supplementation in various pediatric conditions

<i>Disease/condition</i>	<i>Author year (Ref)</i>	<i>Characteristics of included trials</i>	<i>Number of trials/participants</i>	<i>Results</i>
Treatment of acute and persistent diarrhea	Lazzerini M et al. 2008 ¹⁰	Randomized controlled trials comparing oral zinc (≥ 5 mg/d) with placebo in children aged one month to five years with acute or persistent diarrhea, including dysentery.	Eighteen trials enrolling 6165 participants	In acute diarrhea, zinc reduced the duration (MD -12.27 h, 95% CI -23.02 to -1.52 h; 2741 children, 9 trials), and less diarrhea at day three (RR 0.69, 95% CI 0.59 to 0.81; 1073 children, 2 trials), day five (RR 0.55, 95% CI 0.32 to 0.95; 346 children, 2 trials), and day seven (RR 0.71, 95% CI 0.52 to 0.98; 4087 children, 7 trials). The four trials (1458 children) that reported on diarrhea severity used different units and time points, and the effect of zinc was less clear. Zinc also reduced the duration of persistent diarrhea (MD -15.84 h, 95% CI -25.43 to -6.24 h; 529 children, 5 trials). No trial reported serious adverse events, but vomiting was more common in zinc-treated children with acute diarrhea (RR 1.71, 95% CI 1.27 to 2.30; 4727 children, 8 trials).
Treatment of pneumonia	Haider BA et al. 2011 ¹¹	RCTs evaluating supplementation of zinc as an adjunct to antibiotics for pneumonia in children aged two to 59 months.	Four trials with 3267 children.	Zinc supplementation in addition to standard antibiotic therapy in children with severe and nonsevere pneumonia failed to show a statistically significant effect on clinical recovery (risk ratio (RR) 1.02; 95% confidence interval (CI) 0.93 to 1.11). Similarly, zinc supplementation did not show a statistically significant effect on clinical recovery measured as resolution of tachypnea (respiratory rate > 50 breaths per minute) (RR 1.13; 95% CI 0.82 to 1.57) and cessation of chest indrawing (RR 1.08; 95% CI 0.88 to 1.31) as compared to the control group. Zinc supplementation had no effect on the duration of severe pneumonia related hospitalization as compared to the control (RR 1.04; 95% CI 0.89 to 1.22).
Prevention of pneumonia	Lassi ZS et al. 2010 ¹²	Randomized controlled trials evaluating supplementation of zinc in children aged 2-59 months of age.	Six trials and 7850 participants	Zinc supplementation reduced the incidence of pneumonia by 13% (risk ratio (RR) 0.87; 95% confidence interval (CI) 0.81 to 0.94, fixed-effect, six studies) and prevalence of pneumonia by 41% (RR 0.59; 95% CI 0.35 to 0.99, random-effects, one study).
Common cold	Singh M et al. 2011 ¹³	Randomized, double-blind, placebo-controlled trials using zinc for at least five consecutive days to treat, or for at least five months to prevent the common cold.	13 therapeutic trials (966 participants) and two preventive trials (394 participants).	Intake of zinc was associated with a significant reduction in the duration (standardized mean difference (SMD) -0.97; 95% confidence interval (CI) -1.56 to -0.38) ($P = 0.001$), and severity of common cold symptoms (SMD -0.39; 95% CI -0.77 to -0.02) ($P = 0.04$). There was a significant difference between the zinc and control group for the proportion of participants symptomatic after seven days of treatment (OR 0.45; 95% CI 0.2 to 1.00) ($P = 0.05$). The incidence rate ratio (IRR) of developing a cold (IRR 0.64; 95% CI 0.47 to 0.88) ($P = 0.006$), school absence ($P = 0.0003$) and prescription of antibiotics ($P < 0.00001$) was lower in the zinc group. Overall adverse events (OR 1.59; 95% CI 0.97 to 2.58) ($P = 0.06$), bad taste (OR 2.64; 95% CI 1.91 to 3.64) ($P < 0.00001$) and nausea (OR 2.15; 95% CI 1.44 to 3.23) ($P = 0.002$) were higher in the zinc group.
Pregnancy outcome	Mahomed K et al. 2007 ¹⁴	Randomized or quasi-randomized trials of zinc supplementation in pregnancy.	17 RCTs involving over 9000 women and their babies.	Zinc supplementation resulted in a small but significant reduction in preterm birth (relative risk (RR) 0.86, 95% confidence interval (CI) 0.76 to 0.98 in 13 RCTs; 6854 women). This was not accompanied by a similar reduction in numbers of babies with low birthweight (RR 1.05 95% CI 0.94 to 1.17; 11 studies of 4941 women). No significant differences were seen between the zinc and no zinc groups for any of the other primary maternal or neonatal outcomes, except for a small effect favoring zinc for cesarean section (four trials with high heterogeneity) and for induction of labor in a single trial. No differing patterns were evident in the subgroups of women with low versus normal zinc and nutrition levels or in women who complied with their treatment versus those who did not.
Prevention of morbidity and mortality in LBW infants	Gulani A et al. 2011 ¹⁵	Randomized or quasi-randomized trials of zinc supplementation (orally to provide at least 1 RDA of elemental zinc for at least 14 d) in LBW neonates, with individual or cluster allocation.	Three RCTs	There was no evidence of a reduced risk of mortality (1 trial, RR=1.11; 95% CI 0.57 to 2.18 at one year), hospitalization rate (1 trial, odds ratio 1.10; 95% CI 0.87 to 1.39), acute respiratory infection (1 trial), or diarrhea (2 trials). There was no evidence of an increase in weight (3 trials) or height (2 trials) at either 6 months or one year of age, or of an increased risk of vomiting following zinc supplementation. Serum zinc levels at the end of intervention were significantly higher in the supplemented group (2 trials).

adjunct to standard antibiotic therapy for pneumonia in children aged two to 35 months (Table 2).

Regarding role of zinc in preventing pneumonia, the Cochrane systematic review¹² of six RCTs (7850 participants) showed that zinc supplementation reduced the incidence of pneumonia by 13 percent (risk ratio (RR) 0.87; 95 percent confidence interval (CI) 0.81 to 0.94, fixed-effect, six studies) and prevalence of pneumonia by 41 percent (RR 0.59; 95% CI 0.35 to 0.99, random-effects, one study).

The Cochrane review of zinc supplementation in preventing or treating common cold¹³ documented a significant reduction in the duration and severity of common cold symptoms (Table 2). There was a significant difference between the zinc and control group for the proportion of participants symptomatic after seven days of treatment but the adverse effect profile of participants given zinc was not favorable.

Overall, there seems to be some role of zinc in prevention of acute respiratory infections. However, there is no sufficient evidence to recommend its supplementation routinely during the episode.

Malaria

The results of zinc supplementation on the severity and outcome of malaria are conflicting. In a study conducted in Papua New Guinea, a total of 274 preschool children aged 6 to 60 months were given 10 mg elemental zinc (n = 136) or placebo (n = 138) for 6 days a week for 46 weeks.¹⁶ Zinc supplementation resulted in a 38 percent (95% CI 3-60, P = 0.037) reduction in *Plasmodium falciparum* health center-based episodes. Episodes accompanied by any parasitemia were also reduced by 38 percent (95% CI 5-60, P = 0.028). There was no evidence of the effects of zinc on *Plasmodium vivax* morbidity or on health center attendance for causes other than *P. falciparum*. The Zinc Against Plasmodium Study Group evaluated the therapeutic effect of zinc given as an adjuvant to standard therapy during acute malaria in a large double-blind, randomized placebo-controlled clinical trial across 5 countries in Africa and concluded that zinc does not appear to provide a beneficial effect in the treatment of acute, uncomplicated falciparum malaria in preschool children.¹⁷ A trial in Burkina Faso also did not find any reduction in episodes of falciparum malaria among children who received daily supplementation with 10 mg zinc for six months.¹⁸ A recent epidemiological analysis concluded that preventive zinc supplementation has no effect on malaria specific mortality (RR = 0.90; 95% CI: 0.77, 1.06) or incidence of malaria (RR = 0.92; 95 % CI 0.82-1.04).

ZINC AND GROWTH

Zinc plays a critical role in the cellular growth and differentiation. Multiple studies have been carried out to assess

the effect of zinc supplementation on children's growth. The results of these studies are inconsistent, and the factors responsible for these varied outcomes are unknown. In a meta-analysis involving 33 studies, zinc supplementation produced highly significant, positive responses in height and weight increments, with effect sizes of 0.350 (95% CI: 0.189, 0.511) and 0.309 (0.178, 0.439), respectively.¹⁹ There was no significant effect of zinc on weight-for-height indexes (weighted mean effect size: -0.018 (-0.132, 0.097)). Zinc supplementation caused a large increase in the children's serum zinc concentrations, with an effect size of 0.820 (0.499, 1.14). Growth responses were greater in children with low initial weight-for-age z scores and in those aged >6 months with low initial height-for-age z scores. The authors concluded that interventions to improve children's zinc nutriture should be considered in populations at risk of zinc deficiency, especially where there are elevated rates of underweight or stunting and that the population mean serum zinc concentration is a useful indicator of the successful delivery and absorption of zinc supplements in children. However, a subsequent trial in Burkina Faso (709 children aged 6-31 months) has shown no effect of zinc supplementation on growth where similar range of doses of zinc was used even though the supplementation resulted in an increased serum zinc level.²⁰

Zinc supplementation given during pregnancy also does not result in a significant benefit in terms of infant's birth weight¹⁴ or growth (Table 2). Similarly, there is no evidence of neonatal zinc supplementation in terms of infant's weight (3 trials) or height (2 trials) at either 6 months or one year of age¹⁵ (Table 2).

ZINC AND DEVELOPMENT

Zinc is concentrated in the synaptic vesicles of glutamatergic neurons found primarily in the forebrain. During nerve conduction, zinc is released into postsynaptic neurons, serving as a neurotransmitter. Because zinc is considered to be essential for nucleic acid and protein synthesis, zinc deficiency may interfere with these processes and hence compromise subsequent development.

In studies assessing the effect of zinc supplementation on activity, the supplemented group demonstrated increased activity.^{21,22} Improvement in developmental status of very low-birth-weight infants has also been reported after zinc supplementation.²³ However, three studies found no impact of zinc on motor development.²⁴⁻²⁶ Of the four studies that examined mental development in infants and toddlers, three found no impact of zinc supplementation²³⁻²⁵ and one found that zinc-supplemented children had lower scores than control children.²⁶ Among school-age children, one study found no impact of zinc supplementation on cognitive performance²⁷ and two found a beneficial impact of neuropsychological processes,

specifically reasoning.^{28,29} The evidence linking zinc deficiency to children's cognitive and motor functioning lacks a clear consensus, highlighting the need for additional research.

Nutrient Cointerventions with Zinc

Kikafunda et al found that children from the school with the highest socioeconomic status, and therefore a better nutritional background, responded significantly in weight gain to zinc supplementation whereas the children from the poorer schools did not; indicating that zinc was the limiting nutrient in the nutrition of the children with relatively better nutritional status, whereas those with poorer nutritional status were deficient in other nutrients that limited the response in zinc supplementation.³⁰ Sandstead et al conducted a zinc supplementation trial in Chinese children and found that the knee-height increase was significantly greater in the zinc-plus-micronutrients group than in the zinc-alone group.²⁹

It is likely that different effects will be seen when zinc is given in supplemental doses if an individual (1) is without any micronutrient deficits, (2) is uniquely zinc deficient, or (3) has multiple micronutrient deficiencies. This will lead to heterogeneous responses to zinc in free-living populations because all three conditions are likely to coexist.

PROGRAMMATIC ISSUES

As zinc deficiency is a significant public health problem in developing countries, including India, interventions to improve population zinc status are recommended. Supplementation of zinc for 14 days during an episode of acute diarrhea is one such approach due to simultaneous documented benefit in reducing the severity and duration of disease. WHO, UNICEF and Indian Academy of Pediatrics recommend that a daily dose of 20 mg of elemental zinc for children older than 6 months, and 10 mg for children aged 2 months to 6 months should be started as soon as diarrhea starts and continued for a total period of 14 days.³¹ Zinc supplementation is also recommended as part of routine, standard case management in persistent diarrhea and in those with severe malnutrition. Further evidence is required for qualifying its use in treatment of pneumonia and malaria; the use should be discouraged outside research settings.

Tackling zinc deficiency in isolation, however, is inappropriate. In particular, it is important to avoid any further fragmentation of health interventions by creating an additional zinc program. The strategies to combat zinc deficiency must focus on dietary interventions rather than a magic bullet approach. Fluctuation in the status of one micronutrient may alter the metabolism of the other, with functional consequences on the health of the individual, especially in populations with borderline nutriture.³² Medicinal zinc should be perceived only as

a short-term solution in the conditions where it has a documented benefit. Food technology research should be encouraged to identify and assess the feasibility of zinc fortification of candidate foods including complementary diets. Improvement in the quality and quantity of diet should be relied upon as long term strategies to combat zinc deficiency.⁶

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Vitamin A and its Controversies

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INTRODUCTION

Vitamin A (retinol) is an essential nutrient needed in small amounts by humans for the normal functioning of the visual system; growth and development; and maintenance of epithelial cellular integrity, immune function, and reproduction. These dietary needs for vitamin A are normally provided for as preformed retinol (mainly as retinyl ester) and provitamin A carotenoids.

OVERVIEW OF VITAMIN A METABOLISM

Preformed vitamin A in animal foods occurs as retinyl esters of fatty acids in association with membrane-bound cellular lipid and fat-containing storage cells. Provitamin A carotenoids in foods of vegetable origin are also associated with cellular lipids but are embedded in complex cellular structures such as the cellulose-containing matrix of chloroplasts or the pigment-containing portion of chromoplasts. Normal digestive processes free vitamin A and carotenoids from food matrices, which is a more efficient process from animal than from vegetable tissues. Retinyl esters are hydrolysed and the retinol and freed carotenoids are incorporated into lipid-containing, water-miscible micellar solutions. Products of fat digestion (e.g. fatty acids, monoglycerides, cholesterol, and phospholipids) and secretions in bile (e.g. bile salts and hydrolytic enzymes) are essential for the efficient solubilization of retinol and especially for solubilization of the very lipophilic carotenoids (e.g. α - and β carotene, β -cryptoxanthin, and lycopene) in the aqueous intestinal milieu. Micellar solubilization is a prerequisite to their efficient passage into the lipid rich membrane of intestinal mucosal cells (i.e. enterocytes).¹⁻³ Diets critically low in dietary fat (under about 5-10 g daily)⁴ or disease conditions that interfere with normal digestion and absorption leading to steatorrhea (e.g. pancreatic and liver diseases

and frequent gastroenteritis) can therefore impede the efficient absorption of retinol and carotenoids. Retinol and some carotenoids enter the intestinal mucosal brush border by diffusion in accord with the concentration gradient between the micelle and plasma membrane of enterocytes. Some carotenoids pass into the enterocyte and are solubilized into chylomicrons without further change whereas some of the provitamin A carotenoids are converted to retinol by a cleavage enzyme in the brush border.³ Retinol is trapped intracellularly by re-esterification or binding to specific intracellular binding proteins. Retinyl esters and unconverted carotenoids together with other lipids are incorporated into chylomicrons, excreted into intestinal lymphatic channels, and delivered to the blood through the thoracic duct.²

Tissues extract most lipids and some carotenoids from circulating chylomicrons, but most retinyl esters are stripped from the chylomicron remnant, hydrolysed, and taken up primarily by parenchymal liver cells. If not immediately needed, retinol is re-esterified and retained in the fat-storing cells of the liver (variously called adipocytes, stellate cells, or Ito cells). The liver parenchymal cells also take in substantial amounts of carotenoids. Whereas most of the body's vitamin A reserve remains in the liver, carotenoids are also deposited elsewhere in fatty tissues throughout the body.¹ Usually, turnover of carotenoids in tissues is relatively slow, but in times of low dietary carotenoid intake, stored carotenoids are mobilized. A recent study in one subject using stable isotopes suggests that retinol can be derived not only from conversion of dietary provitamin carotenoids in enterocytes—the major site of bioconversion—but also from hepatic conversion of circulating provitamin carotenoids.⁵ The quantitative contribution to vitamin A requirements of carotenoid converted to retinoids beyond the enterocyte is unknown.

Following hydrolysis of stored retinyl esters, retinol combines with a plasma-specific transport protein, retinol-binding protein (RBP). This process, including synthesis of the unoccupied RBP (apo-RBP), occurs to the greatest extent within liver cells but it may also occur in some peripheral tissues. The RBP-retinol complex (holo-RBP) is secreted into the blood where it associates with another hepatically synthesized and excreted larger protein, transthyretin. The transthyretin-RBP-retinol complex circulates in the blood, delivering the lipophilic retinol to tissues; its large size prevents its loss through kidney filtration.¹ Dietary restriction in energy, proteins, and some micronutrients can limit hepatic synthesis of proteins specific to mobilization and transport of vitamin A. Altered kidney functions or fever associated with infections (e.g. respiratory infections⁶ or diarrhea⁷) can increase urinary vitamin A loss.

Holo-RBP transiently associates with target tissue membranes, and specific intracellular binding proteins then extract the retinol. Some of the transiently sequestered retinol is released into the blood unchanged and is recycled (i.e. conserved).^{1,8} A limited reserve of intracellular retinyl esters is formed that subsequently can provide functionally active retinol and its oxidation products (i.e. isomers of retinoic acid) as needed intracellularly. These biologically active forms of vitamin A are associated with specific cellular proteins which bind with retinoids within cells during metabolism and with nuclear receptors that mediate retinoid action on the genome.⁹ Retinoids modulate the transcription of several hundreds of genes.¹⁰⁻¹² In addition to the latter role of retinoic acid, retinol is the form required for functions in the visual¹³ and reproductive systems¹⁴ and during embryonic development.¹⁵

Holo-RBP is filtered into the glomerulus but recovered from the kidney tubule and recycled. Normally vitamin A leaves the body in urine only as inactive metabolites resulting from tissue utilization and in bile secretions as potentially recyclable active glucuronide conjugates of retinol.⁸ No single urinary metabolite has been identified which accurately reflects tissue levels of vitamin A or its rate of utilization. Hence, at this time urine is not a useful biological fluid for assessment of vitamin A nutriture.

BIOCHEMICAL MECHANISMS FOR VITAMIN A FUNCTIONS

Vitamin A functions at two levels in the body. The first is in the visual cycle in the retina of the eye; the second is in all body tissues where it systemically maintains the growth and soundness of cells. In the visual system, carrier bound retinol is transported to ocular tissue and to the retina by intracellular binding and transport proteins. Rhodopsin, the visual pigment critical to dim-light vision, is formed in rod cells after conversion of all-trans-retinol to retinaldehyde, isomerization to the

11-cis-form, and binding to opsin. Alteration of rhodopsin through a cascade of photochemical reactions results in the ability to see objects in dim light.¹³ The speed at which rhodopsin is regenerated is related to the availability of retinol. Night blindness is usually an indicator of inadequate available retinol, but it can also be due to a deficit of other nutrients that are critical to the regeneration of rhodopsin, such as protein and zinc, and to some inherited diseases, such as retinitis pigmentosa. The growth and differentiation of epithelial cells throughout the body are especially affected by vitamin A deficiency (VAD). In addition, goblet cell numbers are reduced in epithelial tissues and as a consequence, mucous secretions (with their antimicrobial components) diminish. Cells lining protective tissue surfaces fail to regenerate and differentiate, hence they flatten and accumulate keratin. Both factors—the decline in mucous secretions and loss of cellular integrity—reduce the body's ability to resist invasion from potentially pathogenic organisms. Pathogens can also compromise the immune system by directly interfering with the production of some types of protective secretions and cells.¹¹ Classical symptoms of xerosis (drying or non-wetability) and desquamation of dead surface cells as seen in ocular tissue (i.e. xerophthalmia) are the external evidence of the changes also occurring to various degrees in internal epithelial tissues. Current understanding of the mechanism of vitamin A action within cells outside the visual cycle is that cellular functions are mediated through specific nuclear receptors. Binding with specific isomers of retinoic acid (i.e. all trans- and 9-cis-retinoic acid) activates these receptors. Activated receptors bind to DNA response elements located upstream of specific genes to regulate the level of expression of those genes.¹² These retinoid-activated genes regulate the synthesis of a large number of proteins vital to maintaining normal physiologic functions. There may, however, be other mechanisms of action that are as yet undiscovered.¹⁰

DEFINITION OF VITAMIN A DEFICIENCY

VAD is not easily defined. World Health Organization defines it as tissue concentrations of vitamin A low enough to have adverse health consequences even if there is no evidence of clinical xerophthalmia.¹⁶ In addition to the specific signs and symptoms of xerophthalmia and the risk of irreversible blindness, nonspecific symptoms include increased morbidity and mortality, poor reproductive health, increased risk of anemia, and contributions to slowed growth and development. However, these nonspecific adverse effects may be caused by other nutrient deficits as well, making it difficult to attribute non-ocular symptoms specifically to VAD in the absence of biochemical measurements reflective of vitamin A status.¹⁶

DIETARY SOURCES OF VITAMIN A

Preformed vitamin A is found almost exclusively in animal products, such as human milk, glandular meats, liver and fish liver oils (especially), egg yolk, whole milk, and other dairy products.¹⁶ Provitamin A carotenoids are found in green leafy vegetables (e.g. spinach, amaranth, and young leaves from various sources), yellow vegetables (e.g. pumpkins, squash, and carrots), and yellow and orange non-citrus fruits (e.g. mangoes, apricots, and papayas).

INDICATORS OF VITAMIN A DEFICIENCY

Clinical Indicators of Vitamin A Deficiency

The term xerophthalmia encompasses the clinical spectrum of ocular manifestations of VAD, from milder stages of night blindness and Bitot's spots, to potentially blinding stages of corneal xerosis, ulceration and necrosis (keratomalacia),¹⁷ as listed in Table 1. The stages of xerophthalmia are regarded both as disorders and clinical indicators of VAD, and thus can be used to estimate an important aspect of morbidity and blinding disability as well as the prevalence of deficiency.

Subclinical Indicators of Vitamin A Deficiency

Measuring serum retinol concentrations in a population constitutes the second major approach to assessing vitamin A status in a population, with values below a cut-off of 0.70 µmol/L representing VAD,¹⁷ and below 0.35 µmol/L representing severe VAD. Although there is not yet international consensus, a serum retinol concentration below a cut-off of 1.05 µmol/L has been proposed to reflect low vitamin A status among pregnant and lactating women.¹⁷

TOXICITY OF VITAMIN A

Since vitamin A is a fat-soluble vitamin and is mainly stored in liver, routine consumption of large amounts of vitamin A results in toxic symptoms, including liver damage, bone abnormalities and joint pain, alopecia, headaches, vomiting, and skin desquamation. Hypervitaminosis A appears to be due to abnormal transport and

distribution of vitamin A and retinoids.¹⁶ Very high single doses can also cause transient acute toxic symptoms that may include bulging fontanelles in infants; headaches in older children and adults; and vomiting, diarrhea, loss of appetite, and irritability in all age groups.

VITAMIN A PROGRAMME IN INDIA—WHY THE CONTROVERSY?

The Universal Vitamin A Supplementation Programme in India

Since 1970, vitamin A supplementation programme has been operational in India. In 1970, it was initially started as the National Prophylaxis Programme against Nutritional Blindness as an urgent remedial measure to eliminate the unacceptably high magnitude of xerophthalmic blindness. But now it has been going on for the last four decades and its continuation has become a subject of national debate.

The controversy is not confined to the campaign-type approach to vitamin A distribution.¹⁸ Also in question is the very existence of vitamin A deficiency (VAD) as a public health problem in India and the need for supplementation.¹⁹

Recent Trend in Clinical Vitamin A Deficiency

In under-5 children, clinical vitamin A deficiency including severe xerophthalmia was a major public health problem in the early 1960's. However, in the past 4 decades keratomalacia has almost disappeared and there is a sharp decline in the prevalence of Bitot's spots.²⁰ This decline is due to better food availability, immunization coverage, access to healthcare facilities and management of childhood diseases. The available evidence indicates that this decline cannot be attributed to the UVAS programme. There is no obvious justification for continuing the UVAS programme to eliminate nutritional blindness.^{20,21} The advocacy of continuing this programme is now targeted towards the subclinical deficiency and the child survival benefits. Subclinical or biochemical vitamin A deficiency is overestimated in our setting because the serum retinol cut-offs are based on western population norms, where the main diet is non-vegetarian.

Child Survival Benefit

A systematic review of Indian trials concluded that for the prevention of mortality and morbidity, the findings of 'vitamin A trials are not consistent, and there is no evidence as yet in favor or against substantive benefit of universal vitamin A supplementation to children in India.'²²

Potential Harms Ignored

Potentially important and serious safety concerns have been ignored while framing policy regarding intensification of UVAS.

Table 1: Classification of xerophthalmia

XN	Night blindness
X1A	Conjunctival xerosis
X1B	Bitot's spot
X2	Corneal xerosis
X3A	Corneal ulceration/keratomalacia (< 1/3 corneal surface)
X3B	Corneal ulceration/keratomalacia (≥ 1/3 corneal surface)
XS	Corneal scar
XF	Xerophthalmic fundus

What Went Wrong with Vitamin A Campaign in Assam?

The reported deaths of over a dozen children and the illnesses of a large number following vitamin A administration during a mass campaign in 2001 in the north-eastern state of Assam had caused considerable anxiety and concern among health professionals.^{18,19,21} The campaign was stopped immediately and the Government set-up an inquiry which showed nothing wrong with the vitamin supplied. Since the rate of national immunization coverage is very low, some states including Assam had adopted the vitamin A campaign approach, with UNICEF support, to increase coverage.²¹ During third round, UNICEF replaced the traditional 2 ml spoons with 5 ml cups for administering vitamin A. It was possible that the newer method and inadequate training of health workers might have led to overdosing in some cases.

The Assam episode started with the death, after consuming vitamin A, of a two-year-old child from the Tea-garden community. This triggered panic among the parents. Thousands of people rushed with their children to the nearest health center, some of them complaining of fever, vomiting and diarrhea. Normally, these symptoms do not attract mass attention, but the media has sensationalized the event in Assam leading to a wave of mass concern. All deaths and illnesses that occurred in children during the following week were attributed to vitamin A. There is no evidence that vitamin A causes death, even if a child had received twice the recommended amount (400,000 IU). This is the dose recommended by the WHO for treatment of xerophthalmia. The vitamin A program has been in operation for the past several years in India and in sixty other countries. So far, not a single case of death attributable to vitamin A dosing was reported. The lethal dose of vitamin A is not known, but a review of the case reports of children getting 300,000 to 900,000 IU do not suggest severe toxic effects that could be fatal. It is not surprising that the investigation conducted by the State Department of Health and UNICEF revealed that, in most of the cases, deaths were due to causes unrelated to vitamin A.²¹

The Way Forward

The current evidence suggests that UVAS cannot be justified as a public health intervention for prevention of xerophthalmic blindness or childhood mortality in India. There is an urgent need of a national evidence-based process to examine an appropriate shift in the vitamin A supplementation policy.

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Trace Elements in Pediatric Nutrition

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Although minerals constitute <5 percent of the daily dietary intake, they have a vital role in homeostasis. Trace elements are those minerals that are required in amounts of 1 to 100 mg daily in an adult and they constitute less than 0.01 percent of the body weight. The trace elements that are essential for human body are iron, zinc, copper, manganese, fluoride and selenium. Although iodine is required in amounts less than 1 mg daily, it also is a vital nutrient for human nutrition. Recommended intakes for trace elements are expressed as recommended dietary allowances (RDA) or adequate intake (AI). When limited data exists to assess the population needs of a trace element, the recommended intake is expressed as AI. The upper limit (UL) is the quantity of the nutrient considered to cause no adverse effects in healthy individuals.

CHROMIUM

Deficiency is noticed in patients who are hospitalized with increased catabolism (patients with burns, short bowel syndrome, trauma) and severe malnutrition. Low levels of chromium have been associated with impaired glucose tolerance and lipid profile. In diabetic patients on total parenteral nutrition, chromium deficiency has been associated with increased insulin requirement. Dietary sources of chromium include whole grains, fruits and vegetables.

COPPER

Although found in all organs and tissues of the human body, copper was recognized to be vital to human nutrition only recently. Around 60 percent of the dietary copper comes from vegetable products especially grains and pulses. Highest content of copper is found in liver. Copper plays a vital role in the functioning of many enzymes in homeostasis viz Zinc Copper superoxide dismutase, Dopamine mono-oxygenase, lysyl oxidase, ceruloplasmin, cytochrome C

oxidase, Factor V, tyrosinase, etc. Inherited diseases caused by inborn errors of copper metabolism include Wilson's disease and Menkes disease. Wilson's disease is characterized by signs and symptoms of copper toxicity whereas Menkes disease is a disorder of copper intake from the intestine, characterized by features of copper deficiency. Acquired causes of copper deficiency includes patients with malnutrition, following extensive gastric surgeries, formula-fed babies who have not received adequate supplementation, malabsorptive diseases, and patients on zinc supplementation also as zinc also retards copper absorption.

The recommended dietary intake of copper is 340 mcg daily for young children and 900 mcg for adults.

Deficiency

Deficiency of copper manifests with reduced skin pigmentation, muscle weakness, abnormal depigmented hair, neurological abnormalities like cognitive defects, ataxia, etc. anemia, hepatosplenomegaly and osteoporosis. Anemia is microcytic hypochromic and mimics iron deficiency. Treatment with iron supplements alone can worsen copper deficiency and iron further decreases copper absorption. Neutropenia and thrombocytopenia also may be noticed.

Menkes disease also known as Menkes kinky hair disease is an inherited X linked genetic disorder that occurs due to a mutation in the transport protein mediating copper absorption from the intestine. This results in severe copper deficiency with neurological deterioration. Hypopigmentation of skin and hair and bony abnormalities are the main clinical features.

FLUORIDE

Although fluoride is very common in the earth's crust, its concentration in water is very variable. Fluoride is important in preventing dental caries. Important sources of fluoride in

diet include seafood with edible shells and bones and dietary supplements. The adequate intake for fluoride is 0.7 mg daily for young children, and 3 to 4 mg daily in adults.

Deficiency has been found to increase the incidence of dental caries. Toxicity leads to pain abdomen, nausea and vomiting. Chronic toxicity leads to dental and skeletal fluorosis. Fractures are seen along with calcification of ligaments and tendons, leading to reduced joint mobility.

IODINE

Iodine is important for synthesis of thyroid hormones. It is predominantly found in the thyroid gland where it is bound to tyrosine as mono iodo and di-iodo tyrosine and thyroxine. Iodine deficiency leads hyperplasia of the gland and formation of goiter. Thyroid hormones have many physiological roles including regulation of basal metabolic rate. The recommended dietary intake of iron is 90 mcg for young children, 120 mcg for older children and 150 mcg in adolescents and adults. During pregnancy and lactation, the requirement increases to 220 to 290 mcg daily.

Deficiency of iodine is still a major public health problem in many countries. Iodine content of salt and water is very variable. Dietary sources include seafood and vegetables. Iodine fortified salt is the major source of iodine in many countries.

Deficiency leads to hypothyroidism, goiter, mental retardation and growth retardation in children. Maternal iodine deficiency leads to severe irreversible mental retardation in the fetus with deafness (cretinism).

IRON

Iron is the most widely accepted among all the known trace elements. Iron deficiency is a major public health issue worldwide. Among 1 to 1.5 billion of the world population is deficient in iron. Iron deficiency account for 20 to 30 percent of the infant and maternal mortality.

Sources: Iron is absorbed from the gut in 2 forms. Heme iron that is seen in meat and fish is absorbed directly unaffected by the underlying iron status. Nonheme iron is found in vegetables and fruits and iron fortified food products. Its absorption is dependant on transport proteins and it increases when the iron stores are low. Iron absorption is increased by vitamin C and reduced by calcium, phytic acid and tannins. Once absorbed, iron is bound to transferring which is a specific transport protein. During normal homeostasis, nontransferrin bound iron is very low and is taken up readily by the liver. Iron losses from the body are very low and occur in feces from desquamated cells and menstrual blood loss.

Inside the body, 75 percent of iron is in the form of heme proteins. These include hemoglobin, myoglobin, cytochrome C, cytochrome *p 450* and peroxidases. Twenty to thirty percent is in the form of storage proteins like

ferritin and hemosiderin. <1 percent is present in the form of iron metalloenzymes and are important in tyrosine, dopamine and nor adrenaline synthesis.

Deficiency or iron leads to the classical microcytic hypochromic anemia. Other features include tiredness, reduced work capacity and exercise tolerance and are not necessarily related to anemia. In children, iron deficiency also can lead to developmental delay, which may be irreversible, even when anemia is corrected. Maternal iron deficiency leads to premature birth and low birth weight.

Iron overload is seen in hereditary hemochromatosis. This is autosomal recessive and is characterized by iron overload, cardiomyopathy, cirrhosis of liver and diabetes. Iron overload is more commonly seen in diseases requiring repeated blood transfusions like thalassemias, bone marrow failure and malignancies.

MANGANESE

The role of manganese is still unclear in human health. Good sources of manganese are meat, fish, poultry, dried fruit and nuts. Inside the human body, manganese is found in bones, mitochondria (liver, kidney and pancreas) and melanin. The enzymes that require manganese for its metabolism include superoxide dismutase, arginase, glutamate synthetase and pyruvate carboxylase. The tolerable upper limit for manganese is 2 mg in toddlers and up to 11 mg in adults.

In animal models, deficiency leads to poor growth, reduced fertility, ataxia and skeletal deformities. In humans, deficiency has been noted in patients with severely restricted diet.

Toxicity has been observed on exposure to manganese containing dust as in welding and steel factories, as well as in individuals drinking well water with high content of manganese. Parenteral nutrition solutions contain manganese and has raised concerns about toxicity especially in neonates and children in the presence of cholestasis that decreases manganese excretion. Neurotoxicity due to extrapyramidal involvement manifesting as dyscoordination, loss of balance and confusion, hepatic dysfunction and headache has been reported.

SELENIUM

Selenium is a trace mineral with several vital biological functions. The dietary range is narrow and hence, it is potentially toxic. Selenium is seen in two selenium containing amino acids—selenocysteine and selenomethionine. This is incorporated in proteins like glutathione peroxidase and iodo thyronine deiodinase that are important for antioxidant function and thyroid hormone synthesis respectively. Seafood, kidney, liver and meat are good sources of selenium. The content in grains and nuts is variable and is dependant on the selenium content of soil.

Severe deficiency is associated with muscle dysfunction and impaired immune function. Keshan disease is an endemic cardiomyopathy that is linked to selenium deficiency. It has been reported in areas of China where diet is nearly absent in selenium. Chronic TPN users also have been reported to have selenium deficiency. In HIV infected patients, selenium deficiency has been associated with reduction in CD 4 cell counts. Cell mediated and NK cell mediated immunity also is impaired in selenium deficiency. The possibility that increased intakes of selenium might protect against the development of cancer in humans has generated great interest. Low serum selenium levels have been reported in pediatric and adult patients with cancers.

There have been studies linking selenium with prevention of atherosclerosis, but are not conclusive.

Toxicity of selenium occurs with increased dietary intake wither naturally or due to supplementation. Toxicity results in nausea, emesis, diarrhea, hair loss, mental changes and peripheral neuropathy. The recommended dietary intake is 20 mcg in children and 55 mcg daily in adults. Tolerable upper limit is 400 mcg/day.

ZINC

As a cofactor of more than three hundred enzymes, zinc is involved in a variety of general cellular functions, including signal transduction, transcription, and replication. The immune system as a highly proliferative organ is, therefore, strongly influenced by zinc. Dietary source of zinc are meat, nuts and lentils. Zinc absorption is regulated by a metallothionein that is more avid for copper. Hence, zinc supplementation is helpful in Wilson's disease as it competitively blocks copper absorption from the gut. Zinc is a vital component of >200 enzymes in the human body. The important enzymes requiring zinc include angiotensin converting enzyme, alkaline phosphatase, carbonic anhydrase, copper zinc superoxide dismutase and metallothionein.

Although the physiological plasma concentration of zinc is low (12–16 μM), it reflects only a minute component of the total body zinc. This part represents a very mobile and immunologically important pool. Bound to proteins, predominantly albumin, α_2 -macroglobulin and transferrin, zinc is transported to the cells but only free zinc ions seem to be biologically active. In chronic inflammatory conditions, a diminished serum zinc level is often found. This should not necessarily be interpreted as absolute zinc deficiency. More often it reflects a redistribution of serum zinc into the liver within the acute phase reaction, caused by increased production of proinflammatory cytokines, mainly interleukin (IL)-1 and IL-6, and subsequent induction of zinc-binding metallothionein in hepatocytes.

Zinc and Immunity

Decreasing zinc concentrations *in vivo* impair natural killer (NK) cell activity, phagocytosis of macrophages and

neutrophils and certain functions like chemotaxis and generation of the oxidative burst. *p58* killer cell inhibitory receptor (KIR) on NK cells requires zinc for recognition of MHC class I molecules, mainly HLA-C, on target cells.

Zinc deficiency interferes with the earliest steps of T cell maturation because it causes thymic atrophy. Zinc is an essential cofactor for thymulin, an important thymic hormone secreted by thymic epithelial cells and thymus changes are reversible by zinc substitution. Thymulin induces markers of differentiation in immature T cells in the thymus but also has effects in the periphery. It modulates cytokine secretion of peripheral blood mononuclear cells (PBMC) and, in conjunction with IL-2, induces proliferation of CD8 T cells. Zinc also influences maturation of T cells. It induces the expression of the high-affinity receptor for IL-2 and zinc deficiency is associated with decreased T cell proliferation after mitogen stimulation. Zinc regulates lymphocyte homeostasis not only by maintaining proliferation but also by inhibition of apoptosis.

At a molecular level, zinc-binding to specific membrane receptors could trigger a signal transduction cascade but, on the other hand, zinc could also exert its effects directly inside the cell.

Zinc has been shown to have immunomodulatory effects both directly, acting on the immune system and indirectly, acting on the respiratory, gastrointestinal and epithelial linings. Several studies have shown benefits of long-term zinc supplementation on the incidence, severity, and duration of diarrhea and on the incidence of respiratory infections. Prolonged zinc supplementation also improves cell-mediated immunity in severely malnourished children. Lymphocyte proliferation response and antigen specific IgG response are significantly higher after zinc supplementation compared with placebo. Zinc may also reduce the duration and severity of febrile neutropenia and associated complications.

Deficiency of zinc results in impaired growth velocity. Other features include delayed sexual maturation, hypogonadism, oligospermia, alopecia, altered taste, impaired wound healing and immune dysfunction. Skin changes include erythematous bullous or pustular lesions around body orifices, easy pluck ability of hair and changes in hair color. Deficiency has been observed in patients who are have chronic malnutrition, malabsorption, and following necrotizing enterocolitis in preterm infants.

Acrodermatitis enteropathica is an autosomal recessive condition with impaired zinc absorption.

Dietary requirement varies between 3 mg/days in children and 8 to 10 mg/day in adults.

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Vitamin D and its Role in Health

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Two forms of vitamin D exist: vitamin D₃ or cholecalciferol and vitamin D₂ or ergocalciferol. The former is produced in the skin under the influence of UVB radiation (UVR); the latter is produced by UVR in a variety of plant materials and yeast. The term “vitamin D” when used without further qualification or subscript refers to the total complement of both vitamin D₂ and vitamin D₃ or total complement of vitamin D₂ and vitamin D₃ metabolites. The active form of vitamin D (1,25 dihydroxy vitamin D [1,25(OH)₂D] is known as calcitriol. Vitamin D has been shown to have widespread and diverse activity in various body systems. The traditional role of vitamin D involves calcium absorption and skeletal health. Yet, we now know that many diverse cell types have the vitamin D metabolic machinery intact, and it has multiple functions.

The vitamin D system is complex, influencing expression of more than 200 genes, and is involved in many tissues—anything approaching even a partial understanding is many years away. Most tissues in the body have receptors for calcitriol. These receptors are named appropriately vitamin D receptors (VDRs), and tissues with VDR are potential target tissues.

In terms of evolution, two distinct functions of vitamin D exist. The more primitive function is that of a cytokine generated to protect the inside environment of the host (single cell organisms to man) from microbial invaders in the external environment.¹ The 1,25(OH)₂D cytokine is synthesized primarily by monocyte-macrophages and acts in an intracrine mode via interaction with the VDR to modulate the innate immune response to invading microbial agents.² When produced in sufficient quantities, 1,25(OH)₂D can escape the confines of the monocyte-macrophage to interact with and control the cytokine profiles of activated, VDR-expressing T- and B-lymphocytes in the local, inflammatory microenvironment (Table 1).¹

The more evolutionarily advanced function of vitamin D is that of a hormone. This function is reserved for species bearing an endoskeleton where the 1,25(OH)₂D hormone serves as a circulating regulator of both mineral and skeletal homeostasis in the host. The only recognized source of the hormone in man is the CYP27B1-hydroxylase; this enzyme is confined principally but not entirely to the proximal tubular epithelial cell of the kidney. 1,25(OH)₂D synthesis in the kidney is regulated by other hormones. It is stimulated primarily by PTH and inhibited by circulating fibroblast growth factor 23 (FGF23) made by osteocytes.³

VITAMIN D: AN OVERVIEW

Production

Vitamin D enters the human body through the production of vitamin D in the skin upon exposure to sunlight and through ingestion of either foods containing vitamin D₃, or vitamin D₂ (or dietary supplements of these

Table 1: Summary of distinctions between phylogenetically discrete functions of vitamin D one as a circulating hormone (left) and the other as a locally produced, locally active cytokine made by monocyte-macrophages (right)⁴

Hormone	Cytokine
Advanced function	Primitive function
Skeletal homeostasis	Host protection
Made by the kidneys	Made by macrophages
Acts at a distance	Acts locally
Regulated by hormones	Regulated locally
25D deficiency leads to increased 1,25D	25D deficiency leads to decreased 1,25D

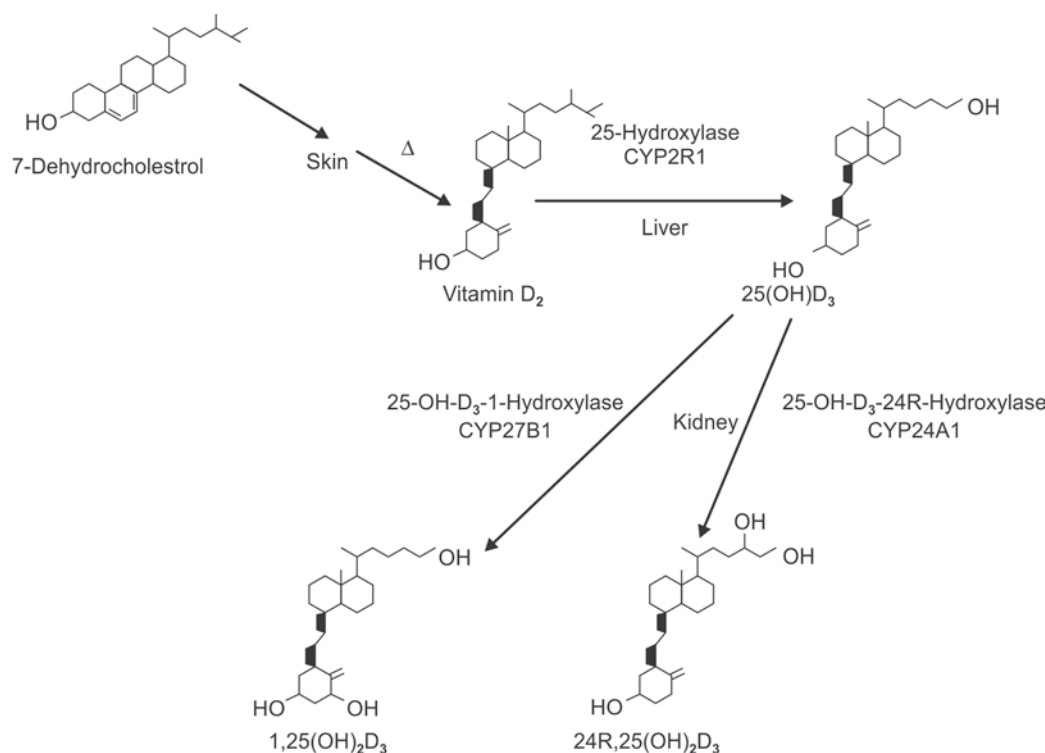


Fig. 1: Metabolism of vitamin D₃ in the skin, liver and kidney⁵

substances). 7-dehydrocholesterol present in epidermal cells is converted to pre-vitamin D₃ upon exposure to UVR (wavelength, 290–315 nm). Following thermal rearrangement of triene system, vitamin D₃ (D₃) is released into the blood. The amount of D₃ made by the skin is determined by the exposure of the epidermal cells to UVR, which in turn depends on several geographical, physical, and cultural conditions. Some of the well-defined factors include proximity to the equator; altitude and degree of skin pigmentation. Cultural factors like type of clothing and use of sunscreen also affect vitamin D production.⁵

Metabolism (Fig. 1)

After entering the body through either endogenous production from the skin or through ingestion, D₃ is released into the circulation where the majority is quickly hydroxylated in the liver at the C25-position of the side chain. The product of this enzymatic modification, 25-hydroxyvitamin D₃ 25(OH)D₃; (25D₃) is the major circulating D₃ derivative. To be biologically active, vitamin D must first be converted to 25D₃. The enzyme that catalyzes the 25-hydroxylation of vitamin D is a cytochrome P-450-dependent enzyme. D₂ undergoes similar, if not identical metabolism after ingestion.⁵ In the discussion that follows the term “1,25D” is used to denote 1,25(OH)₂D derived from both D₂ or D₃.

The major circulating form of vitamin D, and the form that is currently used as a measure of an individual's

vitamin D status, is 25-hydroxyvitamin D (25D). The site of 25-hydroxylation of vitamin D is the liver where the enzyme 25-hydroxylase, a liver cytochrome P450 (CYP2R1) microsomal enzyme, acts as a specific hydroxylase. Recently, low levels of CYP2R1 have also been detected in the testis.

1 α ,25(OH)₂D (1,25D) is the primary hormonally active form of vitamin D. To be fully active, 25D must be further converted to 1,25D via CYP27B1, a mitochondrial P450 enzyme which acts as 1 α -hydroxylase. Although the proximal renal tubule is the major source of 1,25D production for the body, the enzyme is also found in a number of extrarenal sites such as immune cells, epithelia of many tissues, bone, and parathyroid glands,⁶ in which it functions to provide 1,25D for local consumption as an intracrine or paracrine factor.

Mechanism of Action (Fig. 2)

In an individual, changes in hormonal vitamin D metabolism and action occur quickly to maintain normocalcemia in the face of vitamin D insufficiency/deficiency and a reduction in the efficiency of intestinal calcium absorption. Decreased intestinal calcium absorption results in a small but real decrease in the serum calcium concentration as well. This decrease is detected by the calcium-sensing receptor in the plasma membrane of the parathyroid cell that activates a signal to release PTH from the gland and to increase PTH gene expression. Interaction of PTH

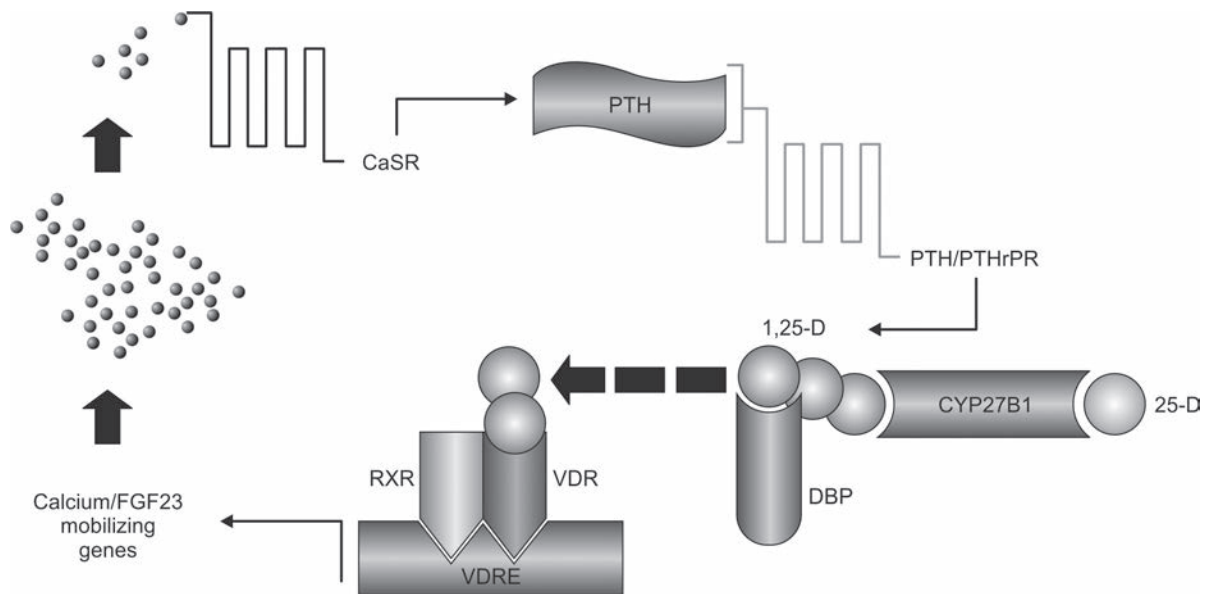


Fig. 2: Serial endocrine responses to a decrease in vitamin D directed intestinal calcium absorption in acquired vitamin D insufficiency/deficiency; the final step in the process is 1,25-D stimulation of genes controlling calcium absorption from the gut, mobilization of calcium from the skeleton and, finally, synthesis and release of FGF23, which acts to return previously enhanced PTH and CYP27B1-hydroxylase gene expression to normal. DBP, Vitamin D binding protein; RXR, retinoid X receptor

with the PTH/PTHrP receptor in the plasma membrane of the proximal tubular epithelial cell of the kidney signals an increase in CYP27B1 gene expression and conversion of available substrate 25D to 1,25D. 1,25D finds its way back into the serum and onto a serum vitamin D binding protein, whereby it gains access to control regions [vitamin D responsive elements (VDREs)] of VDR-regulated genes in the gut and bone to:

- Promote intestinal calcium and phosphate absorption.
- Liberate calcium and phosphate from the mineral phase of bone, respectively.

The mechanism of action of the active form of 1,25D is similar to that of other steroid hormones and is mediated by its binding to VDR. VDR is a member of the superfamily of nuclear hormone receptors including receptors for steroid and thyroid hormones and retinoic acid. VDR functions as a heterodimer generally with the retinoid X receptor for regulation of vitamin D target genes. These heterodimeric complexes interact with specific DNA sequences (VDREs), generally within the promoter of target genes, resulting in either activation or repression of transcription. The control of transcription requires the additional recruitment of co-regulators. These VDREs can be many thousand nucleotides away from the transcription start site, however.⁷⁻¹²

Regulation of 1,25D Synthesis in the Kidney

The three main influences on 1,25D production by the kidney are direct negative feedback by 1,25D itself,

parathyroid hormone (PTH) as a signal of calcium status and fibroblast growth factor 23 (FGF23) as a signal of phosphate homeostasis. Additionally 1,25D negatively regulates its own levels by inducing CYP24, like CYP27B1, a mitochondrial P450 that catabolizes both 1,25D and 25D.¹³

Once the deficit in the serum calcium concentration is corrected by the previously discussed means, the activated 1,25D:PTH axis is subsequently down-regulated by FGF23 released from bone.¹⁴

Feedback Regulation by 1,25D3

A universally observed negative feedback mechanism is the 1,25D status of the individual.¹⁵ This effect is a transcriptional one and is most likely mediated through the interaction of the hormone with its VDR. This down-regulates expression of the gene for CYP27B1 through a negative response element (nVDRE) in or near the promoter region of the gene.

Regulation of 1,25D Synthesis by Calcium/PTH

With deficiency of vitamin D there is a significant decrease in the intestinal calcium absorption. This leads to an increased secretion of parathyroid hormone (PTH). PTH in turn enhances the tubular reabsorption of calcium and stimulates the kidneys to produce 1,25D. It also activates osteoblasts, which stimulate the transformation of pre-osteoclasts into mature osteoclasts.^{8,16-19}

The activity of 1α -hydroxylase is inversely proportional to the dietary and serum calcium status. This regulation is mediated by PTH, the effect is exerted directly on the kidney cell, and it involves the second messengers generated by protein kinases A and C.²⁰ Regulation of the ability of the kidney to produce 1,25D by PTH is specific to the proximal cells of the kidney²¹ and is exerted at both the transcriptional and post-transcriptional levels. The promoter region of the CYP27B1 gene contains a region that renders its transcription sensitive to stimulation by PTH.^{22,23} Recently a role for DNA methylation and demethylation in the regulation of CYP27B1 expression by PTH has been reported with demethylation and transcriptional activity resulting from PTH stimulation.²⁴

Regulation of 1,25D by Phosphate/FGF23 (Fig. 3)

Hypophosphatemic disorders are associated with renal phosphate excretion, defective skeletal mineralization, osteomalacia in adults and rickets in children and inappropriately (for the given serum phosphate levels) low serum 1,25D levels. In addition to the role of FGF23 as the hypophosphatemic agent it also seems to mediate the regulatory effect of serum phosphate levels on vitamin D metabolism, in particular the lowering of 1,25D levels in the blood.²⁵ The underlying mechanism by which the synthesis and secretion of FGF23 synthesis in the bone cells is stimulated by elevated phosphate levels has not been elucidated, but it is clear that FGF23 is integral to

maintenance of phosphate homeostasis, one aspect of which is the modulation of vitamin D metabolism.

As previously mentioned, PTH, secreted in response to low serum calcium levels, stimulates the transcription (and possibly post-transcriptional activation) of CYP27B1 and 1,25D inhibits it. Since 1,25D also stimulates the movement of phosphate into the blood from the intestine and bone, it is not surprising that an inverse relationship between the synthesis and circulating concentrations of 1,25D and the serum phosphate levels has been known for decades. Recent studies have shown that the basis of this relationship lies in the inhibition of the transcription of CYP27B1 in the kidney by FGF23, which is secreted by bone osteocytes in response to elevated serum phosphate concentrations. Thus, in the kidney FGF23 causes, at the same time, increased phosphate excretion in the urine, through reduction in the number of sodium-phosphate co-transporters in the brush border membranes^{26,27} and decreased 1,25D synthesis by the proximal renal tubules.²⁸

Extrarenal 1,25D Production

Although the kidney is the major endocrine organ that produces 1,25D in response to other calcium- and phosphate-regulating hormones, the presence of CYP27B1 and the ability to convert 25D to 1,25D in fact resides in many other tissues (major sites previously mentioned). In general extrarenal 1α -hydroxylase activity is not regulated by

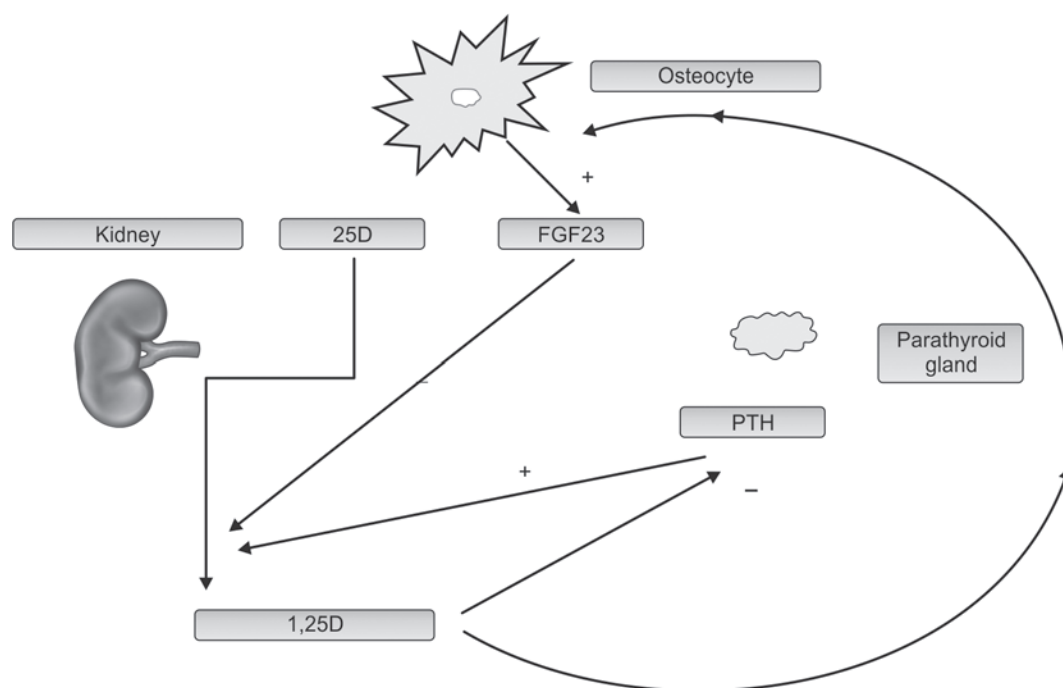


Fig. 3: Regulation of 1,25D production in the kidney. PTH stimulates and FGF23 inhibits 1,25D production in the kidney. In turn 1,25D inhibits PTH production and secretion from the parathyroid glands and stimulates FGF23 production from bone

the classical calcium and phosphate-regulating hormones, but the enzyme's activity may be subject to changes specific to the cell's environment or function.

Control of 1,25D production (and levels) by non-renal tissues differs. When macrophages are activated via specific toll-like receptors (TLRs), CYP27B1 is induced. In these cells 1,25D production appears to be governed primarily by the availability of substrate.²⁹ The keratinocyte also contains CYP27B1, which like the macrophage enzyme can be induced by activation of specific TLRs.³⁰ Both TNF- α and interferon (IFN)- γ stimulate 1,25D production by keratinocytes, suggesting that the keratinocyte like the macrophage uses 1,25D for important host defence mechanisms.^{31,32}

Inactivation of 1,25D in its Target Tissues

CYP24 is one of the most dramatically activated genes in target tissues of 1,25D with increases of mRNA levels from barely detectable to several hundred or a few thousand fold above basal levels. Clearly the induction of this CYP24, which can carry out the catabolism of 1,25D to inactive product(s) is an important element of negative feedback to curtail the hormone's action in its target cells.

Renal Production of 24,25D

The physiological significance of 24R,25D has long been the subject of debate. The kidney produces circulating levels of 24,25D and it is known that renal 24R hydroxylase activity is inversely related to 1 α -hydroxylase activity. This is largely due to the opposing effects of 1,25D on the expression 24R-hydroxylase activity (stimulation) and 1 α -hydroxylase expression.

Sources and Daily Requirements in the Pediatric Population (Table 2)

A potential source of vitamin D is synthesis in the skin from the ultraviolet-B light fraction of sunlight. However, the amount of vitamin D synthesized in the skin varies widely due to factors previously discussed. This makes it very difficult to determine the adequacy of sunshine exposure for any given infant or child.

The usual diet of infants contains only small amounts of vitamin D. Breast milk content is low, and bovine milk content is even lower. Human milk typically contains a vitamin D concentration of 25 IU/L or less.³³⁻³⁵ Thus, the recommended adequate intake of vitamin D cannot be met with human milk as the sole source of vitamin D for the breastfeeding infant. Cereals, vegetables, and fruits contain only negligible amounts. Vitamin D sources are limited in the diet and mainly include oily fish, mushrooms, and some fortified milks and foods.

The previous AI was 200 IU/day for all infants and children.³⁶ The authors of two recent statements (a joint

Table 2: Vitamin D intake recommendations⁴⁴

Age	Vitamin D, recommended intake ^a (IU/d)
0-6 months	400
6-12 months	400
1-3 years	600
4-8 years	600
9-18 years	600

a: Recommended intake values are the RDA values for children aged 1 year and older. AI values for infants younger than 1 year.

report from the American Academy of Pediatrics Committee on Nutrition and Section on Breastfeeding³⁷ and a separate statement from the Pediatric Endocrine Society [PES]³⁸ recommended a vitamin D intake of 400 IU/day for all children; in addition, the PES statement indicated a usual target for serum 25D (25[OH]) of ≥ 50 nmol/L (20 ng/ml).³⁸ Vitamin D deficiency is defined by most experts as a 25D level of less than 20 ng/ml (50 nmol/L).³⁹⁻⁴² A level of 25D of 21 to 29 ng/ml (52-72 nmol/L) can be considered to indicate a relative insufficiency of vitamin D, and a level of 30 ng/ml or greater can be considered to indicate sufficient vitamin D.⁴³

Role of Vitamin D in Health

Traditionally vitamin D has been known to be involved in calcium absorption and skeletal health. Vitamin D is essential for normal mineralization of bone or osteoid tissue.

Osteoblasts initiate new bone formation and are responsible for matrix deposition and subsequent mineralization. They secrete collagen and changes in polysaccharides, phospholipids, alkaline phosphatase, and pyrophosphatase follow until mineralization occurs. However, normal mineralization occurs only in the presence of adequate calcium and phosphorus. Osteoclasts on the other hand are responsible for resorption of bone through enzymes secreted on the bone surface, which dissolve and remove both matrix and mineral. Osteocytes covered by bone both resorb and redeposit bone. Many incompletely delineated factors affect bone growth through poorly defined pathways, but phosphorus, calcium, fluoride, and growth hormone are known to be involved.

Vitamin D deficiency leads to low serum calcium levels which in turn stimulates calcium release from the bones to maintain normocalcemia. However, this is at the cost of decreased bone mineralization. In the absence of vitamin D, only 10 to 15 percent of dietary calcium and about 60 percent of phosphorus is absorbed.^{8,17,18} The interaction of 1,25D with the vitamin D receptor increases the efficiency of intestinal calcium absorption to 30 to 40 percent and phosphorus absorption to approximately 80 percent.⁴⁵ Deficiencies of calcium and vitamin D in utero and

in childhood may prevent the maximum deposition of calcium in the skeleton.³⁶ As vitamin D deficiency progresses, the parathyroid glands are maximally stimulated, causing secondary hyperparathyroidism.^{39,41-43} In children, the deficiency of vitamin D leads to rickets (discussed extensively in a separate chapter).

Vitamin D deficiency causes muscle weakness. Skeletal muscles have a vitamin D receptor and may require vitamin D for maximum function.^{16,39,40,46}

Nonclassic Roles of Vitamin D

Over the last few years it has been found the VDRs are present in most of the body tissues in humans. Also, many of these tissues contain CYP27B1 which is essential for the synthesis of 1,25D. Hence, in the past few years, there has been growing appreciation for the many roles of vitamin D and its active metabolites in a large number of tissues. An exciting concept regarding the role of vitamin D in a large number of physiologic functions beyond that of the classic actions involved with bone mineral metabolism is rapidly emerging.

Based on recent research in this area, the nonclassic actions of vitamin D can be categorized into three general effects:

1. Regulation of hormone secretion.
2. Regulation of immune function.
3. Regulation of cellular proliferation and differentiation.

REGULATION OF HORMONE SECRETION AND METABOLISM

Vitamin D has a relatively well-known role in regulation of hormone secretion to control bone mineral density. 1,25D inhibits the secretion of PTH and prevents the proliferation of the parathyroid gland.^{47,48} This action is mediated through a negative VDRE on the parathyroid gene. 1,25D also upregulates the calcium-sensing receptor,⁴⁹ thus sensitizing the parathyroid gland to calcium inhibition and providing an additional means by which 1,25D regulates PTH production and secretion. PTH stimulates 1,25D production in the kidney, hence this inhibition of PTH production and secretion provides an important feedback loop. These actions of 1,25D are exploited clinically through the use of 1,25D and analogs to control secondary hyperparathyroidism in renal failure. Furthermore, the ability of the parathyroid gland to make its own 1,25D provides an explanation for the reciprocal relationship between 25D and PTH levels, but not between 1,25D and PTH levels, in the blood of subjects with vitamin D insufficiency.⁵⁰

Apart from this, its role in insulin secretion is a recently identified area of nonclassic action that appears to have significant therapeutic importance. 1,25D stimulates insulin secretion and significant case control and observational studies have suggested that vitamin D deficiency may

contribute to increased risk for type 2 diabetes mellitus. The mechanisms by which this effect is mediated have still not been fully elucidated, however VDR and calbindin-D28k are found in pancreatic β -cells,^{51,52} and studies using calbindin-D28k null mice have suggested that calbindin-D28k, by regulating intracellular calcium, can modulate depolarization-stimulated insulin release.⁵³ Furthermore, calbindin-D28k, by buffering calcium, can protect against cytokine mediated destruction of β -cells.^{54,55}

FGF23 is primarily produced by osteoblasts and osteocytes in the bone. 1,25D stimulates this process by ill-defined pathways.⁵⁶ FGF23 in turn inhibits renal synthesis of 1,25D, thus forming a negative feedback loop which ensures control over the levels of these important hormones. Mutations in the phosphate-regulating gene on the X chromosome (PHEX) or FGF23 itself (which prevent its proteolysis) or conditions such as McCune-Albright disease and tumor-induced osteomalacia in which FGF23 is over-expressed in the involved tissue lead to hypophosphatemia and inappropriately low 1,25D accompanied by osteomalacia.

There is growing evidence of association of low 25D levels with increase in cardiovascular mortality in the form of coronary artery disease, heart failure and peripheral vascular disease.⁵⁷ In fact, review of recent vitamin D deficiency epidemiological data has revealed a striking inverse correlation of the 25D levels not only to cardiovascular disease but also to essentially all elements of the human metabolic syndrome, namely (1) hypertension, (2) obesity and (3) insulin resistance and glucose intolerance.

Vitamin D-Fat-Bone Axis: An intriguing new hypothesis postulates that there may be causal association between increasing obesity, its attendant cardiovascular risks and vitamin D deficiency/insufficiency. Low 25D levels observed in association with obesity may be due in part to: (1) the increased volume of distribution to fat of lipid soluble vitamin D as it leaves the general circulation after being synthesized in the skin or obtained through the diet; and (2) preferential retention of vitamin D in those fat stores. Also, studies in mice indicate that vitamin D deficiency may promote increase in body weight by itself. It is hypothesized that this increase in body fat mass acts in a “feed-forward” fashion to further increase the volume of distribution for vitamin D, deepen the state of vitamin D deficiency, and amplify the consequences of secondary hyperparathyroidism on the skeleton and body fat. There are some data now to suggest that there exists a leptin-mediated “negative feedback” loop to interrupt this cycle of fat accumulation.⁵⁸

REGULATION OF IMMUNE FUNCTION

Three important discoveries about two decades ago heralded the identification of the potential role of vitamin D and 1,25D in the modulation of immune response. These were:

- The presence of VDRs in activated human inflammatory cells.⁵⁹
- The ability of 1,25D to inhibit T cell proliferation.⁶⁰
- The ability of disease activated macrophages to produce 1,25D (i.e. express CYP27B1)⁶¹

Vitamin D and CYP27B1 both play notable roles in innate and adaptive immunity. In this regard the description of cathelicidin, an antimicrobial peptide that enhances killing of the mycobacterium tuberculosis is notable.² The monocyte activated by mycobacterial lipopolysaccharide induces CYP27B1 which in turn produces 1,25D. This 1,25D induces the production of cathelicidin. Other recent studies have shown that 1,25D-directed production of cathelicidin is not restricted to monocyte-macrophages. Indeed, this appears to involve an antimicrobial mechanism also employed by epithelial cells from a variety of tissue “barrier” sites, like the gut,⁶² lung,⁶³ placenta,⁶⁴ and skin.⁶⁵⁻⁶⁸

Also, it has been observed in several studies that vitamin D deficiency and/or living at higher altitudes (i.e. lesser sunlight) is associated with several autoimmune diseases like type 1 diabetes mellitus, multiple sclerosis, and Crohn's disease.⁶⁹ In a large Finnish study, providing infants with 2000 IU vitamin D for their first year of life reduced the incidence of type 1 diabetes mellitus by 80%.⁷⁰ Other studies have linked vitamin D deficiency to increased risk of multiple sclerosis, asthma, and other immunologic diseases.^{71,72}

Role of Vitamin D in Regulation of Adaptive and Innate Immunity

Vitamin D has an inhibitory action on the adaptive immune system. Adaptive immunity is constituted by the ability of the B- and T-cells to secrete immunoglobulins and cytokines respectively in response to specific antigenic stimulation. In particular, 1,25D suppresses proliferation and immunoglobulin production and retards the differentiation of B-cell precursors into plasma cells.⁷³ It also inhibits T-cell proliferation, especially T helper (Th-1) cells capable of producing IFN- γ and IL-2 and activating macrophages.⁷⁴ In contrast IL-4, IL-5, and IL-10 production can be increased, shifting the balance to a Th-2 cell phenotype. CD4/CD25 regulatory T cells (Treg) are also increased by 1,25D.^{75,76} At least in part, these actions on T cell proliferation and differentiation stem from actions of 1,25D on dendritic cells to reduce their antigen presenting capability.

As previously mentioned 1,25D has a beneficial role in many autoimmune conditions due to its propensity to suppress adaptive immunity.

Activation of toll like receptors (TLRs) in polymorphonuclear cells, monocytes, macrophages and also lining epithelium in various tissues plays a central role in innate immunity. This leads to the induction of antimicrobial

peptides and reactive oxygen species, which kill the organism. Among those antimicrobial peptides is cathelicidin, an antimicrobial peptide that is induced by 1,25D in both myeloid and epithelial cells.^{77,78} Stimulation of TLRs by appropriate inflammatory stimuli leads to increased expression of CYP27B1, thus eliciting expression of cathelicidin in the presence of adequate 25D.

Regulation of Proliferation and Differentiation

Vitamin D has a unique relation with the keratinocyte in the epidermis. It is not only synthesized in this cell, but it can also be converted to its active form here and finally the keratinocyte is capable of responding to this 1,25D. It enables this cell to mount an innate immune response, promotes its differentiation and also inhibits its proliferation. Vitamin D is closely linked to the sequential differentiation and orderly progression of the keratinocyte from the basal layer of the epidermis to ultimately forming the enucleated corneocyte (permeability barrier of the skin).

Hair follicle cycling is the best example of a role for VDR independent of 1,25D. The mechanism by which VDR regulates hair follicle cycling remains unclear. Studies suggest an important role for the VDR in regulating the proliferation and differentiation of these cells during the process of hair follicle cycling.⁷⁹

Analogues of 1,25D, such as calcipotriol, as well as calcitriol itself have proved effective therapy for moderate forms of psoriasis.⁸⁰ This form of therapy likely works by inhibiting the inflammatory component via a direct action on the T-cells⁸¹ as well as by reducing keratinocyte proliferation and enhancing their differentiation.⁸²

Role in cancer: A variety of malignant cells express VDRs. The hypothesis proposed to explain the possible role of vitamin D in the prevention and treatment of cancer includes its anti-proliferative, pro-differentiating effects on most cell types. In particular 1,25D stimulates the expression of cell cycle inhibitors p21 and p27 and the expression of the cell adhesion molecule E-cadherin and inhibits the transcriptional activity of β -catenin.⁸³⁻⁸⁶ In keratinocytes, 1,25D has been shown to promote the repair of DNA damage induced by UVR,⁸⁷ reduce apoptosis and increase survival after UVR, and increase p53.⁸⁸ There is epidemiological evidence to support the role of adequate vitamin D in the prevention of cancers. However, some recent trials have provided inconclusive and often conflicting data regarding the ability of this vitamin to prevent cancer.^{89,90} Trials of 1,25D and its analogues for the treatment of cancer have been disappointing. Studies in prostate cancer^{91,92} have shown some possible role for vitamin D in therapy. But the results have not been uniform. Hypercalcemia and hypercalciuria have been noted as significant adverse effects following therapy with vitamin D in some studies. It is likely that role of vitamin D

in cancer therapy will be better realized only once a non-hypercalcemic and efficacious vitamin D analog is developed.

MISCELLANEOUS FUNCTIONS

Schizophrenia and mental illness: Maintenance of adequate vitamin D levels in utero and early life may be essential to satisfy the vitamin D receptor transcriptional activity in the brain, may be important for brain development as well as for maintenance of mental function later in life.⁹³

Wheezing illness: Normal levels of vitamin D have been shown to help maintain higher levels of forced expiratory volumes at one second on pulmonary function testing. Vitamin D deficiency during pregnancy has been associated with higher incidence of wheezing illnesses in their children.

Hypervitaminosis D

Both ergocalciferol and cholecalciferol can be used for the treatment and prevention of vitamin D deficiency.⁹⁴ Many people consume vitamin supplements on the assumption that vitamins are safe, and while there is a large margin of safety between adequate vitamin D levels and toxicity, this can result in toxicity. Patients should be advised to desist from self-prescription and use of vitamin supplements, especially for prolonged periods and to always consult their health care provider before initiating vitamin D supplementation at a daily dose greater than 1000-2000 IU. This will go a long way in ensuring that the intended dose is safe and that appropriate monitoring is performed if necessary.

Hypervitaminosis D has rarely been reported and usually occurs in the setting of gross excess of supplemental vitamin D₂ or D₃.⁹⁵⁻⁹⁷ Because any excess previtamin D₃ or vitamin D₃ is destroyed by sunlight, excessive exposure to sunlight does not cause vitamin D₃ intoxication. The main toxicities of hypervitaminosis D are hypercalcemia and hyperphosphatemia. Hypervitaminosis D is unlikely to occur until the 25D level, the main storage form of vitamin D, exceeds 150 ng/mL.⁹⁸ Patients may also experience nonspecific symptoms such as nausea, vomiting, anorexia, confusion, and weakness, typically secondary to the resulting hypercalcemia.⁹⁹ The upper limit of daily vitamin D intake required to cause toxicity is unknown; however, up to 10,000 IU daily has been considered safe in a healthy population.⁹⁸ Patients with chronic granulomatous disorders are more sensitive to serum 25D levels above 30 ng/mL because of macrophage production of 1,25D, which causes hypercalciuria and hypercalcemia.¹⁰⁰

Discontinuation of any supplements being used should be the first step in the management of hypervitaminosis. Decreasing calcium intake is also an essential measure. In more severe cases oral aluminium hydroxide is useful as

adjunctive therapy. Occasionally, chelation therapy may be indicated.

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Malnutrition in Children

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Malnutrition is a state of deficiency or excess of energy, protein, and other nutrients, this chapter deals with under nutrition and specifically protein energy malnutrition (PEM). Under nutrition ranges from a lower than desired intake of one or more nutrients leading to a clinical spectrum from no symptoms or only vague symptoms to severe malnutrition. World Health Organization (WHO) defines malnutrition as “the cellular imbalance between the supply of nutrients and energy and the body’s demand for them to ensure growth, maintenance, and specific functions.” Some pediatric textbooks use the term severe childhood undernutrition (SCU) as an alternative to PEM as it is always accompanied by deficiencies of other nutrients. The terms primary malnutrition and secondary malnutrition refer, respectively, to malnutrition resulting from inadequate food intake and malnutrition resulting from increased nutrient needs, decreased nutrient absorption, and/ or increased nutrient losses.¹

FAILURE TO THRIVE (FTT) VS MALNUTRITION

Failure to thrive (FTT) as understood in the western texts, was not usually considered to be primarily due to dietary malnutrition and was divided into either Organic FTT, marked by an underlying medical condition or nonorganic or psychosocial FTT. However if applied generically, the term FTT only means failure to gain weight adequately which in the larger context (especially in developing country context) is mostly due to dietary malnutrition. As failure to thrive indicates impairment of growth velocity, it helps to detect growth faltering (malnutrition) at the earliest when absolute growth values may still be within the normal range.

However western texts now consider the term FTT (as used earlier) as an imprecise, archaic and obsolete term.² It is now recognized that in all cases of nonorganic FTT and few cases of organic FTT, the proximate cause of

growth failure is malnutrition whether primary or secondary. The modern diagnosis and treatment of FTT focus on the assessment and therapy for malnutrition and its complications.^{3,4} It is suggested that growth failure or growth faltering may be a better term in place of FTT.²

BURDEN OF MALNUTRITION

International

Among the four principal causes of mortality in young children worldwide, undernutrition has been ascribed to be the cause of death in 60 to 70 percent of children with diarrheal diseases, 52.3 percent of those with pneumonia, 44.8 percent of measles cases, and 57.3 percent of children with malaria.⁵ Malnutrition is a major public-health problem throughout the developing world and is an underlying factor in over 50 percent of the 10–11 million children under 5 years of age who die each year of preventable causes.^{6,7}

National

Almost half of children under five years of age (48 percent) are stunted and 43 percent are underweight. The proportion of children who are severely undernourished (more than three standard deviations below the median of the reference population) is also notable—24 percent according to height-for-age and 16 percent according to weight-for-age. Wasting is also quite a serious problem in India, affecting 20 percent of children under five years of age (Fig. 1). Very few children under five years of age are overweight.

Undernutrition is substantially higher in rural areas than in urban areas. Even in urban areas, 40 percent of children are stunted and 33 percent are underweight. Children who are judged by their mothers to have been small or very small at the time of birth are more likely to be undernourished than those who were average size or larger. Thus



Fig. 1: Proportion of malnourished children 0-59 months NFHS-3, India

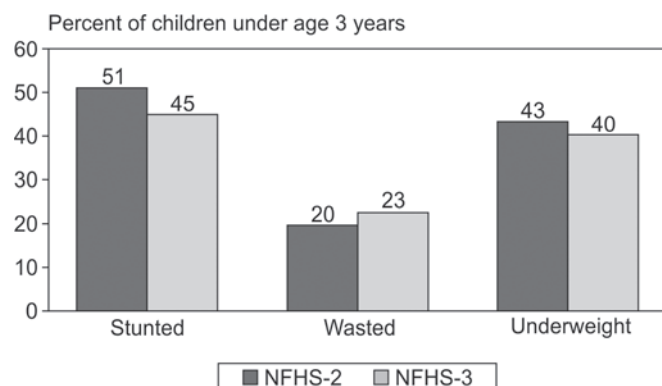


Fig. 2: Trends in nutritional status in India

low birth weight is a major contributing factor to deficient growth in under 5 children. Undernutrition has a strong negative relationship with the maternal education.⁸

The nutritional status of children is strongly related to maternal nutritional status. Undernutrition is much more common for children of mothers whose body mass index is below 18.5 than for children whose mothers are not underweight. In NFHS-3 compared to NFHS-2, the prevalence of children who were underweight decreased slightly more in urban areas than in rural areas, but there was very little improvement in the percentage of children who were severely underweight, even in urban areas (Fig. 2).⁸

ANTHROPOMETRY

Anthropometric parameters can assess growth cross-sectionally or longitudinally. If children are measured once, their growth status for age can be assessed by comparing this measurement with the appropriate reference curve.

If they are measured more than once, and plotted on an appropriate growth curve, growth velocity data is obtained which can be even more useful. Particular care should be taken to use appropriate equipment and techniques for measurement of stature/length and weight.

Weight

Infant scales, beam balances and readout scales are available. Preferably the nude weight should be taken (to the least count of the available scale after correcting the zero error/calibration) or else the estimated weight of the clothing should be subtracted. The newborn weight should be taken close to the nearest gram. As weight is the earliest anthropometric parameter to be affected by undernutrition, it is the most important index of early and current malnutrition.

Length and Height

It is the most useful indicator of long term growth status. Recumbent length is measured in children less than 2 years of age and stature/standing height is measured in children more than two years of age. It is most important that correct methodology is followed when either of the parameters are being recorded. When possible, the parents' stature should be taken to determine the influence of genetics on growth. Length or height is affected in long standing malnutrition, therefore stunting is usually a reflection of long standing undernutrition.

Head Circumference

It must be measured with a narrow and a nonstretchable tape. It is a useful parameter until 3 years of age when the head growth slows down.

Mid Upper Arm Circumference (MUAC)

The MUAC is an indicator of muscle growth in all ages. This is also a labile (early affected) parameter of nutrition.

GROWTH STANDARDS

In 2006, the WHO released new multicentric growth reference standards (MGRS) for assessing the growth and development of children from birth to 5 years of age. These new standards are based on breastfed infants and appropriately fed children of different ethnic origins raised in optimal conditions and measured in a standardized way. The WHO charts are based for the first time on a prescriptive, prospective, international sample of infants selected to represent optimum growth. The MGRS was a population-based study conducted between 1997 and 2003 in Brazil, Ghana, India, Norway, Oman, and the United States. The MGRS combined a longitudinal follow-up from birth to 24 month with a cross-sectional component of children aged between 18 and 71 month. In the longitudinal component, mothers and newborns were enrolled at birth and visited at home a total of 21 times at week 1, 2, 4 and 6; monthly from 2 to 12 months; and bimonthly in the 2nd year. In the cross sectional component the children were exclusively breast fed for a minimum of 3 months and appropriate complementary feeds introduced. The same cohort was used to produce standards of MUAC in relation to age. The new WHO growth standards confirm earlier observations that the effect of ethnic differences on the growth of infants and young children in populations is small compared with the effects of the environment. Studies have shown that there may be small ethnic differences among groups, just as there are genetic differences among individuals, but for practical purposes they are not considered large enough to invalidate the general use of the WHO growth standards population as a universal standard. These new standards have been endorsed by international bodies such as the United Nations Standing Committee on Nutrition, the International Union of Nutritional Sciences and International Pediatric Association and have been adopted in more than 90 countries. Even the CDC now recommends the use of WHO standards in US population up to 2 years of age (Table 1).

Growth Reference vs Growth Standard

The CDC and WHO growth charts differ in their overall conceptual approach to describing growth. The WHO charts are growth standards that describe how healthy children should grow under optimal environmental and health conditions whereas CDC growth charts are a growth reference, not a standard, and describe how certain children grew in a particular place and time. The numerous

concerns about the CDC charts include a lack of racial diversity in the infant sample, an infant sample composed of infants who were almost all formula fed, and the disjunction in length and stature measurements when transitioning from the charts for younger children to those for older children. Also there are concerns that the CDC charts are predisposing children to obesity by promoting excessive weight gain in infancy.

Age Independent Nutritional Anthropometry (Table 2)

Recording of individual parameters of growth and comparing them with reference standards for the age is used for assessing and grading the nutritional status. However in actual field conditions actual age of the child is often not available, then a comparison of a relatively labile parameter (weight/mid arm circumference, etc.) with a 'nonlabile' parameter like length/height or head circumference can be used to assess nutritional status. Various indices have been arrived at for use as tools in this 'Age Independent Nutritional Anthropometry' (Table 2). Kanawati index is one such which is obtained by dividing mid arm circumference by head circumference. More than 0.31 is normal.

Mid Upper Arm Circumference

Requires minimum equipment and is relatively stable between 1 and 5 years with a value between 16 and 17 cm. Any value below 13.5 cm is abnormal and suggestive of malnutrition. WHO recommends MUAC to be used in girls and boys 6 to 59 months of age, as an age independent criteria for assessing malnutrition. A value below 115 mm is an independent indicator for severe malnutrition. Shakir's Tape is a useful tool for peripheral health worker as it utilizes the MUAC in three visual zones-Red <12.5 cm, yellow between 12.5 and 13.5 cm (Borderline) and green >13.5 cm (Normal).

Bangle test: A bangle is passed above the elbow, whose internal diameter is 4 cm (circumference about 12.5 cm). If the bangle can be passed above the elbow it indicates that the child has severe malnutrition (Table 3).

Cole's classification: Cole's classification is another alternative classification based upon the use of BMI scores for the classification of malnutrition. It classifies low BMI scores for age as thinness in children and adolescents. Low BMI scores correlate well with low lean body mass and not just the opposite of fatness as in thin children BMI is a better predictor of lean mass than fat mass.¹⁰

IAP classification of malnutrition: IAP classification is a modified Jelliffe's classification based on weight for age values based on the 50th centiles of older Harvard standards. This classification is still used in the ICDS classification of malnutrition to be used by peripheral health worker (Anganwadi worker) (Table 4).

Table 1: Growth charts WHO vs CDS standards⁹

<i>Characteristic</i>	<i>CDC growth reference (2000)*</i>	<i>WHO growth standard (2006)⁺</i>
Data sources	National vital statistics (birth weights) Missouri and Wisconsin vital statistics (birth lengths) Pediatric Nutrition Surveillance System (lengths, 0.1 to <5 mos) NHANES I (1971–1974) (12–23 mos) NHANES II (1976–1980) (6–23 mos) NHANES III (1968–1994) (2–23 mos)	MGRS longitudinal component, with sites in the following locations: Pelotas, Brazil Accra, Ghana Delhi, India Oslo, Norway Muscat, Oman Davis, California
Type and frequency of data collection	Cross-sectional data on weight and length starting at age 2 mos, with mathematical models used to connect birth weights and lengths to survey data	Longitudinal data with measurements of weight and length at birth; 1, 2, 4, 6, and 8 wks; and 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, 18, 20, 22, and 24 mos
Sample size	4,697 observations for 4,697 distinct children	18,973 observations for 882 distinct children
Exclusion criteria	Very low birth weight (<1,500 g [<3 lbs, 4 oz])	Low socioeconomic status Birth at altitude > 1,500 m Birth at <37 wks or ≥42 wks Multiple birth Perinatal morbidities Child health conditions known to affect growth Maternal smoking during pregnancy or lactation Breastfeeding for <12 mos Introduction of complementary foods before age 4 mos or after age 6 mos Weight-for-length measurements >3 standard deviations above or below study median for sex
Breastfeeding among infants in sample	Approximately 50% ever breastfed Approximately 33% breastfeeding at 3 mos	100% ever breastfed 100% predominantly breastfeeding at 4 mos 100% still breastfeeding at 12 mos Complementary foods introduced at mean age of 5.4 mos

Abbreviations: MGRS = Multicentre Growth Reference Study; NHANES = National Health and Nutrition Examination Survey; WHO = World Health Organization.

**Source:* Kuczmarski RJ, Ogden CL, Guo SS, et al. 2000 CDC growth charts for the United States: methods and development. *Vital Health Stat* 2002;246.

⁺*Sources:* World Health Organization. WHO child growth standards: length/height-for-age, weight-for-age, weight-for-height and body mass index-for-age: Methods and development. Geneva, Switzerland: World Health Organization; 2006. Available at http://www.who.int/childgrowth/publications/technical_report_pub/en/index.html. Accessed June 1, 2010; and WHO Multicentre Growth Reference Study Group; Enrolment and baseline characteristics in the WHO Multicentre Growth Reference Study, *Acta Paediatr Suppl* 2006;450:7-15.

Table 2: Age independent indices

<i>Name of index</i>	<i>Calculation</i>	<i>Normal value</i>	<i>Value in malnutrition</i>
Kanawati and McLaren's index	Mid arm circumference/head circumference (cm)	0.32–0.33	Severely malnourished: <0.25
Rao and Singh's index	(Weight (kg)/height ² (cm))×100	0.14	0.12–0.14
Dugdale's index	(Weight (kg)/height ^{1.6} (cm))×1	0.88–0.97	<0.79
Quackers arm circumference measuring stick (quac stick)	Mid arm circumference that would be expected for a given height		75–85%–malnourished <75%–severely malnourished
Jeliffe's ratio	Head circumference/chest circumference		Ratio <1 in a child >1 year: malnourished

Table 3: Classifications of malnutrition in children

Classification	Definition	Grading	
Gomez	Weight below % median weight for age (WFA)	Mild (Grade 1) Moderate (Grade 2) Severe (Grade 3)	75–90% WFA 60–74% WFA <60% WFA
Waterlow	Percentage below weight for height (WFH)	Mild Moderate Severe	80–90% WFH 70–80% WFH <70% WFH
WHO (wasting)	Z score (SD) below weight for height (WFH)	Moderate Severe	≥ -3 z score < -2 Z score < -3
WHO (stunting)	Z score (SD) below weight for height (WFH)	Moderate Severe	≥ -3 z score < -2 Z score < -3
Kanawati	MUAC divided by occipito frontal head circumference	Mild Moderate Severe	<0.31 <0.28 <0.25
Cole	Z scores of BMI for age	Grade 1 Grade 2 Grade 3	BMI for age z score < -1 BMI for age z score < -2 BMI for age z score < -3

Table 4: IAP classification of malnutrition (0-6 years)

Grade of Malnutrition	% Wt. for age of standard median *
Normal	>80
Grade I	71-80
Grade II	61-70
Grade III	51-60
Grade IV	<50

*50th percentile of Harvard Standard is taken as standard median

WELLCOME TRUST CLASSIFICATION OF MALNUTRITION

This system takes weight for age and presence or absence of edema for classifying malnutrition.

Weight for age	Edema	Type of malnutrition
>80%	Nil	Normal
>80%	+ve	no undernutrition (Look for cause of edema)
60–80%	–ve	Undernutrition
60–80%	+ve	Kwashiorkor
<60%	–ve	Marasmus
<60%	+ve	Marasmic Kwashiorkor

WHO CLASSIFICATION OF MALNUTRITION

As per WHO severe malnutrition is defined if the child has either edematous malnutrition or has body weight (for height) less than -3 SD (wasting). Moderate malnutrition is defined if the body weight is between -2 SD and -3 SD.

Similarly stunting is classified as severe if the height for age is <3 SD (less than 85% of expected) (Table 5).

ECOLOGICAL OF MALNUTRITION

A large number of socioeconomic factors are involved in causation of malnutrition in a child. Poverty, illiteracy, lack of health education, poor environmental sanitation (with increased diseases burden) are some of these factors. (Flow chart 1).

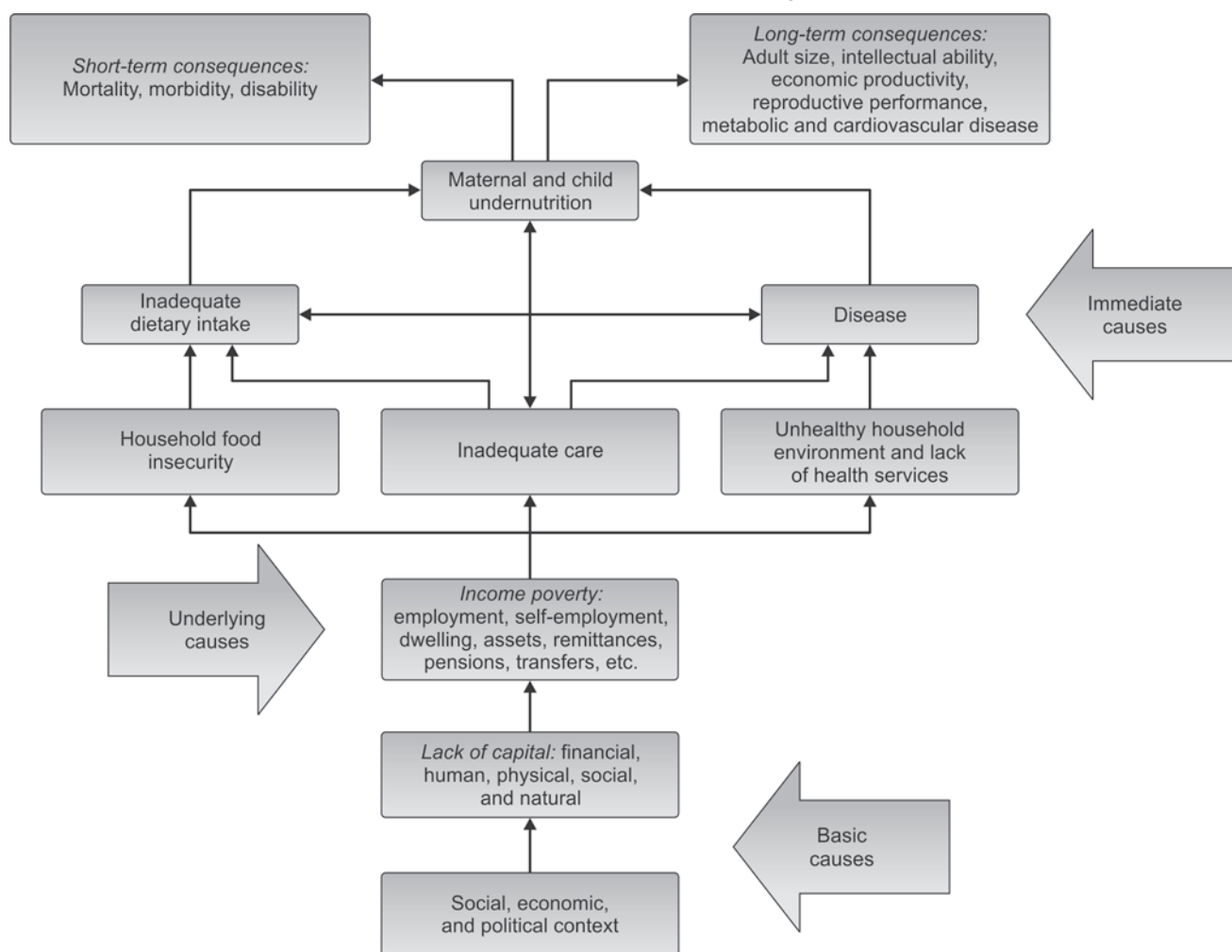
PATHOPHYSIOLOGY AND ADAPTATION

Inadequate energy intake leads to various physiologic adaptations, including growth restriction; loss of fat, muscle, and visceral mass; reduced basal metabolic rate, and reduced total energy expenditure. The biochemical changes in prolonged starvation involve complex metabolic, hormonal, and glucoregulatory mechanisms. Metabolic changes progress from the early phase, where there is rapid gluconeogenesis with resultant loss of skeletal muscle caused by use of amino acids, pyruvate and lactate, to the later protein conservation phase, with fat mobilization leading to

Table 5: WHO classification of malnutrition

	Moderate malnutrition	Severe malnutrition
Symmetrical edema	No	Yes (edematous malnutrition)
Weight for height	SD score between -2 and -3 (moderate wasting)	SD score < -3 (severe wasting)
Height for age	SD score between -2 and -3 (moderate stunting)	SD score < -3 (severe stunting)

Flow chart 1: Framework of the relations between poverty, food insecurity, and other underlying and immediate causes to maternal and child undernutrition and its short-term and long-term consequences



lipolysis and ketogenesis. Major electrolyte changes including sodium retention and intracellular potassium depletion can be explained by decreased activity of glycoside-sensitive energy-dependent sodium pump to increased permeability of cell membranes in kwashiorkor. Some studies suggest that marasmus represents an adaptive response to starvation, while kwashiorkor is a maladaptive response. Aflatoxins have been proposed to have a role in the pathogenesis of kwashiorkor. Reactive oxygen species also have been postulated to have a role in its pathogenesis.

Pathological Effects of Malnutrition in Various Organ Systems (Flow chart 1)

Endocrine System

Reduced levels of tri-iodothyroxine (T3), insulin, insulin-like growth factor-1 (IGF-1), and raised levels of growth hormone and cortisol have been demonstrated in malnutrition. Glucose levels are often initially low, with depletion of glycogen stores. Patients frequently also develop some degree of glucose intolerance of unclear etiology

and are at risk of profound hypoglycemia during the re-nourishment phase.

Immune System

Cellular immunity is affected most because of the atrophy of the thymus, lymph nodes, and tonsils. Changes include reduced CD4 but relatively preserved CD8-T lymphocytes, loss of delayed hypersensitivity, impaired phagocytosis, and reduced secretory immunoglobulin A (IgA). These changes increase the susceptibility of malnourished children to invasive infections.

GI System

Villous atrophy with loss of disaccharidases, crypt hypoplasia and altered intestinal permeability results in malabsorption. Bacterial overgrowth is common with reduced gastric acid secretion. Pancreatic atrophy occurs with resultant fat malabsorption. Fatty infiltration of the liver is common but synthetic functions are usually preserved.

Protein synthesis, gluconeogenesis, and drug metabolism are decreased.

CVS

Cardiac myofibrils are thinned with impaired contractility. Cardiac output is reduced proportionate to weight loss. Bradycardia and hypotension are also common in the severely affected. Intravascular volume is frequently decreased. The combination of bradycardia, impaired cardiac contractility, and electrolyte imbalances predispose these children to arrhythmias.

CNS

Malnutrition has been recognized to cause reductions in the numbers of neurons, synapses, dendritic arborization, and myelinations, all of which result in decreased brain size. Delays in global function, motor function, and memory loss have been associated with PEM, with neonates and infants being most susceptible despite the plasticity of the infant's brain.

Respiratory System

Reduced thoracic muscle mass, decreased metabolic rate may lead to impaired ventilatory response. Malnourished children often develop pneumonia without manifesting any respiratory distress.

CLINICAL FEATURES OF MALNUTRITION

Mild to moderate malnutrition (body weight between 60 and 80 percent of median or $<2SD$ and $>-3SD$) is the most common form of malnutrition and is usually between 9 months to 3 years. Failure to gain weight adequately and weight for age $<2SD$ are usually the earliest sign of malnutrition. Its features include growth failure, increased incidence of infection, decreased activity and sometimes evidence of micronutrient deficiencies like anemia vitamin A and D deficiency. These children also have loss of muscle mass (wasting) indicated by decrease in MUAC but may be reasonably active. They may have increased predisposition to infections which may predispose to further worse bouts of malnutrition.

The two main clinical syndromes of severe malnutrition are marasmus and kwashiorkor, although mixed pictures are also seen frequently. These are differentiated on the basis of clinical findings, with the primary distinction between the two syndromes being the presence of edema in kwashiorkor.

Marasmus

Marasmus is more common than kwashiorkor and is characterized clinically by depletion of subcutaneous fat stores, muscle wasting, and absence of edema. It results

from the body's physiologic adaptation to starvation in response to severe deprivation of calories and other nutrients. It most commonly occurs in children younger than 5 years because of their increased caloric requirements and increased susceptibility to infections. These children often appear emaciated, are weak and lethargic, and have associated bradycardia, hypotension, and hypothermia. Their skin is xerotic, wrinkled, and loose because of the loss of subcutaneous fat but is not characterized by any specific dermatosis. Muscle wasting often starts in the axilla and groin, then thigh and buttocks, followed by chest and abdomen, and finally the facial muscles, which are metabolically less active. The loss of buccal fat pads commonly gives the child an appearance of monkey-like or aged facies in severe cases. In the absence of infection, these children are usually alert with preserved appetite.

Kwashiorkor

The clinical picture is characterized by borderline decrease in body weight (usually between 60 and 80 percent of the expected weight for age), marked generalized edema, dermatoses, hypopigmented hair, distended abdomen, and hepatomegaly. The term sugar baby also has been used to describe these children, as their typical diet is low in protein but high in carbohydrate. Edema usually results from a combination of low serum albumin, increased cortisol, and inability to activate antidiuretic hormone. Hair is usually dry, sparse, brittle, easily pluckable and depigmented, appearing reddish yellow. With adequate protein intake, hair color is restored and may result in alternating bands of pale and normal-colored hair, also known as the flag sign, reflecting periods of poor and good nutrition. Cutaneous manifestations are characteristic and progress over days from dry atrophic skin with confluent areas of hyperkeratosis and hyperpigmentation, which then splits when stretched, resulting in erosions and underlying pale skin. These patchy areas of dark and pale skin give the impression of crazy paving or flaky paint, particularly over limbs and buttocks. Various skin changes in children with kwashiorkor include: shiny, varnished-looking skin (64 percent), dark erythematous pigmented macules (48 percent), xerotic crazy paving skin (28 percent), residual hypopigmentation (18 percent), and hyperpigmentation and erythema. These children also have hepatomegaly, abdominal distension and muscle wasting but tend to retain subcutaneous fat.

Marasmic Kwashiorkor

A child with marasmic kwashiorkor presents with a mixed picture with features of both marasmus and kwashiorkor. Characteristically, these children have concurrent gross wasting and edema and frequently are stunted. They usually have mild hair and skin changes and an enlarged palpable fatty liver.

WHAT IS SEVERE ACUTE MALNUTRITION (SAM)? (TABLE 6)

WHO and UNICEF have recently recommended the use of the term severe acute malnutrition (SAM) and recommended the use of a cut-off for weight-for height of below -3 standard deviations (SD) of the WHO standards to identify infants and children as having SAM. In conventional terminology they would just be referred as severe malnutrition or marasmus (Fig. 3). These groups of children have been separated as they have:

- The highly elevated risk of death compared to those who are above it.
- A higher weight gain when receiving a therapeutic diet compared to their diets, which results in faster recovery.

In simpler terms all children with body weight less than 60 percent of the expected and or nutritional edema should be considered to have severe malnutrition and to be at great risk of death due to any intercurrent illness.

However to our mind SAM is a misnomer as severe malnutrition or marasmus is never acute and develops over weeks and months. However, these children can develop acute complications usually due to a secondary infection to which they are very prone. Further infections in these children are usually very subtle and may cause few or no symptoms. Thus, they do not develop fever or respiratory distress even with the presence of pneumonia. Also infections tend to get very fulminant because of their compromised immunological status. These children are very prone to develop complications like dyselectrolytemia, hypoglycemia and even shock as a consequence of any acute intercurrent illness. It is only in this context (development of severe illness in a rather acute manner) in children with severe malnutrition can the terminology of SAM can be applied. WHO standards for mid-upper arm circumference (MUAC) for age show that in a well-nourished population there are very few children aged 6 to 60 months with a MUAC less than 115 mm. Children with a MUAC less than 115 mm have a highly elevated risk of death compared to those who are above it (Table 6).

Table 6: Diagnostic criteria for SAM in children aged 6 to 60 months

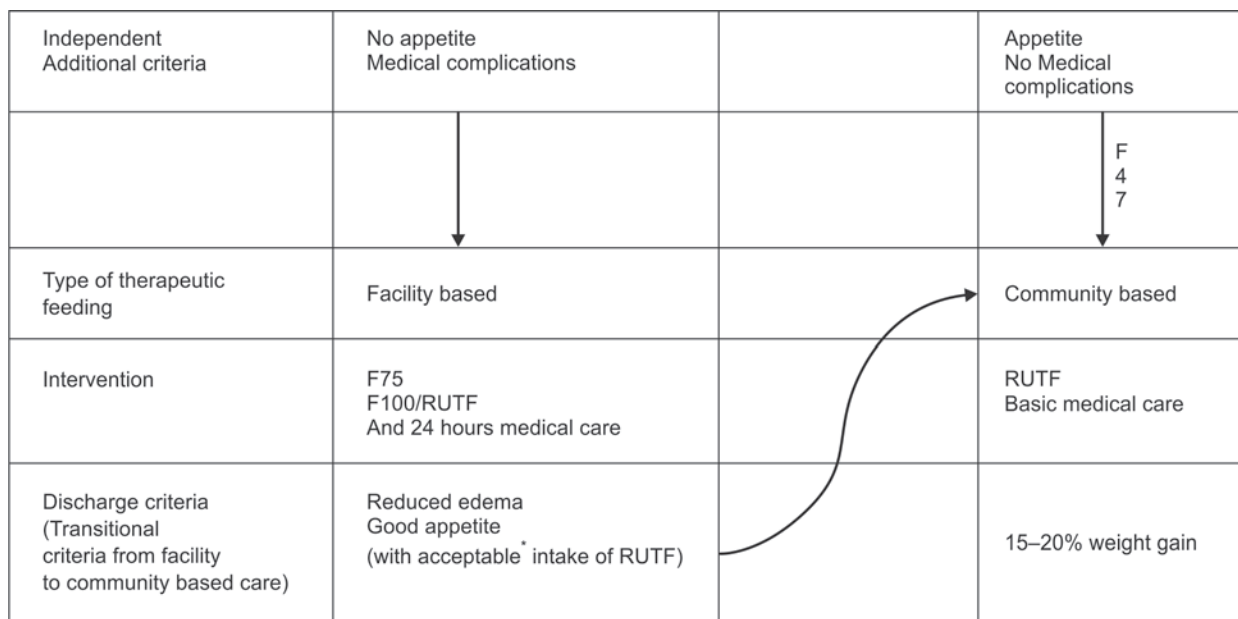
Indicator	Measure	Cut off
Severe wasting**	Weight for height*	<-3 SD
Severe wasting**	MUAC	< 115 mm
Bilateral edema***	Clinical sign	

*Based on WHO standards

, *Independent indicators of SAM that require urgent action

MANAGEMENT OF MALNUTRITION

Periodic weighing and charting on growth charts (road to health chart) is the key to detect early growth faltering or FTT and enables institution of corrective measures at an early stage. Intervention at the community level is usually sufficient for their management. Increasing the energy intake up to 150 kcal/kg/day with frequent energy dense (increased oil content) and the protein intake of 3-3.5 gm/kg/day is usually sufficient. Intercurrent infections need to



* Child eats at least 75% of their calculated RUTF ration for the day

Fig. 3: SAM management (WHO)

be treated promptly. Also it is very essential to maintain adequate nutritional intake during acute illness as food deprivation (mostly iatrogenic) during acute illness is a very important factor in further worsening of the nutritional status. Best measure of the efficacy of treatment is weight gain.

Children with severe malnutrition (body weight <60 percent or <3 SD) with no complications can also be possibly managed in the community but would require very close supervision. In any case if they develop any inter-current illness then they should be promptly hospitalized as they can deteriorate very fast. It should be remembered that decrease in appetite in a marasmic child is very ominous sign for which they need prompt evaluation (usually an infection), hospitalization and management (Flow chart 2).

Initial Assessment of a Severely Malnourished Child

The initial assessment of a severely malnourished child involves a good history and physical examination. The key points to be covered include history of (i) Recent intake of food and fluids; (ii) Usual diet (before the current illness);

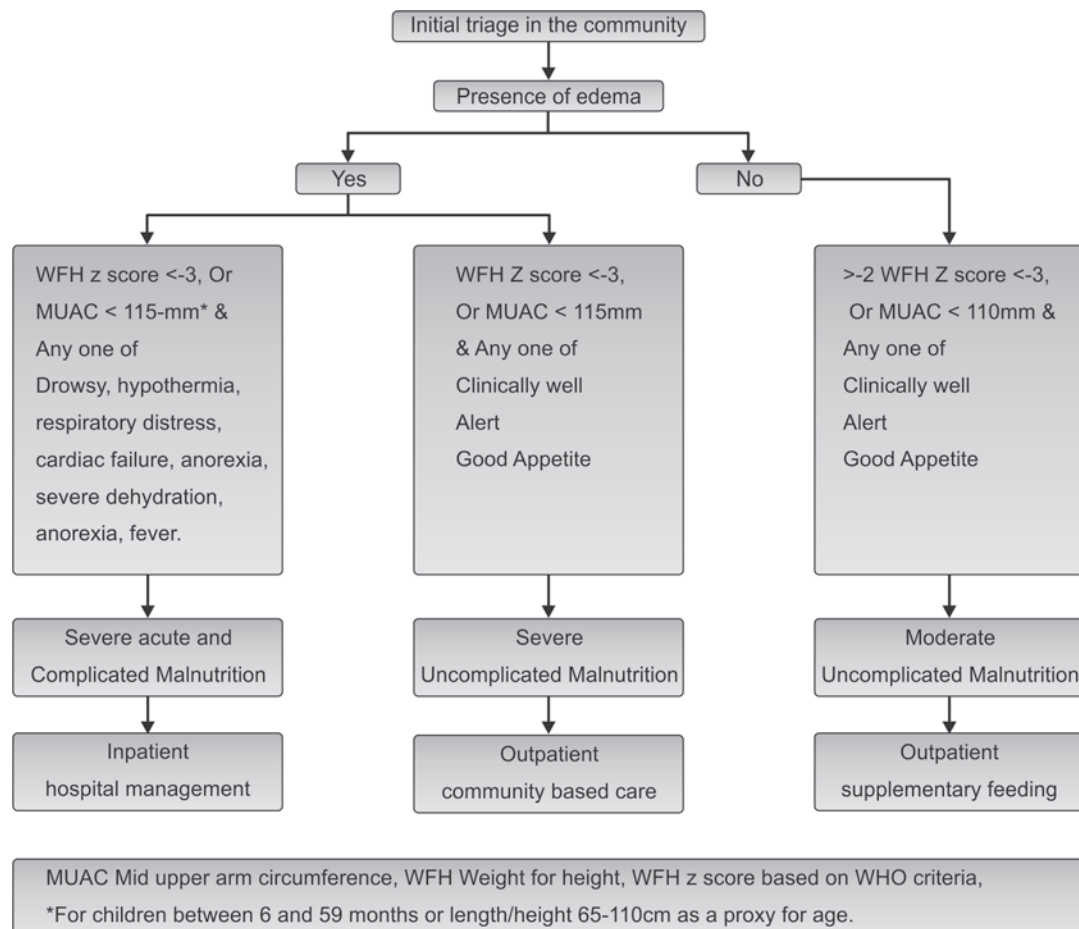
(iii) Breastfeeding; (iv) Duration and frequency of diarrhea and vomiting; (v) Type of diarrhea (watery/bloody); (vi) Loss of appetite; (vii) Fever; (viii) Symptoms suggesting infection at different sites; (ix) Family circumstances (to understand the child's social background); (x) Chronic cough and contact with tuberculosis; (xi) Recent contact with measles and (xii) Known or suspected HIV infection.

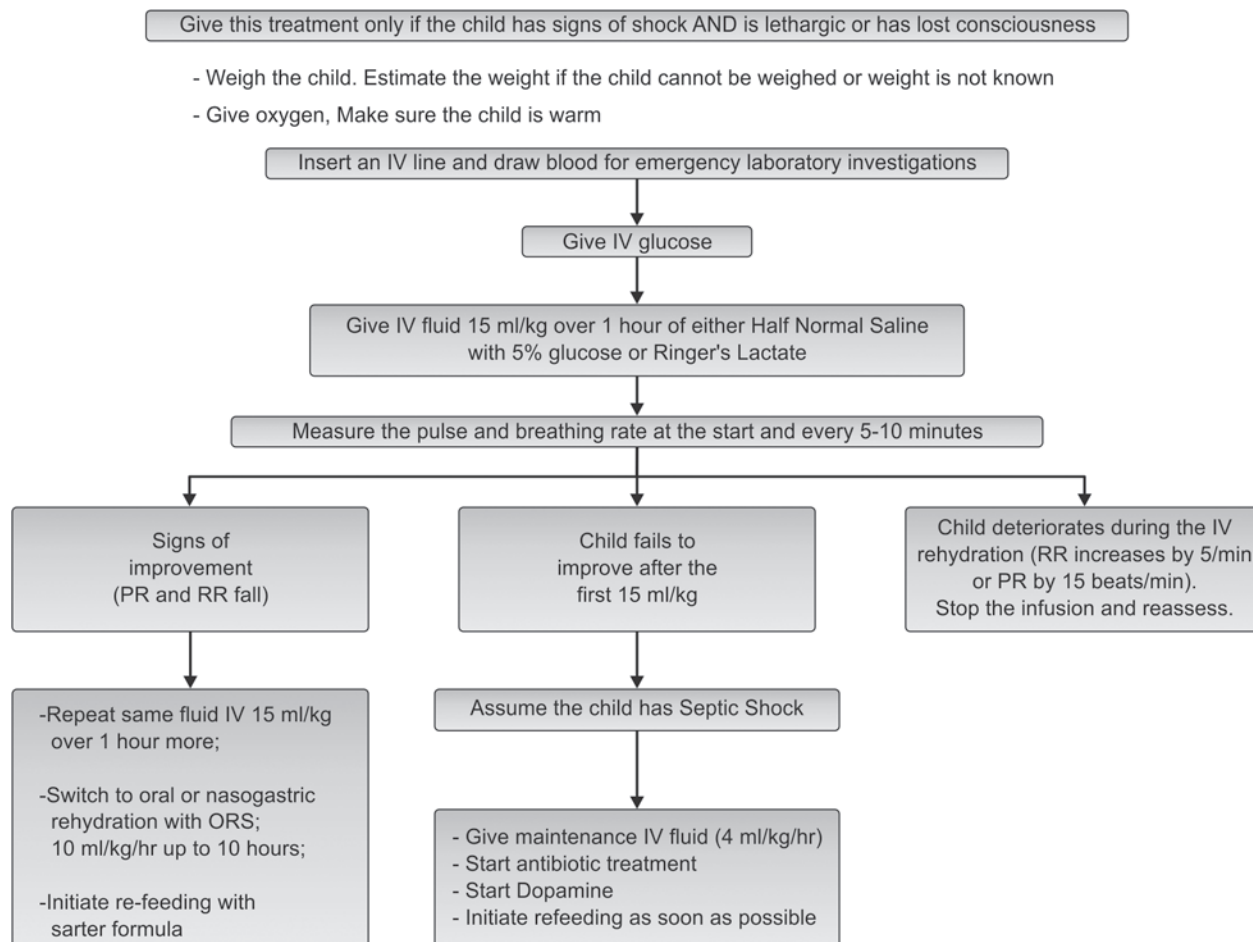
On examination the following points should be looked for:

Anthropometry-weight, height/length, mid-arm circumference; (ii) Signs of dehydration; (iii) Shock (cold hands, slow capillary refill, weak and rapid pulse); (iv) Lethargy or unconsciousness; (v) Severe palmar pallor; (vi) Localizing signs of infection, including ear and throat infections, skin infection or pneumonia; (vii) Fever (temperature $\geq 37.5^{\circ}\text{C}$ or $\geq 99.5^{\circ}\text{F}$) or hypothermia (rectal temperature $< 35.5^{\circ}\text{C}$ or $< 95.9^{\circ}\text{F}$); (viii) Mouth ulcers; (ix) Skin changes of kwashiorkor; (x) Eye signs of vitamin A deficiency and (xi) Signs of HIV infection.

Inpatient treatment of severely malnourished children (WHO Guidelines for the inpatient treatment of severely malnourished children, 2003).

Flow chart 2: The clinicians to decide whether the malnourished child needs hospitalization



Flow chart 3: Management of shock in a child with severe acute malnutrition

The treatment guidelines are divided into ten essential steps as shown below (Fig. 4):

1. Treat/prevent hypoglycemia
2. Treat/prevent hypothermia
3. Treat/prevent dehydration
4. Correct electrolyte imbalance
5. Treat/prevent infection
6. Correct micronutrient deficiencies
7. Start cautious feeding
8. Achieve catch-up growth
9. Provide sensory stimulation and emotional support
10. Prepare for follow-up after recovery.

Step 1: Treat/Prevent Hypoglycemia

All severely malnourished children are at risk of hypoglycemia. There is evidence to suggest association between the hypoglycemia and risk of mortality in severely malnourished children, hence blood glucose should be measured immediately at admission by using glucose estimating reagent paper strips such as dextrostix-reagent strips. Blood glucose level <54 mg/dl or 3 mmol/L is defined as hypoglycemia in a severely malnourished child. If blood

glucose cannot be measured, hypoglycemia should be assumed to be present and treated. Hypoglycemia could be asymptomatic or symptomatic. Symptomatic hypoglycemia manifests as lethargy, unconsciousness or seizures. Sympathetic manifestations of hypoglycemia like pallor and sweating are rare in severe malnutrition but may occur. Peripheral circulatory failure and hypothermia may be a manifestation of hypoglycemia. Hypothermia, infection and hypoglycemia generally occur as a triad. Presence of one should alert for the presence of others.

Treatment Asymptomatic Hypoglycemia

Give 50 ml of 10 percent glucose or sucrose solution (1 rounded teaspoon of sugar in 3½ tablespoons of water) orally or by nasogastric tube. Start feeding 2 hourly day and night (Initially one can give 1/4th of the 2 hourly feed every 30 minutes till the blood glucose stabilizes).

Symptomatic Hypoglycemia

Give 10 percent dextrose iv 5 ml/kg (if unavailable give 50 ml of 10 percent dextrose or sucrose solution by nasogastric

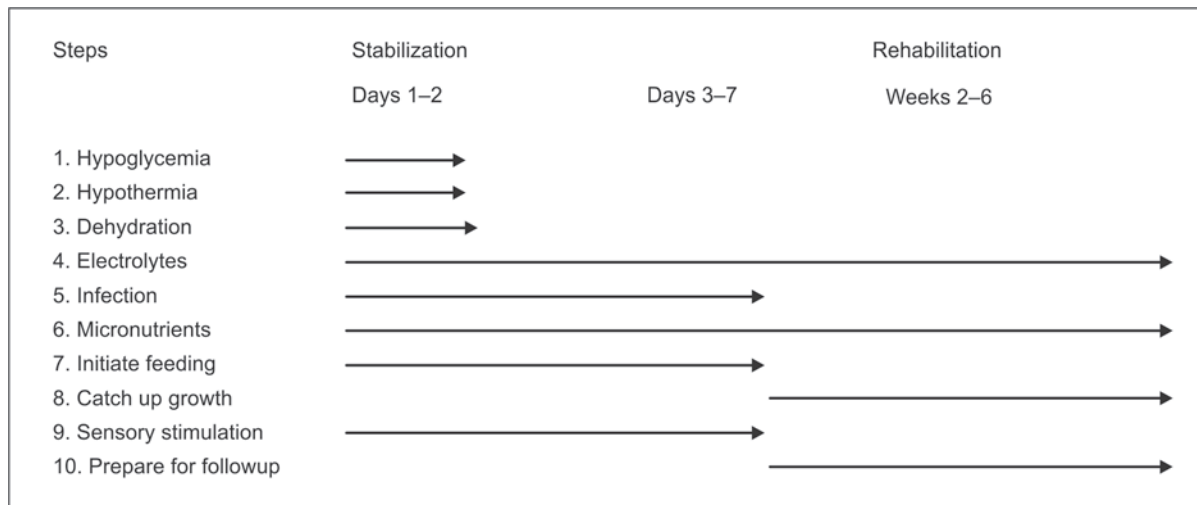


Fig. 4: Time frame for initiating/achieving 10 steps¹¹

tube). Follow with 50 ml of 10 percent dextrose or sucrose solution by nasogastric tube. Start feeding as quickly as possible with the starter F75 diet and then continue the feeds 2 to 3 hourly day and night (Initially one can give 1/4th of the 2 hourly feed every 30 minutes till the blood glucose stabilizes). Start appropriate antibiotics.

Monitoring

If the initial blood glucose was low, repeat an estimation using finger or heel-prick blood after 30 min. If the blood glucose is again low, repeat 50 ml of 10 percent dextrose or sucrose solution (as described above). Blood glucose monitoring may have to continue every 30 min till the blood glucose becomes normal and stabilizes; thereafter, start 2 hourly feeding. In case the body temperature falls (axillary temperature is less than 35°C or rectal temperature is less than 35.5°C) or consciousness deteriorates measure the blood sugar again and act accordingly.

Prevention

The cornerstone of prevention is feeding at regular intervals (2 hourly) starting immediately (if necessary, rehydrate first). Ensure the child is fed regularly throughout the night.

Step 2: Treat/Prevent Hypothermia

All severely malnourished children are at risk of hypothermia due to a lowered metabolic rate and decreased body fat. Children with marasmus, concurrent infections, denuded skin and infants are at a greater risk. Always look for and manage hypoglycemia in a hypothermic child.

Hypothermia is diagnosed if the rectal temperature is less than <35.5°C or 95.5°F. If axillary temperature is less than 35°C or 95°F or does not register on a normal thermometer, assume hypothermia. Use a low reading thermometer (range 29–42°C), if available. Hypothermia can occur in summers as well. Whenever Hypothermia

is present, measure blood glucose and screen for infections.

Treatment

Ensure that the head is also covered well with a scarf or a cap. Feed the child immediately, Clothe with warm clothes and use a warm blanket. Avoid a hot water bottle (Risk of burns followed by hypothermia). Child could also be put in contact with the mother's bare chest or abdomen (skin to skin) as in kangaroo mother care to provide warmth. Treat with appropriate antibiotics.

Step 3: Treat/Prevent Dehydration

IV route is best avoided for rehydration except in cases of shock. It is because of danger of overhydration and possible dyselectrolytemia. The malnourished children may have edema with intravascular dehydration and may develop congestive cardiac failure if overaggressive iv rehydration is used. Use of reduced osmolarity ORS with potassium supplements is preferable. Feeding must be initiated within two to three hours of starting rehydration. Give F75 starter formula on alternate hours (e.g. hours 2, 4, 6) with reduced osmolarity ORS (hours 3,5,7).

Be alert for signs of overhydration (increasing respiratory rate by 5 per min and pulse rate by 15 per min, increasing edema and periorbital puffiness), which can be dangerous and may lead to heart failure. If you find any sign of overhydration, stop ORS immediately and reassess after one hour (avoid the use of diuretics). Stop ORS for rehydration if any four hydration signs are present (child less thirsty, passing urine, tears, moist oral mucosa, eyes less sunken, faster skin pinch).

Step 4: Correct Dyselectrolytemia

Excess body sodium exists even though the plasma sodium may be low in severely malnourished children. Giving high

amounts of sodium could kill the child. In addition, all severely malnourished children have deficiencies of potassium and magnesium; these may take two weeks or more to correct. Edema may partly be due to these deficiencies. Do not treat edema with a diuretic.

Treatment

All severely malnourished children need to be given supplemental potassium at 3–4 mmol/kg/day orally for at least 2 weeks. Potassium can be given as syrup potassium chloride; the most common preparation available has 20 mEq/15 ml. Severe hypokalemia (Serum K^+ < 2.5 mEq or EKG changes with serum K^+ < 3.5 mEq would warrant a K^+ iv bolus of 0.3–0.5 mEq/kg/hr). On day 1, give 50 percent magnesium sulphate (equivalent to 2 mmol/ml). IM once (0.3 ml/kg up to a maximum of 2 ml) Thereafter, give extra magnesium (0.4–0.6 mmol/kg daily) orally. Injection magnesium sulphate can be given orally as a magnesium supplement mixed with feeds. Prepare food without adding salt. Potassium and magnesium can also be supplemented daily by preparing a stock solution of the WHO electrolyte and mineral mix and adding 20 ml of this solution to 1 liter of feed.

Step 5: Treat/Prevent Infection

In severe malnutrition, multiple infections are common and the usual signs of infection such as fever are often absent. Studies have documented high rates of blood stream and urinary tract infections in children with SMN. Investigations may be done for identifying the infections in SMN children, whenever and wherever feasible/available. Broad spectrum antibiotics (ampicillin and Gentamicin/Amikacin) should be used and hiked to ceftriaxone/cefotaxime if no response within 48 hours. Tuberculosis and Malaria should be considered early in the course of infections but empirical therapy in the absence of evidence should be discouraged. Ectoparasite and helminthic infections should be taken care of when the child is stable. Prevention of hospital acquired infections with good hand hygiene practices and good housekeeping practices as in intensive care areas should be encouraged.

Step 6: Correct Micronutrient Deficiencies

All severely malnourished children have vitamin and mineral deficiencies. Micronutrients should be used as an adjunct to treatment in safe and effective doses. Up to twice the recommended daily allowance of various vitamins and minerals should be used.

- Vitamin A orally or im on day 1 unless a dose has been given in the last month.
- Folic acid 5 mg on D1 followed by 1 mg/d.
- Zinc 2 mg/kg/d.
- Copper 0.2 to 0.3 mg/kg/d (multivitamin/mineral commercial preparation).
- Iron 3 mg/kg/d, only once child starts gaining weight; after the stabilization phase (infection free).

Step 7: Initiate Refeeding

Start feeding as soon as possible with a diet which has Osmolarity less than <350 mosm/L, Lactose not more than 2 to 3 g/kg/day, Adequate bioavailability of micronutrients, low viscosity, easy to prepare and socially acceptable and can be adequately stored, cooked and refrigerated. Start cautious feeding as soon as possible as frequent small feeds. Initiate nasogastric feeds if the child is not being able to take orally, or takes <80 percent of the target intake. Recommended daily energy and protein intake from initial feeds is 100 kcal/kg and 1 to 1.5 g/kg respectively. Total fluid recommended is 130 ml/kg/day reduced to 100 ml/kg/day if there is severe, generalized edema. Continue breast feeding *ad lib*. The volume of feeds should be increased gradually while decreasing the frequency of administration. The calories should be increased only after the child is able to accept the increased volume of feeds (Table 7).

Starter Diets

These diets are basically low lactose concentration (diluted milk), energy dense (by addition of oil and sugar and sugar) and protein moderate of good biologic value (milk protein \pm cereal) and reasonable palatability for the initial feeds of severely malnourished children.

Step 8: Achieve Catch-up Growth

Once appetite returns which usually happens in 2 to 3 days higher intakes should be encouraged. The frequency of feeds should be gradually decreased to 6 feeds/day and the volume offered at each feed should be increased. It is recommended that each successive feed is increased by 10 ml until some is left uneaten.

Breast feeding should be continued *ad libitum*. Make a gradual transition from F-75 diet to F-100 (100 kcal/100 ml) diet. The starter F-75 diet should be replaced with F-100 diet in equal amount in 2 days (Tables 8 and 9).

Complementary foods should be added as soon as possible to prepare the child for home foods at discharge. They should have comparable energy and protein concentrations. Once the catch-up diets are well tolerated, Kichri, dalia, banana, curd-rice and other culturally acceptable and locally available diets can also be offered liberally.

Step 9: Provide Sensory Stimulation and Emotional Support

Age appropriate structured play therapy for at least 15 to 30 min/day and principles of tender loving care (TLC).

Table 7: Feeding patterns in initial days of rehabilitation

Days	Frequency	Volume/kg/feed	Volume/kg/day
1–2	2 hourly	11 ml	130 ml
3–5	3 hourly	16 ml	130 ml
6	4 hourly	22 ml	130 ml

Table 8: Composition of F-75 starter diets

<i>Diets contents (per 100 ml)</i>	<i>F-75 starter</i>	<i>F-75 starter (Cereal based) Ex: 1</i>	<i>F-75 starter (Cereal based) Ex: 2</i>
Cow's milk or equivalent (ml)	30	30	25
(approximate measure of one <i>katori</i>)	(1/3)	(1/3)	(1/4)
Sugar (g)	9	6	3
spoons	1 + 1/2	1	1/2
Cereal: Powdered puffed rice* (g)	—	2.5	6
spoons		1/2	1 +
Vegetable oil (g)	2	2.5	3
(level teaspoon)	(1/2)	(1/2 +)	(3/4)
Water: make up to (ml)	100	100	100
Energy (kcal)	75	75	75
Protein (g)	0.9	1.1	1.2
Lactose (g)	1.2	1.2	1.0

*Powdered puffed rice may be replaced by commercial pre-cooked rice preparations (in same amounts)

Table 9: Composition of F-100 diets

<i>Diets Contents (per 100 ml)</i>	<i>F-100 catchup</i>	<i>F-100 catchup Cereal based Example 1</i>
Cow's milk or equivalent (ml)	95	75
(approximate measure of one <i>katori</i>)	(3/4 +)	(1/2)
Sugar (g)	5	2.5
(approximate measure of one level teaspoon)	1	(1/2 -)
Cereal: Powdered puffed rice(g)	—	7
(approximate measure of one level teaspoon)	—	2
Vegetable oil (g)	2	2
(approximate measure of one level teaspoon)	(1/2)	(1/2)
Water: make up to (ml)	100	100
Energy (kcal)	101	100
Protein (g)	2.9	2.9
Lactose (g)	3.8	3

- regain appetite by day 4
- start losing edema by day 4
- gain at least 5g/kg/day-by-day 10
Or still has edema on day 10.

Secondary failure to respond is indicated by:

Failure to gain at least 5g/kg/day for 3 consecutive days during the rehabilitation phase.

What is Poor Weight Gain?

- Good weight gain is >10 g/kg/day and indicates a good response. It is recommended to continue with the same treatment.
- Moderate weight gain is 5 to 10 g/kg/day; food intake should be checked and the children should be screened for systemic infection.
- Poor weight gain is <5 g/kg/day and is alarming. Search should be made for underlying cause such as:
 - a. Inadequate feeding
 - b. Specific nutrient deficiencies
 - c. Untreated infections (UTI, Tuberculosis, otitis media, Giardiasis, malaria)
 - d. HIV/AIDS/Celiac disease.

Hospital Discharge Criteria

Severely malnourished children are ready for discharge when the following criteria have been fulfilled:

- Absence of infection.
- The child is eating at least 120 to 130 Kcal/kg/day and receiving adequate micronutrients.
- There is consistent weight gain (of at least 5 g/kg/day for 3 consecutive days) on exclusive oral feeding (at least 15% weight gain). The child is still likely to have a low weight-for-age because of stunting.
- Absence of edema for at least two weeks before discharge.
- Caretakers are sensitized to home care.

It is important to look at the immunization status of the child and try to give age appropriate immunizations prior to discharge.

NUTRITIONAL REHABILITATION PHENOMENON

1. *Benign intracranial hypertension* (Pseudotumor Cerebri) results from over energetic correction in malnourished infants. It is usually self-limiting.
2. *Nutritional recovery syndrome* (Kahn's syndrome) presents with abdominal distension, hepatomegaly, ascites, prominent thoracoabdominal venous network, gynecomastia, parotid enlargement, eosinophilia and splenomegaly.

It is seen in children who are fed with high quantity of protein during the initial stages of treatment. Causative factors may be endocrine disturbances by release of trophic hormones by recovering pituitary gland and increased circulating estrogen levels.

Step 10: Prepare for Follow-up After Recovery

Assessing Response

Response to therapy may be considered inadequate if the child fails to:

3. *Encephalitic like syndrome*: It is seen in 20 percent of the children with kwashiorkor who may become drowsy in initial stages of initiation of nutritional therapy. Most often self-limited. On rare occasions symptoms of basal ganglia dysfunction (tremors, parkinsonian rigidity, bradykinesia and myoclonus) may be present.
4. *Refeeding syndrome*: Clinical manifestations of RFS are a direct result of the electrolyte and hormonal changes that occur as the basal metabolic rate rapidly increases. Once nutrition is reintroduced to a patient who has been starved for an extended period, anabolism begins instantaneously. The body shifts back to carbohydrate metabolism from protein and fat catabolism, and glucose becomes the primary source of energy once again. The increased glucose load, with a corresponding increase in the release of insulin, leads to cellular uptake of glucose, potassium, magnesium, and phosphate. This shift of electrolytes back into the cell causes hypokalemia, hypomagnesemia and hypophosphatemia. Insulin also exhibits a natriuretic effect on the kidneys. Hence, sodium is retained; causing fluid retention and expansion of the extracellular fluid volume. The patient may manifest signs and symptoms of hypophosphatemia, hypokalemia, hypomagnesemia, hyperglycemia, fluid overload, or thiamine deficiency. Should the signs and symptoms of RFS emerge, nutritional support should be stopped immediately. Electrolyte abnormalities should be corrected without delay, and supportive measures should be administered, such as the administration of intravenous thiamine for encephalopathy, iv phosphate supplementation, vasopressors for hypotension, oxygen for respiratory distress, and diuretics for fluid overload. Once these conditions are addressed, feeding can be restarted.

Community Based Therapeutic Care

A new model of delivering care has been proposed, called community-based therapeutic care (CTC), which is designed to address the limitations of inpatient care with the advantages of CTC programs use decentralized networks of outpatient treatment sites (usually located at existing primary health-care facilities), small inpatient units (usually located in existing local hospital facilities) and large numbers of community-based volunteers to provide case detection and some follow-up of patients in their home environments. Patients with severe malnutrition, with good appetite, and without medical complications are treated in an outpatient therapeutic program (OTP) that provides ready-to-use therapeutic food (RUTF) and medicines to treat simple medical conditions.¹¹ Home-based management has many advantages as the children have reduced exposure to hospital acquired infections and receive continuity of care after discharge. It also benefits by increasing the time available to mothers to spend with family and reduces the risk of possible neglect of siblings.¹²

Ready to Use Therapeutic Foods (RUTF)

RUTF are soft or crushable foods that can be consumed easily by children from the age of six months without adding water. RUTF have a similar nutrient composition to F100, which is the therapeutic diet used in hospital settings. But unlike F100, RUTF are not water-based, meaning that bacteria cannot grow in them. Therefore these foods can be used safely at home without refrigeration and even in areas where hygiene conditions are not optimal. Imported RUTF may need a cautious approach in India as our administrative system is porous and there is a chance of commercial exploitation of malnutrition.¹² Recent studies have shown effectiveness of locally produced RUTF in the treatment of mild and moderate undernutrition in the community.¹³

PREVENTION OF MALNUTRITION

Interventions to prevent childhood undernutrition and its adverse outcomes include promotion of breastfeeding; strategies to promote complementary feeding, provision of food supplements; micronutrient interventions; and general supportive strategies to improve family and community nutrition.

The measures to prevent malnutrition can be stratified at national, community and family level. The adoption of National Nutrition Policy by the government has been a significant achievement at the national level. Various programs directed against general malnutrition like integrated child development services program (ICDS), National Program of Mid-day Meals in Schools, National Nutrition Anemia Prophylaxis Program and many others have been launched or strengthened in pursuance of these policies.

Promotion of education and literacy in the community with special focus on health and nutrition education should be implemented as a key measure at the community level. Exclusive breast feeding for first 6 months of life, introduction of complementary foods at 6 months and periodic growth monitoring on growth cards should be vigorously promoted and encouraged. Primary health care packages should be made available to all sectors of the population and iatrogenic restriction of feeding in fevers and diarrhea should be discouraged. Regular growth monitoring should be included in all child health programs to enable early detection of FTT and institution of appropriate measures. Adequate time should be allowed between two pregnancies with promotion of family planning programs to limit the family size.

Above interventions should be supplemented by improvements in the underlying determinants of undernutrition, such as poverty, illiteracy, disease burden, and lack of women empowerment.

SUMMARY

Malnutrition is a very common entity in developing countries with short term, medium term and long term

consequences to family, society and world. WHO classification of malnutrition is the most widely used classification in children. Protocol based care of hospitalized children with severe complicated malnutrition should be encouraged with additional stress on stimulation, emotional support and follow up. Early detection and nutritional rehabilitation of malnourished children in the community is of outmost importance. Locally produced cost effective RUTF is the need of the hour.

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Section 10

Nephrology

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ASSESSMENT OF GLOMERULAR FUNCTION

Glomerular filtration rate (GFR) is the best indicator of renal function in children and adolescents and is critical for diagnosing acute and chronic kidney impairment. Accurate means of determining GFR is essential for determining doses of fluids and medications, monitoring for nephrotoxicity caused by antibiotics and chemotherapeutic agents, and assessing progression of renal disease.¹ The level of GFR is the product of the single nephron GFR multiplied by the number of functioning nephrons in both kidneys. The total GFR can be used as an index of functioning renal mass.

Serum Creatinine

Creatinine is an amino acid derivative derived from the metabolism of creatine phosphate in muscle, and is usually produced at a fairly constant rate by the body (depending on muscle mass). It is chiefly excreted by glomerular filtration; hence serum creatinine levels reflect changes in GFR. Normal levels of serum creatinine range from 0.2 to 0.5 mg/dl in older children. However, its levels are low when the muscle mass is decreased (malnutrition, muscle wasting) and drugs such as cimetidine, trimethoprim influence its renal tubular secretion.

Serum Cystatin C

Cystatin C is a low molecular weight protein member of cysteine protease inhibitors. It is produced by all nucleated cells and exhibits a stable production rate. Cystatin C is freely filtered by the glomerulus and completely reabsorbed and catabolized by the renal tubules. There are no sites of extra-renal metabolism. Hence serum levels of this product have been proposed as a marker of GFR.² Normal serum levels in adults are ≤ 0.95 mg/L and children >1 years show adult levels. Serum cystatin C levels are not influenced by muscle

mass, age or gender but the estimation is kit based (EIA/immunoturbidimetry) and is expensive.

Blood Urea

Urea is derived from the protein metabolism and synthesized in the liver. Urea is readily filtered, reabsorbed as well as secreted by the tubules. Blood urea levels and excretion are affected by dietary protein intake and state of hydration. However, in a steady state blood urea may not rise beyond upper range of normal (40 mg/dl) even when 75 percent of renal function is lost.

METHODS FOR ESTIMATING GLOMERULAR FILTRATION RATE

Glomerular filtration rate (GFR) can be quantified by measuring the clearance rate of a substance from the plasma. The substance, often referred to as the marker, can be endogenous or exogenous. It must have a stable plasma concentration and should be filtered, not reabsorbed, secreted, synthesized or metabolized by the kidney so that the filtered substance equals the excreted substance. Measurement of GFR is the best clinical test for estimation of functioning renal mass. Knowledge of GFR enables the clinician to prescribe fluids and solutes, determine the progression of kidney disease, predict the development of end-stage renal disease (ESRD), and appropriately dose medications excreted by the kidney.

Inulin Clearance¹

Inulin is considered an ideal marker and the gold standard for measuring GFR. The classic (standard) inulin clearance requires an intravenous priming dose of inulin, followed by a constant infusion to establish a steady-state inulin plasma concentration. After an equilibration for about 45 minutes, serial urine samples are collected every 10 to 20 minutes

through an indwelling bladder catheter or voluntary voiding. The use of inulin clearances has a number of limitations. First, some children may not be toilet trained and are unable to provide accurate collections of timed urine. Second, urologic problems are common causes of chronic kidney disease in infants and young children. The collection of timed urine in such patients is difficult and fraught with error. Third, technical difficulties encountered in performing inulin infusions, and reaching a steady state of inulin distribution, are common. Lastly, inulin is not currently readily available. These problems have rendered the standard inulin clearance to be impracticable in children.

Creatinine Clearance²

Creatinine is an amino acid derivative produced in muscle cells. It is freely filtered and about 10 percent of the creatinine found in urine is secreted by the proximal tubules. Tubular secretion varies among and within individuals. Endogenous creatinine clearance provides an acceptable measurement of GFR for clinical purposes and is calculated by the following equation:

$$\text{Ccr} = \text{Uc} \times \text{V}/\text{Scr}$$

where Ccr is creatinine clearance, Ucr is urine creatinine concentration, V is flow rate of urine in ml/minute, and Scr is serum creatinine. The creatinine clearance is normalized to body surface area (BSA) by being multiplied by the factor 1.73/BSA in square meters. Urinary creatinine excretion should generally be approximately 20 mg/kg per day in children over 3 years of age and values less than this indicates incomplete urine collection.

However, creatinine clearance overestimates the actual GFR (due to presence of non-creatinine chromogens, normally present in plasma are measured along with creatinine giving a falsely high value to serum creatinine and this partly compensates for the tubular secretion of creatinine). The administration of cimetidine to patients with renal disease causes a decrease in tubular creatinine secretion, resulting in a creatinine clearance that approximates the level of true GFR. While the cimetidine protocol is a convenient, inexpensive procedure for estimating GFR, failure to document bladder emptying by ultrasound, lack of toilet training, and the presence of urologic conditions can cause inaccuracies in the results because of problems in urine collection.

Nuclear GFR¹

Glomerular filtration rate (GFR) can be accurately measured using a radioactive tracer such as chromium 51 (⁵¹Cr) EDTA or technetium 99 m (^{99m}Tc) DTPA in children. The most accurate method is based on the plasma disappearance curve after a single bolus injection. The clearance of the radiotracer is given by the injected dose divided by the area under the curve. The initial 'fast'

curve represents the diffusion of the radiotracer in its distribution volume, whereas the late, slow exponential curve represents its renal clearance. The two compartment model requires serial blood sampling to obtain an accurate plasma disappearance curve. A major limitation of these methods is presence of significant edema in which case disappearance of the tracer into an expanded ECF volume will artifactually elevate the calculated GFR. Infiltration of the radiotracer at the injection site can also cause artifactual elevation of GFR. The effective dose of radiation is small.

Equations Predicting Glomerular Filtration Rate (GFR)

For reasons of convenience, GFR is usually estimated from plasma creatinine using prediction equations. Although the Schwartz formula ($\text{GFR} = k \times \text{height}/\text{plasma creatinine}$) is widely used equation in children,³ several reports suggest that this formula overestimates GFR, if originally proposed values of k (constant) are used.² Various studies have reported k values ranging from 0.41 to 0.55 that better estimated GFR than the original k of 0.55.² This is primarily due to more accurate measurement of levels of plasma creatinine, using methods other than those used previously. The equation is also considered unreliable in malnourished children and in anorectic adolescents.² In view of these considerations, it has been suggested that the value of k should be locally derived, taking into consideration the method for estimating creatinine and the nutritional status of the population.² Using the enzymatic method of creatinine estimation, CKiD study recently proposed a new k value of 0.413 for the height/creatinine formula.⁴ However, this might not apply to centers that measure creatinine by non-enzymatic methods and have patients with lower height percentiles as compared to children in the CKiD study. We have derived a new k , for estimating GFR using height and creatinine in children with CKD (Table 1). Developing countries that use kinetic Jaffe method for estimating serum creatinine instead of enzymatic method and ^{99m}Tc-DTPA for measuring GFR could use a k value of 0.42 in the absence of locally derived k value.

The intrinsic biological variability in the GFR and physiological variability in the production and in the extraglomerular elimination of creatinine would mean that even the estimates from a perfect GFR formula would differ substantially from the true GFR. Additionally, these GFR estimating formulae are not accurate when GFR is rapidly changing, such as in critically ill children or in acute renal failure. Therefore, when precise GFR estimate is needed for an individual patient for decisions such as timing for pre-emptive transplant or dosing of chemotherapeutic drugs, invasive but accurate radionuclide GFR measurement would be justified.

Table 1: Equations for predicting GFR (ml/min/1.73 m²) in children¹

Reference	Formula
<i>Creatinine based</i>	
Original Schwartz ³	$0.55 \times \text{ht(cm)}/\text{Scr}$
CKiD study ⁴	$0.413 \times \text{ht(cm)}/\text{Scr}$
AIIMS, Delhi	$0.42 \times \text{ht(cm)}/\text{Scr}$
Léger ⁵	$(0.641 \times \text{Wt})/\text{Scr} \times (0.00131 \times \text{Ht}^2)/\text{Scr}$
<i>Cystatin based</i>	
Filler	$91.62 \times (\text{cysC})^{-1.123}$
Grubb	$84.69 \times (\text{cysC}) \times 1.680 \times 1.384$ if <14 years
<i>Combined cystatin and creatinine</i>	
CKiD study ⁴	$39.1 \times [\text{ht(m)}/\text{Scr}]^{0.516} \times [1.8/\text{cysC}]^{0.294} \times [30/\text{BUN}]^{0.169} \times 1.099^m \times [\text{ht(m)}/1.4]^{0.188}$

ht, height; Wt, weight (kg); Scr, serum creatinine (mg/dl); m, meter; cysC, cystatin C (mg/L); BUN, blood urea nitrogen (mg/dl)

Several equations have been derived using cystatin C for estimation of GFR in both adults and children (Table 1).¹ Recently, a complex equation that includes serum creatinine, cystatin C and blood urea was derived by CKiD study which predicted the measured GFR best; however the mathematical complexity of the equation precludes its bedside use in clinical practice.⁴

ASSESSMENT OF RENAL TUBULAR FUNCTION

Tubular Reabsorption of Phosphate

The tubular reabsorption of phosphate (TRP) is the fraction (or percent) of filtered phosphorous that is reabsorbed by renal tubules. It is useful in assessing hypophosphatemia. It is expressed as [100 - fractional excretion of phosphorous (FEP)], where

$$\text{FEP} = \frac{\text{urine phosphorous} \times \text{serum creatinine} \times 100}{\text{serum phosphorus} \times \text{urine creatinine}}$$

Normally TRP ranges between 85 and 95 percent. It is reduced in proximal tubular defects, hypophosphatemic rickets and hyperparathyroidism. It is also influenced by GFR and dietary intake. Hence, tubular maximum of phosphorus corrected to the GFR (TmP/GFR) is more appropriate measure of renal phosphate handling as it is independent of dietary phosphorous intake, tissue release of phosphorous and GFR. Tubular maximum of phosphorus corrected to the GFR represents the blood concentration above which most phosphate is excreted and below which most is reabsorbed.⁶ The normal TmP/GFR ranges between 2.8 and 4.4 mg/dl. It can be derived from TRP and plasma phosphorous using Bijvoet nomogram.⁷ However, studies in children have demonstrated that Bijvoet nomogram results in overestimation of TmP/GFR.⁸ This is because Bijvoet nomogram has been traditionally calculated by loading fasting adult patient with

phosphate. The threshold in adults is lower than in children and also children do not demonstrate the phosphate splay (non-linear increase in phosphate reabsorption to its maximum) found in fasting adults. It is suggested that TmP/GFR should be used in the pediatric population rather than nomogram. The former represents tubular phosphate reabsorption under fasting or non-fasting conditions without phosphate load.

$$\text{TmP/GFR} = \text{SP} - \text{UP} \times \text{Scr/Ucr}$$

where, SP is serum phosphate, UP is urine phosphate, Scr is serum creatinine and Ucr is urine creatinine.

Fractional Excretion of Sodium

Fractional excretion of sodium (FeNa) is the percentage of the sodium filtered by the kidney which is excreted in urine. It is calculated as:

$$\text{FeNa} = \frac{\text{urine sodium} \times \text{plasma creatinine} \times 100}{\text{plasma sodium} \times \text{urine creatinine}}$$

It is useful for evaluation of acute kidney injury in order to determine if hypovolemia is a cause of renal dysfunction when FeNa is below 1 percent. Higher values (FeNa >1%) suggest sodium wasting due to intrinsic renal failure. Fractional excretion of sodium is affected by diuretics, since many diuretics act by altering the kidney handling of sodium.

Transtubular Potassium Gradient⁹

Potassium is secreted in late distal and cortical collecting tubules. Transtubular potassium gradient (TTKG) reflects potassium secretory process in distal and cortical collecting tubules. It is calculated as

$$\text{TTKG} = \frac{\text{urine K}^+/\text{serum K}^+ \times \text{serum osmolality}}{\text{urine osmolality}}$$

Urinary sodium should be greater than 25 mEq/L to ensure that insufficient sodium delivery is not limiting the potassium secretion. Urine osmolality should exceed serum osmolality since luminal K^+ concentration is affected by water removal in medullary segments. Transtubular potassium gradient (TTKG) is a good indicator of aldosterone activity in presence of normal renal functions. Transtubular potassium gradient (TTKG) is expected to be more than 7 during hyperkalemia and value below 7 indicates inadequate aldosterone effect.

ASSESSMENT OF URINARY ACIDIFICATION

Urine pH

Urine pH is an estimate of the number of free H^+ ions in the urine which are secreted in response to metabolic acidosis. The presence of alkaline urine during metabolic acidosis suggests defective renal acidification, as in distal renal tubular acidosis (RTA). However, alkaline urine may also be found in patients with metabolic acidosis due to extrarenal disorders, as in acute or chronic diarrhea.

Urine Anion Gap¹⁰

Urine anion gap (UAG) is the difference between concentration of principal urinary cations (sodium + potassium) and anion (chloride). Hence, it gives an estimate of unmeasured cations and anions, which normally include ammonium and bicarbonate. Since, bicarbonate is mostly reabsorbed, it is chiefly a measure of ammonium excretion. A positive UAG suggests a low urinary NH_4^+ (e.g. renal tubular acidosis). A negative UAG suggests a high urinary NH_4^+ (due to obligate chloride excretion with ammonium).

Bicarbonate Loading Test¹¹

This test is useful in differentiating proximal and distal renal tubular acidosis (RTA) by assessing fractional excretion of bicarbonate ($FeHCO_3$). Fractional excretion of bicarbonate is a marker of proximal tubular handling of bicarbonate. The proximal tubule normally reabsorbs almost all filtered bicarbonate (fractional excretion below 5%). A value greater than 15 percent indicates proximal RTA while levels are in the normal range in distal RTA. The fractional excretion of bicarbonate should be calculated only after adequate alkalinization. Sodium bicarbonate is administered in a dose of 3 to 5 ml/kg for 4 to 5 days till urine pH exceeds 7.4 or blood bicarbonate level is between 23 to 26 mEq/L (Table 2).

$$\text{Fractional excretion} = \frac{\text{urine bicarbonate} \times \text{plasma creatinine} \times 100}{\text{urine creatinine} \times \text{plasma bicarbonate}}$$

Urine to Blood CO_2 Difference

Based on the observation that urinary CO_2 excretion is an indicator of H^+ secretion, urine to blood CO_2 difference is considered a satisfactory index of distal renal acidification. In the presence of normal blood bicarbonate, low urine to blood CO_2 difference (<10 mm Hg) suggests distal RTA; the levels are normal in proximal RTA (>20 mm Hg). It is necessary that the difference be determined after adequate alkalinization.

Ammonium Chloride Loading Test

This test is used to confirm distal RTA (Type I), in which there is failure of hydrogen excretion by distal renal tubules. Administration of ammonium chloride induces metabolic acidosis to which normal kidney responds with

Table 2: Tests for assessment of renal tubular function

Test	Function assessed	Indications	Result	Interpretation
Fractional excretion of sodium	Sodium excretion	Prerenal failure Renal salt wasting	$<1\%$ $>2.5\%$	Renal hypoperfusion, Intrinsic renal failure
Transtubular potassium gradient	Potassium excretion	Hyperkalemia	<7	Aldosterone deficiency/ resistance
Tubular reabsorption of phosphate, TmP/GFR	Phosphate excretion	Hypophosphatemic rickets, Fanconi syndrome	TRP $<85\%$, GFR <2.8 mg/dl	Phosphaturia
Bicarbonate loading test	Bicarbonate excretion	Renal tubular acidosis	$Fe HCO_3 <5\%$ $>15\%$	Normal Proximal RTA
Urine –Blood CO_2	H^+ secretion		$<10\%$ $>20\%$	Distal RTA Normal
Ammonium chloride loading, Furosemide fludrocortisone test	Proton secretion	Renal acidification (distal RTA)	Urine pH >5.5	Distal RTA
Water deprivation test	ADH induced water reabsorption	Diabetes insipidus		See Table 3

Table 3: Interpretation of water deprivation test

Condition	Urine osmolality (mOsm/kg) on water deprivation	Change in osmolality with dDAVP (mOsm/kg)
1. Normal	>800-900	Minimal/no increase
2. Complete central DI	<300	Substantial increase
3. Partial central DI	300-800	Increase of >10%
4. Nephrogenic DI	<200-300	Minimal or no increase
5. Primary polydipsia	>500	Minimal or no increase

maximal urinary acidification. Ammonium chloride is given orally in a dose of 0.1 to 0.15 g/kg over 30 to 45 minutes usually with fruit juice and is followed by liberal fluid intake. Urine pH is measured every hour over next 6 hours followed by blood pH. Failure to lower the urine pH below 5.5 despite severe acidosis ($\text{TCO}_2 < 15$), suggests distal RTA.

Furosemide Fludrocortisone Test¹²

This test is an easy, effective, and well tolerated alternative to standard ammonium chloride urine acidification test for diagnosis of distal RTA. A baseline urine sample is collected after which the patient is given 1 to 2 mg/kg of furosemide and 0.1 to 0.3 mg of fludrocortisone. This leads to increase distal sodium delivery, principal cell sodium reabsorption and alpha intercalated cell proton secretion. Urine is collected hourly for 6 hours. Patients with distal RTA fail to lower pH <5.3 while normal controls lower pH<5.3 after 3 hours.

ASSESSMENT OF URINARY CONCENTRATION¹³

Urine Osmolality

It is a measure of concentration of the urine and is determined by the number of particles in the solution. The maximum urinary concentration capacity varies with age; while the maximum urine osmolality in neonates is about 700 mOsm/kg, the osmolality in older children and adults can rise up to 1200 mOsm/kg. The test is useful for identifying syndrome of inappropriate antidiuretic hormone secretion (SIADH) (urine osmolality >200 mOsm/kg, low serum sodium, urine sodium >20 mEq/L, for differentiating prerenal from renal failure (high urine osmolality is consistent with prerenal impairment) and, for identifying and diagnosing diabetes insipidus (DI).

Urine Specific Gravity

It measures the kidney's ability to concentrate/dilute urine in relation to plasma and is determined both by the number and the size of particles in the solution. In most cases, it varies with the osmolality, with specific gravity rising by 0.001 for every 35 to 40 mOsm/kg increase in osmolality. But this relationship is altered when there are appreciable

quantities of larger molecules in urine, e.g. glucose, radio contrast, antibiotics. The normal specific gravity in human urine ranges from 1.003 to 1.030 and is measured by hydrometer.

Urinary Concentration Test

It is useful in a setting of polyuria to differentiate central, nephrogenic diabetes insipidus (complete and incomplete forms) and psychogenic polydipsia. It is not done if the first morning void has an osmolality above 700 mOsm/kg.

Water Deprivation Test

No fluid is allowed after dinner. The bladder is emptied at 8 am, and all the subsequent urine specimens are collected. Water deprivation is stopped if weight loss is more than 5 percent or until three consecutive hourly urine osmolality values are within 10 percent of each other. Normal children can achieve a urine osmolality above 900 mOsm/kg. The interpretation of water deprivation test is summarized in (Table 3).

Vasopressin Test¹⁴

This test is used to confirm lack of renal response in nephrogenic diabetes insipidus. dDAVP (desmopressin) is administered nasally (5-10 microgram in neonates/infants, 20 microgram in children) or by an intramuscular injection (0.4-1 microgram in infants and young children, 2 microgram in older children). Hourly urine collection is done over the next 2 to 3 hours.

Response of primary polydipsia to dDAVP resembles nephrogenic diabetes insipidus (NDI), except that basal ADH levels are low compared with elevated levels present in NDI. Also, after prolonged restriction of fluid intake, normal concentrating ability returns within several weeks.

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Urinary Tract Infections: Current Recommendations

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INTRODUCTION

Urinary tract infections (UTIs) are a cause of significant morbidity in childhood, affecting 3 to 10 percent girls and 1 to 3 percent boys and accounting for a proportion of “occult” bacterial infections in febrile infants. A proportion of children with UTI have an underlying urinary tract anomaly, most often vesicoureteric reflux (VUR). In these individuals, UTI may predispose to renal scarring (reflux nephropathy), an important cause of hypertension and chronic renal failure later in life.

Over the last few years, various expert groups have proposed guidelines for the evaluation and management of UTI.¹⁻³ This review focuses on the current evaluation and management of UTI, broadly conforming to the current recommendations of the Indian Society of Pediatric Nephrology.³

When to Suspect UTI?

The symptoms of UTI in young children are nonspecific. Unexplained fever may be the only symptom in young children, and UTI account for 3 to 5 percent cases of pyrexia of unknown origin.^{1,4-5} When UTI occurs during early childhood, a setting of VUR, urinary tract obstruction or systemic sepsis is often present. The risk of UTI is similar in boys and girls during infancy, and is thereafter higher in girls.^{5,6} Older children present with fever, dysuria, urgency, frequency and abdominal or flank pain. Adolescents may have symptoms restricted to the lower urinary tract.

Renal parenchymal involvement may be indicated by fever, chills and rigors and flank pain. It is often difficult to distinguish between infection localized to the bladder (cystitis) and upper tracts (pyelonephritis). This distinction is also not necessary since radionuclide imaging shows that almost 70 to 75 percent of UTI in children below 5 years of age involve the kidney and upper tracts.⁶ UTI in children is thus always considered to involve the upper tract and should be treated promptly to avoid renal parenchymal injury.

DEFINITION

The diagnosis of UTI is based on the growth of significant number of organisms of a single species in the urine, in the presence of symptoms. The number of organisms required to be present to define UTI depends on the site from which urine has been collected. Significant bacteriuria is defined as a colony count of $>10^5$ /ml of a single species of bacteria in a midstream clean catch sample. In samples taken by urethral catheterization, a colony count of $>5 \times 10^4$ colony forming units (CFU)/ml, and on suprapubic aspirates any pathogens are considered significant.³

The time the urine resides in the bladder (bladder incubation time) is an important factor affecting the magnitude of the colony count. In its recent recommendations, the American Academy of Pediatrics recommends that the presence of 50,000 CFUs per ml of a single urinary pathogen should be considered “significant” in infants and children below 2 years, except for commensals such as *Lactobacillus* spp, coagulase-negative staphylococci, and *Corynebacterium* spp.²

The occurrence of significant bacteriuria in absence of symptoms is termed *asymptomatic bacteriuria*.

The distinction between simple and complicated UTI is important for determining the choice of therapy.³ Complicated UTI is diagnosed in the presence of high fever ($>39^\circ\text{C}$), systemic toxicity, persistent vomiting, dehydration, renal angle tenderness or raised creatinine. Patients with low grade fever, dysuria, frequency and urgency, and absence of symptoms of complicated UTI are considered to have simple UTI.

DIAGNOSIS

History regarding prior episodes of UTI, and bowel and bladder habits should be elicited. Important components of clinical evaluation include assessment of hydration,

ability to retain oral intake, signs of systemic toxicity and blood pressure.

Features that suggest an underlying abnormality include urinary incontinence; history of surgery for meningomyelocele or anorectal malformation; poor urinary stream or straining at micturition; palpable kidney(s) or distended bladder; tight phimosis or vulval synechiae; and neurological deficit in lower limbs.³ History may suggest bowel bladder dysfunction, in form of constipation or impacted stools, infrequent (<3 times) or frequent (>8 times) daytime voiding, straining during micturition and holding maneuvers to postpone voiding, e.g. vincent curtsy or squatting.

Investigations

While urinalysis enables a presumptive diagnosis of UTI and facilitates initiation of empirical treatment, the diagnosis of UTI must be confirmed by urine culture.

Urinalysis

Leukocyturia is considered significant if microscopy shows >10 leukocytes per mm³ in a fresh uncentrifuged sample, or >5 leukocytes per high power field in a centrifuged sample. The absence of pyuria in children with UTI is rare. However, the detection of leukocyturia in absence of significant bacteriuria is not sufficient to diagnose a UTI.^{3,7}

Rapid dipstick based tests, which detect leukocyte esterase and nitrite, are useful in screening for UTI. A combination of these tests has moderate sensitivity and specificity for detecting UTI in children, and is diagnostically as useful as microscopy.^{2,8} However, since the conversion of dietary nitrates to nitrites by bacteria requires approximately 4 hours in the bladder, a nitrite test has poor sensitivity for detection of UTI, particularly in infants, who empty their bladders frequently.² Similar to pyuria, false-positive results on leukocyte esterase test are common with various conditions other than UTI, including fever of any cause and vigorous exercise.²

The presence of any bacteria in a fresh, Gram stained specimen of uncentrifuged urine correlates with 10⁵ CFU/ml in culture. Enhanced urinalysis is the combination of the counting chamber assessment of pyuria and Gram staining of uncentrifuged urine. When a threshold of at least one gram-negative bacillus in 10 oil immersion fields is used for assessment, enhanced urinalysis has greater sensitivity, specificity, and positive predictive value than does the standard urinalysis.⁹

Urine Culture

A clean catch midstream sample is advised for urine culture in toilet-trained children.⁵ It is sufficient to clean the

genitalia with soap and water prior to sample collection; antiseptic washes and strong soaps should be avoided. The use of a urine collection bag, in infants, applied to the perineum may be falsely positive in 85 percent. Hence, in infants the specimen should be obtained by suprapubic aspiration or transurethral catheterization. Urine specimen for culture should be processed promptly and plated within an hr of collection. If delay of more than 2 hours is anticipated, the specimen is stored at 4° C for up to 12 to 24 hours.²

Nearly 90 percent of the first UTI and 70 percent of recurrent infections are caused by *Escherichia coli*; *Klebsiella*, *Staphylococcus epidermidis* and *Streptococcus fecalis* are occasionally incriminated. UTI following instrumentation and nosocomial infections may be due to *Proteus* and *Pseudomonas*. Fungal UTI should be suspected in hospitalized newborns and infants who are immunocompromised or have received prolonged parenteral antimicrobials. Tuberculosis of the urinary tract is rare in children.⁵

Other Investigations

Children with complicated UTI should be evaluated with complete blood counts, serum creatinine and blood culture.

TREATMENT

Treatment of UTI should be initiated promptly to prevent potential renal parenchymal injury. Empiric therapy is started once a sample for culture has been taken.

Differentiation of acute pyelonephritis from cystitis is not necessary. Except for afebrile adolescents with chiefly lower tract symptoms, all children with UTI should be treated as for pyelonephritis. The mode of therapy depends on the age and whether the UTI is complicated or uncomplicated.

Parenteral Therapy

Infants below 3 months of age and children with complicated UTI should be treated with parenteral antibiotics. The choice of antibiotic is guided by local sensitivity patterns. A third generation cephalosporin (cefotaxime or ceftriaxone) is preferred, but therapy with a single daily dose of aminoglycoside is as effective (Table 1).¹⁰ A single antimicrobial is used in community acquired infections, and combinations used in more sick patients. The treatment is modified once results of antimicrobial sensitivity are available.

Once oral intake improves and symptoms abate, therapy is switched to an oral antibiotic, usually after 48 to 72 hr. A recent review showed no difference in risk of renal damage at 6 months, between IV followed by oral therapy compared to IV therapy alone.¹¹ The duration of treatment for complicated UTI should be 10 to 14 days.^{2,3}

Oral Therapy

Children above 3 months of age who are accepting by mouth and not toxic (simple UTI) are treated with oral antibiotics for 7 to 10 days. Coamoxiclav, amoxicillin or cefixime may be used for initial treatment, and treatment modified after availability of sensitivity reports. Adolescents with cystitis may receive antibiotics for 3 to 5 days.¹

Supportive Care

It is important to maintain adequate hydration during the infection. Intravenous fluids may be required if the child appears sick, dehydrated or is unable to take orally. Routine alkalization of the urine is not necessary.

Assessing Response to Therapy

With adequate therapy, resolution of toxicity occurs within 24 to 48 hr and fever by 48 to 72 hr. Urine culture is sterile after 48 hr of appropriate antibiotics. However, a repeat urine culture is not required during or following treatment, unless symptoms fail to resolve despite 72 hr of adequate antibiotic therapy; symptoms recur, suggesting recurrent UTI; or contamination of the initial urine culture is suspected.

Antibiotic Prophylaxis

After a course of antimicrobial therapy, long-term low dose antibiotic prophylaxis is administered to patients

with (i) UTI below 1 year of age, while awaiting imaging studies, (ii) VUR, and (iii) frequent febrile UTI (3 or more episodes in a year) even if the urinary tract is normal.³ The medication is given as a single bedtime dose (Table 2). The antibiotic used should be effective, non-toxic with few side effects and not alter the bacterial flora or induce bacterial resistance. Agents that can be used include cotrimoxazole and nitrofurantoin. Cephalexin or cefadroxil is preferred in infants and those with deficiency of glucose-6-phosphate-dehydrogenase. Antibiotic prophylaxis is not advised in patients with urinary tract obstruction (e.g. posterior urethral valves), urolithiasis and neurogenic bladder, and in patients on clean intermittent catheterization.

Breakthrough UTI results either from poor compliance or associated voiding dysfunction. The UTI should be treated with appropriate antibiotics. A change of the medication being used for prophylaxis is usually not necessary. There is no role for cyclic therapy, where the antibiotic used for prophylaxis is changed every 6 to 8 weeks.

Evaluation After the First Episode of UTI

Imaging studies aim to identify urologic anomalies that predispose to pyelonephritis and detect evidence of renal scarring. The investigations are performed judiciously (Table 3), with minimum risks of radiation exposure and other complications.³

Choice of Modalities

Chiefly, combinations of three modalities may be required for evaluation. Renal ultrasonography provides information on kidney size and location, hydronephrosis, urinary bladder anomalies and post-void residual urine. An ultrasound may be performed even during therapy of the UTI. Operator dependence and poor sensitivity for detection of VUR limit its role. Radiocontrast micturating cystourethrogram (MCU) is necessary for diagnosing and grading the severity of VUR (Fig. 1) and defining urethral and bladder anatomy. The MCU is done within 2 to 3 weeks of treatment. Dimercaptosuccinic acid (DMSA) scintigraphy is a sensitive test for detecting renal scars, characterized by decreased uptake with loss of renal contours or presence of cortical thinning with decreased volume (Fig. 2). While DMSA is a sensitive test for detecting acute pyelonephritis,

Table 1: Antimicrobials for treatment of UTI

Medication	Dose, mg/kg/day
Parenteral	
Ceftriaxone	75-100, in 1-2 divided doses IV
Cefotaxime	100-150, in 2-3 divided doses IV
Amikacin	10-15, single dose IV or IM
Gentamicin	5-6, single dose IV or IM
Coamoxiclav	30-35 of amoxicillin, in 2 divided doses IV
Oral	
Cefixime	8-10, in 2 divided doses
Coamoxiclav	30-35 of amoxicillin, in 2 divided doses
Ciprofloxacin	10-20, in 2 divided doses
Ofloxacin	15-20, in 2 divided doses
Cephalexin	50-70, in 2-3 divided doses

Table 2: Antimicrobials for prophylaxis of urinary tract infections

Medication	Dose, mg/kg/day	Remarks
Cotrimoxazole	1-2 of trimethoprim	Avoid in infants <3 months old, glucose-6-phosphate dehydrogenase (G6PD) deficiency
Nitrofurantoin	1-2	May cause vomiting and nausea; avoid in infants <3 months old, G6PD deficiency, renal insufficiency
Cephalexin	10	Drug of choice in first 3-6 months of life
Cefadroxil	5	An alternative agent in early infancy

Usually given as single bedtime dose

Table 3: Evaluation following the first episode of urinary tract infection

Age	Evaluation*
Below 1 year	Ultrasound
	Micturating cystourethrogram (MCU)
	Dimercaptosuccinic acid (DMSA) renal scan
1-5 year	Ultrasound
	DMSA scan
	MCU, if ultrasound or DMSA scan is abnormal
Above 5 year	Ultrasound
	If ultrasound abnormal: MCU & DMSA scan

*Patients with recurrent UTI need detailed evaluation with ultrasonography, DMSA scan and MCU

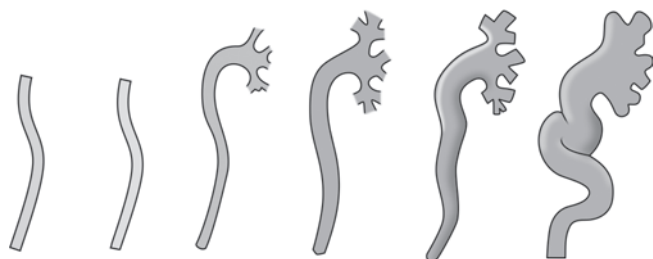


Fig. 1: Grading of vesicoureteric reflux (VUR) on micturating cystourethrogram. Grade I: VUR does not reach the renal pelvis; Grade II: VUR extending up to the renal pelvis without dilatation of pelvis or calyceal fornices; Grade III: VUR extending up to the kidney, with mild dilatation or tortuosity of the ureter and renal pelvis, with no or minor blunting of the calyceal fornices; Grade IV: Moderate dilatation or tortuosity of the ureter, renal pelvis and fornices, with complete obliteration of the sharp angles of the calyceal fornices, but normal appearance of the papillary impressions; Grade V: Gross dilatation and tortuosity of the ureter, renal pelvis and calyces, with loss of papillary impressions on calyces

its diagnosis does not change management; routine use of DMSA scintigraphy in acute UTI is thus not justified. In order to detect renal scarring DMSA scan is recommended 3-months after therapy for UTI.

Direct radionuclide cystography (DRCG) is useful for follow up studies since its sensitivity for detecting VUR is high and involves less radiocontrast exposure. Drawbacks include poor anatomical resolution, lack of urethral visualization and inability to precisely grade VUR.

Recommendations for Evaluation

Recommendations for imaging following the first UTI are variable. All patients are screened with the aim to identify patients at high risk of renal damage, chiefly those below 1 year of age, and those with VUR or urinary tract obstruction. A 'high-risk' approach should be followed to avoid subjecting children with no abnormality to multiple



Fig 2: 99 mTc-DMSA scintigraphy showing multiple scars and loss of volume in the right kidney. The left kidney is normal

investigations. However, this approach is now tempered with the knowledge that intensive imaging and subsequent management do not significantly alter the long-term outcome of children with reflux nephropathy diagnosed following a UTI. In addition, the routine use of antenatal screening leads to a majority of the significant anomalies to be detected and managed after birth.

The Expert Group of the Indian Society of Pediatric Nephrology reviewed the current literature, keeping in view that in our country the diagnosis of UTI is often missed or delayed, and there are limitations of infrastructure and scarcity of resources for routine antenatal screening. Their recommendations on evaluation following the first UTI are summarized in Table 3.³ Briefly, all infants (<1 year) need to be evaluated aggressively using ultrasonography, MCU and DMSA scan. The early detection of scarring, high grade VUR or obstructive uropathy is likely to enable interventions that prevent progressive kidney damage. Since infants are at the highest risk, it is necessary that this group undergo focused evaluation. DMSA scintigraphy and ultrasound are required between 1 to 5 years, and ultrasound above 5 years of age. Further imaging with MCU is necessary if scintigraphy or ultrasound examination is abnormal. A milder grade of reflux, which may be missed by this approach, is not likely to contribute to renal scarring.

The above recommendations are based on the assumption that early detection of urologic abnormalities shall result in improved outcomes. It is possible that application of antenatal ultrasonography and availability of non invasive

methods for evaluating the lower tract might result in modification of the existing recommendations in future.

Asymptomatic Bacteriuria (ABU)

ABU refers to significant bacteriuria in a child who has no symptoms of UTI.¹ The frequency of ABU is about 1 to 2 percent in girls and 0.05 to 0.2 percent in boys. The organisms isolated in most cases are usually *E. coli* of low virulence. The condition is benign, does not cause renal injury and remits spontaneously with time. On the other hand, eradication of these non-pathogenic organisms may be followed by symptomatic infection with more virulent strains. Use of antibiotics to treat asymptomatic bacteriuria or antibiotic prophylaxis is not indicated. The presence of asymptomatic bacteriuria in a patient previously treated for UTI should not be considered as recurrent UTI.¹

Recurrent UTI

Recurrent UTI are observed in 30 to 50 percent children; most recurrences occur within 3 months of the initial episode. Predisposing factors include:

- Female sex
- Age <6 months
- Obstructive uropathy
- Severe (grade III-V) VUR
- Repeated pyelonephritis
- Voiding dysfunction
- Constipation
- Repeated catheterization.

Evaluation

Patients with recurrent UTI at any age should undergo detailed imaging with ultrasonography, MCU and DMSA scintigraphy.³

Prevention

Interventions that have been associated with a decrease in incidence of UTI include relief of constipation and voiding dysfunction.^{1-3,5} Adequate fluid intake and frequent voiding is advised. Antibacterial prophylaxis is indicated in children with recurrences, even in the absence of VUR.

Circumcision

Increased periurethral bacterial colonization in the uncircumcised may be a risk factor for UTI. Circumcision reduces the risk of recurrent UTI in infant boys, and might have benefits in patients with high grade VUR.^{12,13}

Voiding Dysfunction and Bowel Bladder Dysfunction

Voiding dysfunction refers to abnormal patterns of micturition in the presence of intact neuronal pathways without

congenital or anatomical abnormalities.¹⁴ When constipation is associated with a functional voiding disorder, the condition is referred to as bowel bladder dysfunction (BBD).^{3,14}

Children with recurrent UTI are likely to have dysfunctional voiding. A diagnosis of voiding dysfunction can be made based on history of the voiding pattern and urodynamic studies. A record of frequency and voided volume and fluid intake for two to three days is useful. The urinary stream should be observed, including for post void dribbling in boys. Voiding dysfunction should be suspected in children with (i) persistent high grade VUR; (ii) thickened urinary bladder wall >2 mm, (iii) post-void urine >20 ml, and (iv) spinning top configuration of bladder on MCU.³

The child is explained to follow a structured voiding pattern, with frequent voids and double micturition. Constipation is managed with dietary modification and medications. Patients with large post void residues, benefit from timely voiding, bladder retraining and clean intermittent catheterization. In patients with an overactive bladder therapy, with anticholinergic medications (*e.g.* oxybutinin) increases bladder capacity.

VESICoureteric Reflux

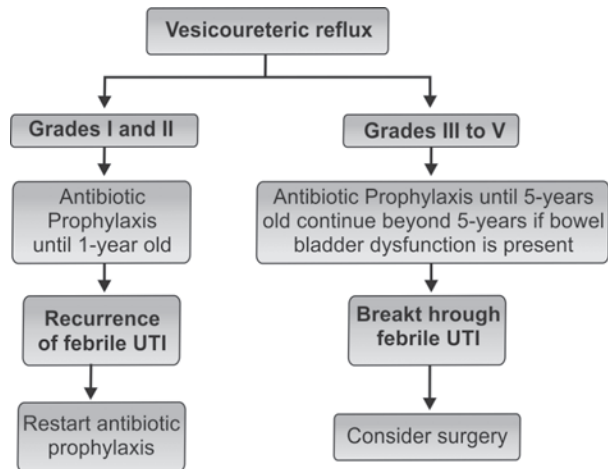
VUR refers to the retrograde flow of urine from bladder to ureters and pelvis at rest or during micturition.¹³ Its severity is graded using the International study classification from grade I to V, based on the appearance of the urinary tract on MCU (Fig. 1).¹⁵ Primary VUR tends to resolve by 6 to 10 year of age. Factors favoring resolution are younger age, and low grade and unilateral VUR. The rate of resolution is 70 to 90 percent for grades I-III and 10 to 35 percent for higher grades.³ Secondary VUR is due to bladder outflow obstruction, as with posterior urethral valves, neurogenic bladder or a functional voiding disorder.

Recognition of significant reflux is important since UTI in this setting predispose to renal parenchymal damage and renal scarring (reflux nephropathy), an important cause of hypertension and progressive renal injury. However, it is recognized that 10 to 20 percent male infants with severe VUR may have small kidneys without any history of UTI.¹⁶ Thus, not all children with reflux benefit from diagnosis or treatment.¹⁷

Therapy

Conventional therapies for VUR include antibiotic prophylaxis and surgical intervention.^{18,19} In patients with dilating reflux, the numbers of breakthrough UTI and risk of renal scarring were similar following surgical repair versus prophylaxis. Experts recommend that the management of patients with VUR should depend on the patient age, grade of reflux and whether there are any breakthrough infections.¹²

Flow chart 1: Management of vesicoureteric reflux. Medical therapy of VUR is based on the principle that VUR resolves over time, and prophylactic antibiotics maintain urine sterility and prevent infections while awaiting spontaneous resolution. Reflux takes longer to resolve if associated with bowel bladder dysfunction or if high grade reflux is present; such patients require prolonged prophylaxis. Surgical correction of VUR is indicated if breakthrough infections occur, since significant parenchymal injury may occur with pyelonephritis



Long term antibiotic prophylaxis is proposed to reduce periurethral colonization, reducing risks of recurrent UTI in patients. Antibiotic prophylaxis is discontinued once reflux subsides. As the risk of scarring decreases after 5 years in children with normal bowel and voiding habits, prophylaxis can be stopped even if VUR persists.²⁰

Surgery is reserved for patients with bilateral grade IV and V reflux persisting by 1 to 2 years of life, and those having breakthrough febrile UTI while on antibiotic prophylaxis, if parents prefer surgical intervention to prophylaxis, or in patients who show appearance of new scars and deterioration of renal function.^{19,20} An evaluation for voiding dysfunction should be done before surgery.

Flow chart 1 summarizes proposed guidelines for management of VUR.³ Patients should initially receive antibiotic prophylaxis while awaiting spontaneous resolution of VUR. Patients are followed closely for occurrence of breakthrough UTI. Repeat imaging is conducted after 18 to 36 months in those with grade III-V VUR, preferring radionuclide cystogram over MCU for follow-up evaluation. Evidence from few studies suggests that the strategy of prompt diagnosis and treatment of UTI might be as effective as antibiotic prophylaxis.^{1,21} Clinicians should however caution the parents regarding the risks of withholding antibiotic prophylaxis.

Dextranomer/hyaluronic acid copolymer (Deflux) endoscopic treatment has been used as an alternative to

surgical repair for patients with VUR.²² While the technique is less invasive and associated with satisfactory outcome, a significant proportion of patients, particularly those with bowel bladder dysfunction, may show persistence and/or recurrence of reflux and progressive renal damage.^{23,24} Endoscopic correction is currently not recommended as first line therapy.¹²

Screening of Siblings and Offspring

Reflux is inherited in an autosomal dominant manner with incomplete penetrance; one-third siblings and offspring of patients show VUR.²⁵ Ultrasonography is recommended to screen for the presence of reflux.

Follow-up

Patients with a renal scar (reflux nephropathy) are counseled regarding the need for early diagnosis and therapy of UTI and follow-up. Physical growth and blood pressure is monitored; investigations include urinalysis for proteinuria and estimation of blood creatinine. Annual ultrasound examinations are done to monitor renal growth.

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Acute Kidney Injury in Children

Kanav Anand

INTRODUCTION

Incidence of acute kidney injury (AKI) in children appears to be increasing and the etiology has shifted from primary renal diseases to multifactorial causes. Children who have suffered from AKI due to any cause are at risk for development of kidney diseases several years after the initial insult. Derangement of renal functions is associated with increased morbidity and mortality.¹ The incidence of AKI in neonatal and pediatric units varies between 1 and 25 percent, depending upon the criteria used for its definition.^{2,3} Despite advances in therapy the mortality due to the condition is still high (30-40%) and a proportion of patients may progress to chronic kidney disease and dialysis dependency. AKI usually occurs in patients with previously normal renal functions, but may occasionally be superimposed on pre-existing renal disease (acute on chronic kidney disease). Derangements can vary from mild increase in the renal parameters to severe loss of organ function which requires supportive care in the form of renal replacement therapy. Initially everything was categorized under the term acute renal failure which generally represents the severe form of disease. Acute renal failure (ARF) is defined as a sudden loss of kidney function, occurring over a period of hours to days, manifested by accumulation of creatinine, urea and other metabolic waste products (azotemia) and often accompanied by reduction in urine volume (oliguria) with associated salt and water retention whereas, the diagnostic criteria for AKI include an abrupt (within 48 hours) reduction in kidney function, defined as 50 percent or greater increase in serum creatinine or oliguria (<0.5 ml/kg/hr) for more than 6 hours.

In 2002, the acute dialysis quality initiative group proposed the RIFLE criteria as interim consensus criteria for the definition and staging of AKI (Table 1).⁴ The acronym RIFLE defines three grades of increasing severity of acute renal dysfunction (risk, injury, and failure; R, I and

F, respectively) on the basis of graded changes in serum creatinine or urine output and two outcome variables (loss and end-stage kidney disease; L and E, respectively) based on the duration of loss of kidney function.⁵ Risk, injury, and failure are defined as increases in serum creatinine levels by 50 percent, 100 percent, or 200 percent respectively, or oliguria for 6, 12 or 24 hours, respectively. Another classification has been proposed by AKIN (Acute kidney injury network) which divides AKI into three stages (Table 1).^{6,7}

ETIOLOGY

There are many causes of AKI and the more common ones are listed in (Table 2). Some causes of AKI, such as rapidly progressive glomerulonephritis (RPGN), may present as AKI but rapidly evolve into chronic kidney disease (CKD). Several renal diseases, such as the hemolytic-uremic syndrome (HUS), Henoch-Schönlein purpura, and obstructive uropathy, may present as AKI. There may be improvement in renal functions to normal or near-normal levels or they may slowly deteriorate, leading to CKD, several months to years later. Children with AKI due to hypoxic/ischemic insults, HUS, acute glomerulonephritis and other causes are more likely to demonstrate oliguria or anuria. Neonates and children with acute interstitial nephritis, nephrotoxic renal insults including aminoglycoside nephrotoxicity and contrast nephropathy are more likely to have AKI with normal urine output, termed as nonoliguric AKI. In neonates, the common causes of AKI are birth asphyxia, sepsis, structural abnormalities of urinary tract (obstructive uropathy), drug toxicity and bilateral renal artery thrombosis secondary to umbilical artery catheterization.² The morbidity and mortality rates of nonoliguric AKI are less than those of oliguric AKI.⁸ Classification of acute kidney injury is shown in (Flow chart 1).

Table 1: RIFLE* and acute kidney injury network (AKIN) staging criteria for acute kidney injury

<i>RIFLE stage</i>	<i>AKIN stage</i>	<i>Serum creatinine criteria</i>	<i>Urine output criteria</i>
Risk	1	Increase in serum creatinine of 1.5- to two-fold from baseline (RIFLE and AKIN) or increase in serum creatinine of ≥ 0.3 mg/dl (AKIN)	< 0.5 ml/kg/h for 6 hours
Injury	2	Increase in serum creatinine of two- to threefold from baseline	< 0.5 ml/kg/h for 12 hours
Failure	3	Increase in serum creatinine of more than threefold from baseline or a serum creatinine of > 4 mg/dl with an acute rise of ≥ 0.5 mg/dl	< 0.5 ml/kg/h for 24 hours or anuria for 12 hours
Loss	Persistent renal failure for > 4 weeks		
End-stage renal disease	Persistent renal failure for > 3 months		

* RIFLE defines three grades of increasing severity of acute renal dysfunction (risk, injury, and failure: Respectively R, I, and F) on the basis of graded changes in serum creatinine or urine output and two outcomes variables (loss and end-stage kidney disease, L and E, respectively) based on the duration of loss of kidney function.

Table 2: Categories of acute renal failure in children

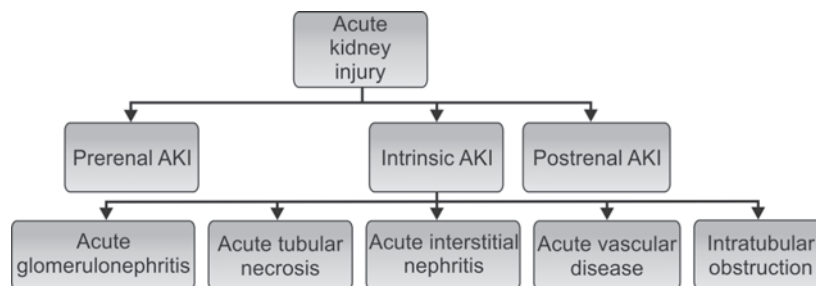
<i>Prerenal</i>	<i>Intrinsic Renal</i>	<i>Postrenal</i>
Intravascular volume depletion Dehydration Gastroenteritis Hemorrhage Diabetes Insipidus Burns Diuretics	Acute tubular necrosis (ATN) Ischemic Injury Prerenal causes Exogenous toxins Nephrotoxic antibiotics Chemotherapeutic agents NSAIDs ACE inhibitors and ARBs Radiographic contrast Venoms Heavy metals Ethylene glycol Endogenous toxins Myoglobinuria/ hemoglobinuria Tumor lysis syndrome	Posterior urethral valves Obstruction of a solitary kidney Bilateral ureteral obstruction Neurogenic bladder Trauma
Redistribution of fluid/vasodilatation Sepsis Pancreatitis Intestinal obstruction Peritonitis Nephrotic syndrome Hepatic failure	Acute interstitial nephritis Drug-induced or idiopathic Acute glomerulonephritis Postinfectious (Streptococcal) HSP, SLE, Goodpasture syndrome Vascular Pathology Renal artery/vein thrombosis HUS/TTP Cortical necrosis Congenital Renal dysplasia/hypoplasia Polycystic kidney disease	
Decreased Cardiac Output Congenital heart failure Cardiogenic shock Myocarditis Cardiac tamponade		

Prerenal Acute Kidney Injury

Prerenal AKI occurs due to renal hypoperfusion and renal functions recover on restoration of normal renal perfusion. There is an increase risk of intrinsic acute kidney

injury if renal hypoperfusion is sustained for long time.⁹ Hypovolemia and hypoperfusion leads to activation of sympathetic nervous system, renin angiotensin, aldosterone and antidiuretic hormone which helps to sustain

Flow chart 1: Classification of acute kidney injury



a near normal glomerular filtration rate (GFR) by maintaining intraglomerular capillary pressure and increasing proximal tubular sodium and water reabsorption. In prerenal AKI, GFR declines inspite of all these compensatory responses leading to excretion of concentrated urine which has low urinary sodium concentration (<20 mmol/L), a low fractional excretion of sodium ($<1\%$), a low fractional excretion of urea ($<35\%$) and high urine osmolality. Treatment of prerenal AKI is correction of underlying cause of renal hypoperfusion. In patients, who have true volume depletion, fluid resuscitation is the primary treatment. In patients with decreased effective arterial blood volume, treatment of primary organ failure will improve prerenal azotemia.

Intrinsic Acute Kidney Injury

Intrinsic AKI is divided into the following categories:

Acute Glomerulonephritis

Acute glomerulonephritis (GN) and rapidly progressive GN comprise a spectrum of glomerular diseases that present as AKI leading to progressive decline in renal function over days to weeks. Prompt recognition of these entities is critical because early initiation of therapy is essential to preserve kidney function and prevent irreversible renal damage. The prototypic form of acute GN is poststreptococcal GN. The presence of dysmorphic red blood cells and red blood cell casts on microscopic examination of the urinary sediment are pathognomonic for an acute glomerular process. Serologic studies including serum complement levels, markers for hepatitis B and C viruses, antistreptococcal antibodies, antinuclear antibodies, anti-neutrophil cytoplasmic antibodies and antiglomerular basement membrane antibodies may be helpful in making a diagnosis; however, renal biopsy usually is necessary for definitive diagnosis. The specific findings on kidney biopsy depend on the underlying glomerular process; proliferative lesions in the glomerulus, often associated with crescentic changes, are characteristic.

Acute Tubular Necrosis

Acute tubular necrosis (ATN) is the most common cause of intrinsic AKI. Most commonly ATN is precipitated by ischemic or nephrotoxic processes. Acute illnesses, sepsis, hypotension and nephrotoxic medications are contributing factors for its development. The clinical course of ATN can be highly variable. Initially there is an oliguric phase, beginning within 24 hours of the inciting event and it lasts for 1 to 3 weeks, followed by a diuretic phase, characterized by a progressive increase in urine volume, which usually is an indicator of renal recovery. Many patients, however, may be nonoliguric throughout their course. Mortality associated with ATN is high, with reported mortality rates as high as 50 percent to 70 percent in some series.¹⁰ Multiple studies have suggested that ATN is an independent risk factor for mortality.^{11,12} Majority of surviving patients recover their renal functions, although complete recovery may not occur.

The urinary sediment in ATN demonstrates many tubular epithelial cells and coarse granular casts, often described as 'muddy brown casts'. Tubular sodium reabsorption is impaired. The urinary sodium is greater than 40 mmol/L with a fractional excretion of sodium being >1 percent.

Ischemic acute tubular necrosis: When the hypoperfusion is more intense or prolonged, tubular cell injury ensues and renal dysfunction persists even after the hemodynamic insult resolves.¹³ As the name implies, the most evident site of injury following renal ischemia is the tubular epithelial cells, with evidence of both epithelial cell death (necrosis) and apoptosis.¹³

Nephrotoxic acute tubular necrosis: Nephrotoxic ATN may result from either endogenous or exogenous toxins. The endogenous heme pigments from hemoglobin and myoglobin cause ATN in the settings of massive intravascular hemolysis or rhabdomyolysis, respectively. Most cases of exogenous nephrotoxic ATN are associated with antimicrobial agents such as aminoglycosides and amphotericin B,

radio contrast media, chemotherapeutic agents including cisplatin and ifosfamide and acetaminophen.

Acute Interstitial Nephritis

Acute interstitial nephritis (AIN) is associated with arthralgia and classic triad of fever, rash and eosinophilia, but this triad may be seen in only 10 to 30 percent of patients.¹⁴ Antibiotics and nonsteroidal anti-inflammatory drugs (NSAIDs) currently are the most common causative agents, although AIN can occur with almost any medication. The urinary findings in AIN include sterile pyuria, white blood cell casts, non-nephrotic range proteinuria, hematuria and eosinophiluria. The gold standard for diagnosis of AIN is renal biopsy.

Acute Vascular Syndromes

Acute vascular syndromes are divided into large-vessel and small-vessel disease. The large-vessel diseases include renal thromboembolism, renal artery dissection and renal vein thrombosis. The common feature of the large-vessel vascular syndromes is renal infarction, usually presenting with flank pain, hematuria and elevated levels of serum lactate dehydrogenase. Unilateral disease will not cause AKI unless it involves a solitary functional kidney. Diagnosis is made by using contrast-enhanced CT scan, radioisotope renography or angiography. Thrombolytic therapy or revascularization is usually not feasible; treatment usually consists of anticoagulation and supportive care.

More common than large-vessel disease is small-vessel disease resulting from atheroembolization or formation of fibrin thrombi into the distal renal vasculature. It is most common after surgical or angiographic manipulation of the aorta, often with a delayed onset of several days to weeks. The diagnosis is made most readily when cutaneous manifestations, including livedo reticularis and digital ischemia are present.

Intratubular Obstruction

Intratubular obstruction from precipitation of either proteins or crystals within the tubular lumen can also cause AKI. It can occur in setting of multiple myeloma, ethylene glycol ingestion and tumor lysis syndrome. In the tumor lysis syndrome, marked hyperuricemia leads to intratubular precipitation of uric acid crystals. Intratubular precipitation of acyclovir, indinavir and methotrexate is the major mechanism of AKI associated with the use of these drugs.

Postrenal Acute Kidney Injury

Postrenal AKI results from obstruction of the urinary collecting system. Obstruction may occur at the level of the bladder or urethra (lower tract obstruction) or at the level of the ureters or renal pelvis (upper tract obstruction)

bilaterally. Unilateral obstruction is usually not associated with a significant decrement in kidney function because of the preservation of function in the contralateral kidney. Common causes of obstruction in children include congenital ureteral strictures or posterior urethral valves. Postrenal AKI can present as a result of either complete or partial obstruction. Complete obstruction usually is associated with anuria, whereas partial obstruction may be asymptomatic or manifest with symptoms of voiding dysfunction such as frequency, hesitancy, intermittency, nocturia and incomplete emptying. Lower tract obstruction usually is diagnosed based on the presence of urinary retention. An elevated postvoid residual bladder volume can be measured by ultrasound or by measuring urine volume after placement of a bladder catheter. Combined plain film radiographs, ultrasonography, and high-resolution CT scans of the abdomen and pelvis are diagnostic in more than 90 percent of cases.¹⁵ Isotopic renography may be useful as a functional test to differentiate obstructive from nonobstructive urinary tract dilatation.

Clinical Evaluation of the Patient with Acute Kidney Injury

The clinical evaluation of the patient who has AKI begins with assessing whether the patient has prerenal, postrenal or intrinsic disease. Postrenal or obstructive disease is suggested by clinical symptoms of voiding dysfunction. Bladder outlet obstruction should be assessed clinically by asking for the urinary stream and radiologically by measuring postvoid residual bladder volume using an ultrasound. Upper tract obstruction should be assessed using renal ultrasound or CT scan.

Prerenal azotemia manifests as signs of intravascular volume depletion in the form of hypotension, orthostatic hypotension, tachycardia, flat neck veins, poor skin turgor and dry oral mucosa. The urinary sediment usually is without casts or cellular elements and the urine is usually concentrated (specific gravity >1.015; urine osmolality >350 mOsm/kg) with a low urine sodium concentration (<20 mmol/L). The fractional excretion of sodium, calculated as the ratio of urine (UNa) to plasma sodium concentration (PNa) divided by the ratio of urine (UCr) to plasma creatinine (PCr) expressed as percentage $\rightarrow ((\text{UNa}/\text{PNa})/(\text{UCr}/\text{PCr})) \times 100$ on a random urine sample and is usually less than 1 percent (Table 3). In patients, who have heart failure or liver disease, concomitant use of diuretics decreases the utility of urinary diagnostic indices. In patients, who have prerenal azotemia, the fractional excretion of urea is usually less than 35 percent, compared with normal values of more than 60 percent.¹⁶

The ultimate determination of whether a patient has prerenal or intrinsic AKI may require a diagnostic trial of

intravenous fluids. The differentiation between the causes of intrinsic AKI requires a careful clinical history and physical examination.

Some investigations which can aid in identifying the cause and complications of AKI are listed in Table 4. Urine microscopy may also provide useful clues to the diagnosis (Table 5). The presence of dysmorphic red blood cells and red blood cell casts are strongly suggestive of an acute glomerular process. The presence of white blood cells, white blood cell casts and eosinophiluria suggests the diagnosis of AIN. Tubular epithelial cells and muddy brown granular casts suggest ATN. Heavy oxalate, uric acid crystalluria or the presence of drug crystals suggests intratubular crystal deposition, whereas, the presence of nonalbumin proteinuria suggests a diagnosis of myeloma kidney. When the diagnosis remains uncertain, especially if there is suspicion of acute GN or AIN, a kidney biopsy may be indicated. The indications of renal biopsy in acute kidney injury have been mentioned in (Table 6).

Table 3: Dehydration/reduced renal perfusion (prerenal) vs. acute tubular necrosis (intrinsic renal)

	<i>Prerenal</i>		<i>Intrinsic renal</i>	
	<i>Child</i>	<i>Neonate</i>	<i>Child</i>	<i>Neonate</i>
UNa (mEq/L)	<20	<20	>40	>40
FeNa (%)	<1	<2	>1	>3
U _{osm} (mOsm/kg)	>500	>400	<300	<300
U _{osm} /P _{osm}	>1.5	>2	<0.8-1.2	<1
BU/creat	> 20:1	> 20:1	< 20:1	< 20:1
Fluid push	Urine↑	Urine↑	No response	No response

FeNa → fractional excretion of sodium = ((urine sodium × serum creatinine)/(serum sodium × urine creatinine)) × 100%;
 UNa → urinary sodium; U_{osm} → urinary osmolality; P_{osm} → plasma osmolality, BU → blood urea; creat → serum creatinine

AKI may occasionally be superimposed on chronic kidney disease. Features such as failure to thrive and growth retardation, hypocalcemia, hyperphosphatemia, hypertensive retinopathy, renal osteodystrophy and small contracted kidneys indicate an underlying chronic kidney disease. Urinary tract infection, use of nephrotoxic drugs, rapid increase in blood pressure and hypovolemia may precipitate AKI in such cases.

A high serum creatinine level, a reliable marker for AKI, signifies that the damage has already occurred as the serum creatinine rises only when about 50 percent loss of renal function has occurred.¹⁷ In order to pick up an early AKI so as to prevent the progression, nowadays a few novel biomarkers are being used such as serum cystatin C, urinary kidney injury molecule 1 (KIM-1), serum and urinary neutrophil gelatinase associated lipocalin (NGAL) and urinary interleukin 18 (IL-18).¹⁸ NGAL and KIM are specific for hypoxic and nephrotoxin mediated renal injury, whereas IL-18 is specific for hypoxic and ischemic renal damage.¹⁷ These markers help in early detection of AKI, approximately 1 to 2 days prior to the rise in serum creatinine values. Commercial kits for these biomarkers will be very soon available in the market.

MANAGEMENT

Fluid Management

Many children would require a fluid bolus to differentiate prerenal from intrinsic renal failure. One or more fluid challenges of 20 ml/kg of isotonic solution (0.9% normal saline or ringer's lactate) over 30 to 60 minutes is used depending on the volume status of the child. Diuretics (furosemide 2-3 mg/kg IV) may be tried if the bolus has no effect. This should normally induce a diuresis over

Table 4: Investigations in patients with acute kidney injury

Blood	Complete blood counts Blood urea and creatinine Electrolytes (sodium, potassium, calcium, phosphate) Blood Gas (pH, bicarbonate)
Urine	Urinalysis Culture (if symptoms of urinary infection are present) Fractional excretion of sodium Osmolality
Radiology	Chest X-ray (for fluid overload, cardiomegaly) Ultrasonography (to identify any obstruction or dilatation) Renal doppler (for suspected arterial or venous thrombosis) Micturating cysto urethrography (if suspecting urethral obstruction) DTPA (to rule out obstructive uropathy)
ECG (for hyperkalemia)	
Investigations to establish the cause	Peripheral smear examination, platelet count, reticulocyte count, blood LDH levels, stool culture (in suspected D+ hemolytic uremic syndrome) Blood ASO, serum C3 levels, antinuclear antibodies (ANA), antineutrophil cytoplasmic antibodies (ANCA) Renal Biopsy

Table 5: Urinalysis findings in acute renal failure

<i>Prerenal azotemia</i>	<i>Acute tubular necrosis</i>	<i>Cortical necrosis</i>	<i>Interstitial nephritis</i>	<i>Glomerulonephritis</i>	<i>Postrenal</i>
Increased specific gravity, normal urinalysis	Granular casts, epithelial cells, epithelial casts, pigmentation	Gross or microscopic hematuria, proteinuria	Pyuria, WBC casts, eosinophiluria	Gross or microscopic hematuria, RBC casts, dysmorphic RBCs, proteinuria	Normal urinalysis

Table 6: Indications of renal biopsy in acute kidney injury

- Rapidly progressive glomerulonephritis
- AKI in transplanted kidney
- Unremitting AKI lasting for more than 4 weeks
- AKI in children on nephrotoxic drugs
- Prognostication in hemolytic uremic syndrome
- AKI of unknown etiology

next 2 to 3 hours if renal tubular function is intact.¹⁷ Fluid needs to be restricted in established oliguric/anuric renal failure. Total fluids should be restricted to 400 ml/m² of body surface area plus the urine output. Extra losses, e.g. from overhead warmers, gastrointestinal losses etc. needs to be replaced as well.

Electrolyte Management

Sodium levels are usually low in AKI because of fluid overload. Urinary sodium should be used as a marker for total body sodium. Sodium intake should be restricted to 2 to 3 mEq/kg body weight per day, together with fluid restriction, to prevent sodium and fluid retention with resultant hypertension. Symptomatic hyponatremia may need to be corrected with hypertonic saline.

Patients with oligoanuric AKI should not receive potassium or phosphorus unless they exhibit hypokalemia or hypophosphatemia. Hyperkalemia is common in AKI as the kidneys handle 90 percent of daily potassium excretion. Hyperkalemia needs to be treated aggressively as it can be life threatening.

Emergency management includes,

IV Calcium Gluconate 0.5 to 1 ml/kg

Salbutamol nebulisation 5 to 10 mg

IV Sodium bicarbonate 1 to 2 mEq/kg

Regular insulin 0.1 to 0.2 U/kg, with glucose (50%) 0.5 to 1 gm/kg.

Potassium binding resins 1 gm/kg/dose every 6 to 8 hourly.

Hyperphosphatemia is treated with the help of phosphate binders like calcium acetate, lanthanum carbonate, sevelamer which are given along with food so as to bind with the dietary phosphate.

Patients with AKI secondary to nephrotoxic medications or interstitial nephritis often demonstrate polyuria, placing them at risk for severe fluid and electrolyte losses.

In order to appropriately manage these patients, it is ideal to have a urinary catheter *in situ* and obtain weights and serum electrolyte levels at least once per day.

Nutrition

Adequate nutrition in critically ill children with AKI is a crucial component of their treatment, as they are at an increased risk of developing protein-energy malnutrition. Presence of renal replacement therapy (RRT) contributes to nutritional losses, especially amino acids and water-soluble vitamins.

The major goals of nutrition management are:

- Adequate calorie intake
- Protein intake of 2 to 3 gm/kg/day, with an adequate increase during renal replacement therapy to account for the losses
- Minimize potassium and phosphate intake
- Restrict fluid intake, which may mean increasing calorie density of feeds.

Treatment of the Underlying Disease

The basic pathological process which has caused the AKI should be targeted in order to prevent the ongoing renal injury. The strategy would include fluid resuscitation for intravascular fluid depletion which could have led to pre-renal AKI, treatment of sepsis with appropriate antibiotics, adequate cardiac support in conditions of decreased cardiac output, omission of nephrotoxic drugs, immunosuppression for lupus and Henoch Schonlein purpura nephritis, relieving the renal vessel occlusion and fulguration of posterior urethral valves.

Renal Correction of Drug Doses

Drug dosing must be altered for patients with AKI, not only for avoiding kidney injury, but also to avoid toxic accumulation of drugs and their metabolites which should be excreted by the kidney. When glomerular filtration rate falls to less than 50 percent of normal, most of the drugs excreted by the kidney will require modifications in scheduled dosing. This modification can be in terms of reduction of dosage or increasing the dosing interval. These drug dosages need to be further modified if the patient is on renal replacement therapy (RRT), depending on the clearance characteristics of the drug by the particular RRT modality.

Pharmacological Therapy

Inotropic agents are used for preservation of renal perfusion in critically ill patients unresponsive to volume repletion. At low or so called “renal doses” of dopamine (0.5–2 mcg/kg/min), there is an increase in renal plasma flow and sodium excretion but these effects are short-lived. A number of trials have seriously questioned the utility of “renal dose” dopamine in reversing oliguria and many centers have abandoned its use for this purpose.¹⁹

Dobutamine and norepinephrine have shown proven benefits in patients with AKI by increasing the cardiac output, leading to an increase in renal blood flow.

Vasopressin too has been effective in maintaining renal perfusion in patients with septic shock who were unresponsive to catecholamines. It increases the systemic vascular resistance by direct action on the vascular smooth muscle cells.

Renal Replacement Therapy

There are various modalities of RRT available to the pediatric intensivists today to support the renal system, giving it the much needed time to recover from any injury. The usual indications are:

Renal

- Oliguria (unresponsive to diuretics and/or fluid challenge)
- Anuria (nonobstructive)
- Severe Metabolic acidosis (pH <7.2, despite bicarbonate therapy)
- Severe or persistent Hyperkalemia ($K^+ >6.5$ mEq/L, $K^+ = 5.5$ -6.5 mEq/L with ECG changes)
- Azotemia

Uremic symptoms (encephalopathy, seizures, myopathy, pericarditis, bleeding)

Hyponatremia ($Na^+ <120$ -125 mEq/L, esp. if symptomatic)

Nonrenal

Fluid overload

Anticipated large transfusion in trauma or coagulopathy

Inborn errors of metabolism

Sepsis

Postcardiopulmonary bypass systemic inflammatory response syndrome

Pancreatitis

Drug overdose

The modalities available for RRT include peritoneal dialysis (PD), hemodialysis (HD), continuous renal replacement therapy (CRRT). CRRT can be arteriovenous or venovenous in nature, having 3 different subtypes, namely hemofiltration, hemodialysis and hemodiafiltration.

Solute removal is termed as “clearance” and fluid removal is called “ultrafiltration”. Clearance and ultrafiltration across a membrane (peritoneum in PD, filter membrane in HD and CRRT) forms the basis of renal replacement therapy. The effectiveness of any RRT is a measure of its effectiveness in ultrafiltration and clearance.

There are two mechanisms involved in the transfer of solutes across any semipermeable membrane: diffusion and convection. Diffusion is the movement of solute along its concentration gradient between the dialysate and blood. The “dragging” movement of solute with the moving stream of ultrafiltrate is known as convection or “solvent drag”.

Tables 7 and 8, give the comparison between the various modalities of renal replacement therapy.

Table 7: Comparison between the three techniques of renal replacement therapy

	PD	HDi	CRRT
<i>Method specificities</i>			
Vascular access (ECC)	No	Yes	Yes
Complex method with specific expertise	Low	Moderate	High
Systemic anticoagulation	No	Frequent	Frequent
<i>Dialysis dose</i>			
Efficacy to remove a toxin	Moderate	High	High
Efficacy to remove fluid	Moderate	Moderate	High
<i>Clinical situation indication</i>			
Hemodynamic instability	Yes	No	Yes
Intracranial hypertension	Yes	±	Yes
ARDS	±	Yes	Yes
Abdominal surgery	±	Yes	Yes

PD → peritoneal dialysis; HDi → intermittent hemodialysis; CRRT → continuous renal replacement therapy; ECC → extracorporeal circulation; ARDS → acute respiratory distress syndrome

Table 8: Renal replacement therapy

<i>RRT Modality</i>	<i>Advantages</i>	<i>Disadvantages</i>
Peritoneal dialysis	<ul style="list-style-type: none"> • Minimal equipment needs • Minimal training needs • Feasible in small infants • Minimum hemodynamic compromise • No systemic anticoagulation • More physiological due to its continuous nature • No need for vascular access 	<ul style="list-style-type: none"> • Slow and less efficient solute removal • Unreliable and variable ultrafiltration • Respiratory compromise – abdominal compartment syndrome • Peritonitis • Catheter obstruction, leakage
Hemodialysis	<ul style="list-style-type: none"> • Maximum solute clearance • Readily available • Short treatment time • Accurate ultrafiltrate 	<ul style="list-style-type: none"> • Hemodynamic instability • Rapid fluid and solute compartment shifts • Difficult to use in small infants • Complex equipment • Requires vascular access • Heparin anticoagulation
CRRT	<ul style="list-style-type: none"> • Continuous control of fluid status • Accurate ultrafiltrate • Well tolerated by hemodynamically unstable patients • Excellent solute clearance • More physiological • Able to pump in huge amounts of fluids in oligo-anuric patients • Smaller circuit volumes 	<ul style="list-style-type: none"> • Systemic anticoagulation (though regional anticoagulation may be used) • Frequent filter clogging • Hypotension in small infants • Cost • Requires expertise • Vascular access necessary

Outcomes

Despite all the advances in renal replacement therapies, the morbidity and mortality due to AKI remains high (30-50%).²⁰ The recovery and long-term outcome of the children with AKI depends upon the underlying condition, associated sepsis, multiorgan dysfunction and delay in onset of appropriate therapy.

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Approach to Hematuria in Children

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Hematuria signifies blood in the urine and it can be macroscopic or microscopic. It can be true hematuria with RBC's in urine or can be red colored urine which is called pseudohematuria. Children with hematuria are brought to the notice of pediatric nephrologist often early in the disease course as it alarms the child, parents and the pediatrician. Normal children do excrete RBC's in urine with prevalence of 0.5 to 2.0 percent which can increase in the presence of fever or after exercise.¹ In nonlife-threatening situations when the cause of hematuria is not found on initial evaluation, these children are kept under regular follow-up with re-evaluation done as per need.

DEFINITION

Various definitions are available once we consider hematuria in children.² Understanding the concept of these definitions will help us towards the correct diagnosis and hence proper evaluation can be done based on the diagnosis.

Macroscopic hematuria: In this situation the hematuria is obvious. Parents bring the child with blood in the urine and dipstick and microscopic examination of urine is done to confirm the hematuria. Dipstick is positive for true hematuria, myoglobinuria and hemoglobinuria and negative in pseudohematuria due to rifampicin, colored food and beetroot while sediment examination shows RBC's and RBC casts in true hematuria.

Microscopic hematuria: Most of the times this is diagnosed on examination of urine only either for a symptom or for screening purposes. This indicates presence of abnormal number of RBCs in urine. More than 5 RBC/mm³ in uncentrifuged urine and more than 5 RBC/HPF in a centrifuged specimen (10 ml urine, 2000 rpm for 5 minutes) will denote significant hematuria.

Transient hematuria: This condition is usually microscopic and benign and seen in fever, infections, trauma and exercise. These children need repeat urine examination to see for persistence.

Persistent hematuria: This usually indicates a renal disease. Persistent presence of RBC's in 3 urine analysis obtained at least one week apart with or without other cellular deposits or recurrent macroscopic hematuria constitutes persistent hematuria.

Symptomatic hematuria: It always indicates underlying disease and needs a detailed evaluation. Usually it occurs in association with features like hypertension, edema and urinary symptoms.

Asymptomatic hematuria: It is usually microscopic but it can be macroscopic also. It may be the sole abnormality with neither history nor physical examination providing any indication of systemic, renal or urological disorders. These children should be kept on long-term follow-up to identify a benign or a slowly progressive disease process in them.

Isolated hematuria: Children belonging to this group can have both gross and microscopic hematuria. Persistent isolated hematuria with severe renal histological changes in a child is unusual. Persistent microhematuria interspersed with episodes of gross bleeding or with proteinuria signifies serious illness and it is mostly renal in origin. These children need long-term follow-up as hematuria can disappear, or the child can develop additional renal or systemic abnormalities, or rarely isolated hematuria can persist.

DETECTION OF HEMATURIA

Dipstick examination of urine can be used as a screening procedure but documentation of hematuria by microscopic examination is always mandatory. Dipsticks depends on peroxidase like chemical reaction between

free hemoglobin or hemoglobin present in intact RBC or myoglobin in urine and a chemical tetramethylbenzidine present in the strip producing a blue color. It is capable of detecting 3-10 RBC/μl of uncentrifuged urine. It has 100 percent sensitivity and 99 percent specificity. They are costly but good as screening test for hematuria.

Macroscopic hematuria is visible to the naked eye and can be associated with significant proteinuria or RBC casts. Presence of RBC's in urine should always be confirmed by microscopic examination of 10 to 15 ml of freshly collected sample centrifuged at 2000 rpm for 5 minutes, decanting the supernatant, then resuspending the sediment in remaining 0.5 ml.^{3,4} Microscopic hematuria seen in asymptomatic cases should be given importance in the presence of significant proteinuria.⁵

Absence of RBC on microscopic examination with positive dipstick test suggests hemoglobinuria or myoglobinuria which can be distinguished by spectrophotometry. Bedside test to identify hemoglobinuria is by centrifugation of urine wherein the supernatant fluid is uniformly pink whereas in true hematuria it is dirty brown.⁵ Dipsticks can be false positive in alkaline urine pH >9.0 or contamination with menstrual blood or fever or exercise or contamination with oxidizing agents and false-negative in the presence of formalin or ascorbic acid.¹

MECHANISM OF HEMATURIA

Blood in urine can have its origin either from the glomeruli or from renal tubules and interstitium. It can also originate from the urinary tract including the collecting systems, ureters, bladder and urethra. In glomerular hematuria the RBC's cross the glomerular endothelial-epithelial barrier and enters the capillary lumen through structural discontinuities in the capillary wall. These discontinuities seem to be at the capillary wall-mesangial cell reflections. One should note that the renal papillae are susceptible to necrotic injury from microthrombi and anoxia in children with a hemoglobinopathy like sickle cell disease or in those exposed to toxins. Episodes of transient microscopic or macroscopic hematuria during systemic infections or after moderate exercise are seen due to altered renal hemodynamic responses and may not signify a primary renal disease. Mechanical erosion of the mucosal surfaces in the urinary tract by the calculi or gravel can result in hematuria.⁶

CAUSES OF HEMATURIA

Various conditions causing hematuria are given in Table 1.² Common systemic conditions that can cause hematuria include disseminated intravascular coagulation (DIVC) and bleeding diathesis.² Glomerular diseases causing hematuria include postinfective glomerulonephritis (PIGN) which is the commonest followed by chronic glomerulonephritis like IgA glomerulonephritis (IgA GN)

Table 1: Causes of hematuria

Systemic disease

Disseminated intravascular coagulation (DIVC)
Anticoagulant therapy
Snake bite envenomation
Hemorrhagic disease
Thrombocytopenia

Glomerular disorders

Acute glomerulonephritis (ANS)
Chronic glomerulonephritis (membranous nephropathy, membranoproliferative GN)
IgA nephropathy
Systemic lupus erythematosus, hemolytic uremic syndrome, Henoch-Schönlein purpura
Renal vasculitis
Alport's syndrome
Benign familial hematuria
Renal vein thrombosis
Acute cortical necrosis

Nonglomerular disorders

Hypercalciuria
Hyperuricosuria
Hyperoxaluria
Renal stone disease
Cystitis (viral hemorrhagic, drug induced)
Genitourinary anomalies with infection
Tumors
Polycystic kidney disease
Trauma
Foreign body
Sickle cell hemoglobinopathy
Urinary tract infection

Conditions mimicking hematuria (pseudohematuria)

Foods containing beetroot
Drugs—furazolidone, pyridium, rifampicin
Pigmenturia—hemoglobinuria, myoglobinuria, bilirubinuria

and membranoproliferative glomerulonephritis (MPGN). Acute cystitis due to adenovirus, hypercalciuric conditions, renal stone disease and lastly tumors are common causes of nonglomerular hematuria.

FEATURES OF HEMATURIA

One should look into various presenting features and clinical examination findings to determine the source of bleeding as renal parenchymal (intrarenal) or from collecting system (extrarenal) of the kidneys.^{2,7} Some of the common presenting features of diseases causing hematuria are given in Table 2.²

Glomerular hematuria: Urine is usually tea colored and blood is seen throughout urinary stream and hence is termed total hematuria.⁷ Hematuria is usually painless and edema, hypertension and history of preceding or

Table 2: Presenting features of hematuria

<i>Etiological condition</i>	<i>Associated features</i>
<i>Glomerular</i>	
Acute postinfective GN	Edema, hypertension, oliguria, mild proteinuria
Membranoproliferative GN	Edema, proteinuria, hypertension
Henoch-Schönlein purpura	Purpura, arthralgia, abdominal symptoms
IgA nephropathy	Recurrent hematuria, synpharyngitic
Alport's syndrome	Ear, eye abnormalities, family history
Hemolytic uremic syndrome	Microangiopathic hemolytic anemia, renal insufficiency \pm dysentery
<i>Nonglomerular</i>	
Acute interstitial nephritis	Fever, rash, eosinophilia; history of drug intake
Urinary tract infection	Fever, flank pain, dysuria
Hypercalciuria, hyperuricosuria, hyperoxaluria	Colicky pain; family history of stones
Urolithiasis	Colicky pain, graveluria, family history
Hydronephrosis	Flank pain, abdominal mass
Wilms tumor	Abdominal mass
Hemorrhagic cystitis	Follows drug intake or viral infection with suprapubic pain or passage of clots
Coagulation disorder	Bleeding from other sites
Polycystic kidney	Abdominal mass, hypertension
AV malformations	Passage of clots, malformations elsewhere

associated infection are commonly seen. Family history of renal failure and deafness can be present. History of recurrent or persistent fever, arthralgia, arthritis, recurrent wheeze, recurrent jaundice and abdominal pain may be present pointing towards secondary glomerulonephritis. Presence of RBC casts in urine signifies glomerular hematuria and is associated with persistent or heavy proteinuria of 2+ or more or spot urine protein to creatinine ratio of >0.5 . The RBC's are dysmorphic by phase contrast microscopy and acanthocytes are common.² Blood clots and crystals are absent.

Nonglomerular hematuria: Urine is bright red. Dysuria and increased frequency are noted. Prolonged irregular fever of UTI can be seen. Features of renal stone disease like abdominal pain, vomiting and passage of gravel may be present. Absence of RBC casts and less than 15 percent dysmorphic RBCs in urine may signify nonglomerular hematuria.² Blood clots and crystals may be seen. Though proteinuria is seen it is not heavy and is less than 2+ or spot urine protein to creatinine ratio is <0.5 .

Exercise related hematuria: Rarely children following exercise can develop microscopic or macroscopic hematuria. Glomerular RBC and RBC casts were documented in few of them and otherwise urine analysis is normal at other times. Usually they are kept under surveillance.²

Benign familial hematuria: These children with hematuria will have first degree relative with hematuria without chronic kidney disease or sensorineural deafness. On the contrary children with Alport's syndrome of familial hematuria will have first degree relative with hematuria, chronic kidney disease and sensorineural deafness. Benign familial hematuria usually runs a nonprogressive course and end stage renal disease is very rarely reported.² Electron microscopy of kidney biopsy show thin glomerular basement membrane.

APPROACH TO HEMATURIA

A good history, physical examination and urine analysis helps to determine the type of hematuria (glomerular or nonglomerular) and the urgency of evaluation of the cause for hematuria.² Special stress should be given to family history of renal disease/deafness, identification of anatomic abnormalities and presence of macroscopic hematuria.

Family history is important in the evaluation of hematuria in children. Alport's syndrome should be doubted in a child when there is a first degree relative of the child with hematuria, sensorineural deafness and renal failure. Other diseases that carry a genetic origin include lupus nephritis, hemophilia and sickle cell disease. Nephrolithiasis and IgA GN also have a familial association. The thin glomerular basement membrane disease is a common cause of benign familial hematuria in children. Family members may not be aware that they have microscopic hematuria and should always be screened with a microscopic urinalysis.

Systemic diseases with thrombocytopenia or disseminated intravascular coagulation can present as hematuria. The use of furosemide for congenital heart disease can lead to hypercalciuria and subsequently, hematuria. Antibiotics and over-the-counter medications may cause interstitial nephritis. Chemotherapy (cyclophosphamide) and radiation for malignancies can explain isolated hematuria in children.

In the neonatal period, hematuria due to thrombosis of the renal vein or artery can occur especially after umbilical catheterization. Predisposing factors for renal vein thrombosis include perinatal asphyxia, dehydration, septicemia, shock, and coagulopathies secondary to protein C deficiency. Clinically, they present as gross hematuria with unilateral or bilateral renal mass. Renal ultrasonogram and Doppler studies of renal vessels help in the diagnosis.

Periorbital edema is frequently the first site of renal edema in children. Raised JVP, presence of gallop and

basal lung fields with crackles indicate fluid overload. Nephrotic edema may not have features of fluid overload as mentioned above. Costovertebral angle tenderness may indicate upper UTI. Recent trauma can be detected by findings of flank bruises and pain. Examining the abdomen for masses is critical for the identification of tumors, polycystic kidneys or hydronephrosis. Ascites usually suggests nephrotic syndrome. The examination of the skin can give evidence of pallor or rash. Pallor indicating anemia may signify either acute loss of blood as in hemolytic uremic syndrome or a chronic kidney disease. A fundoscopic examination of the retina, looking for evidence of long-standing hypertension or lenticonus as seen in Alport's syndrome, should be performed.

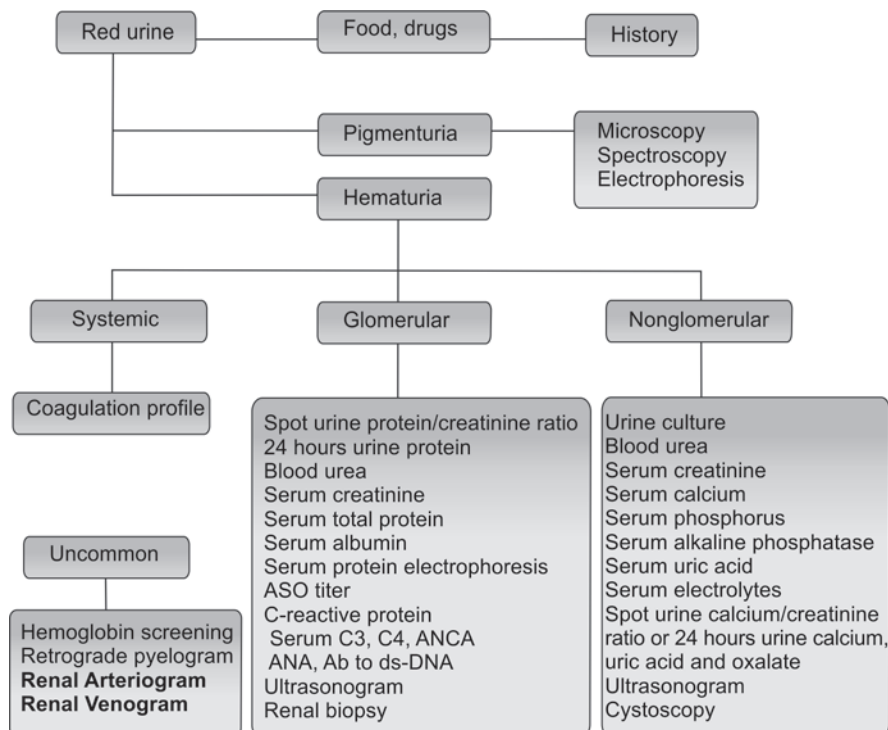
The presence of proteinuria and hematuria on urinalysis suggests glomerulonephritis. Proteinuria should not exceed 2+ if the only source of protein is from the blood.⁷ The presence of proteinuria, hypoalbuminemia and hypercholesterolemia suggest nephrotic syndrome. Pertinent to glomerulonephritis, laboratory investigations include a complete blood count, throat culture, ASO titer and serum estimation of C3, C4 levels, albumin, creatinine and electrolytes. The complement C3 level is low in acute poststreptococcal glomerulonephritis, subset of MPGN, and lupus nephritis. Microscopic hematuria almost always warrants referral to a pediatric nephrologist. Indications for renal biopsy in them include persistent microscopic hematuria for more than 1

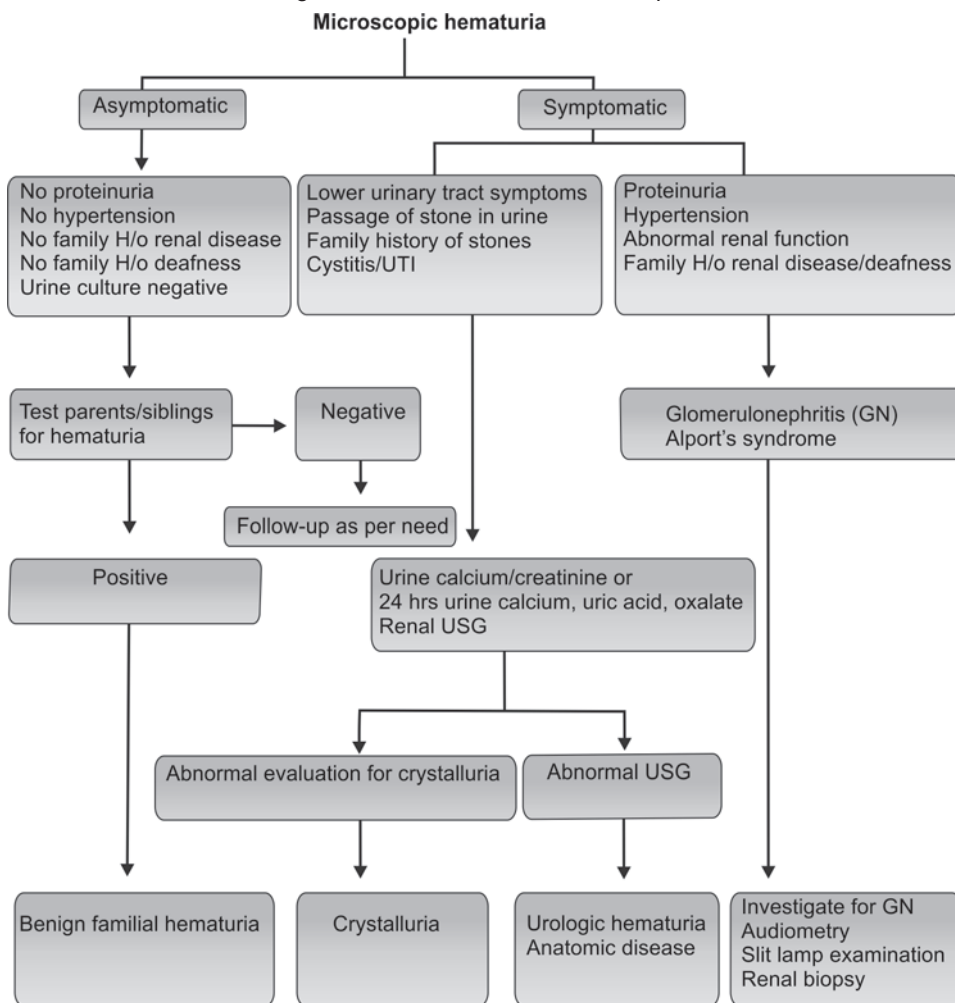
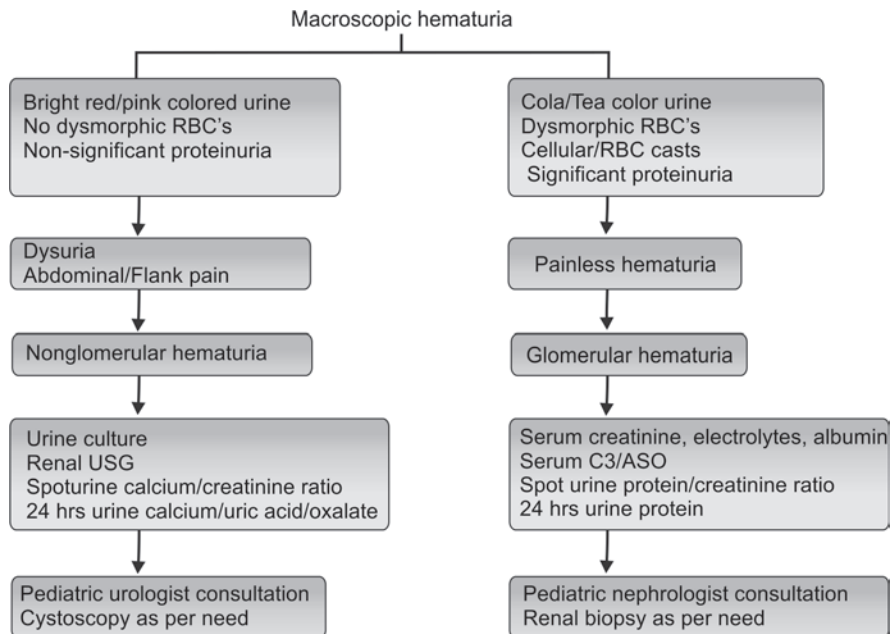
year and recurrent gross hematuria with decreased renal function, proteinuria or hypertension.⁸

In crystalluria or renal stone disease, the initial work up consists of ultrasonogram and screening the urine for calcium excretion by Ca/Cr ratio or estimation of 24-hour urine calcium, uric acid, oxalate and citrate excretion, serum creatinine, electrolytes, uric acid, calcium and albumin levels. There have been reports of recurrent abdominal and flank pain in children with idiopathic hypercalciuria. In addition, noncalculous idiopathic hypercalciuria is an important contributing factor to recurrent UTI in children. If the kidney-ureter-bladder is negative for stones, abdominal and pelvic spiral computed tomography scan should be obtained in children with a clinical picture of renal stone disease. A nephrology/urology consultation is appropriate if a stone is detected. Rare causes include tumors and some anatomic or vascular problems.⁵ Arteriovenous malformation of the kidney can present with gross hematuria. Renal ultrasonogram and CT scan of the abdomen may locate the tumor or malformation. Renal angiography offers a definitive diagnosis. Most of the conditions requiring advanced work up should be referred to a pediatric nephrologist or urologist.

A simple practical approach towards laboratory evaluation is given in Flow chart 1.² Algorithmic approach to microscopic and macroscopic hematuria is given in Flow chart 2 and 3.⁹

Flow chart 1: Laboratory evaluation of hematuria



Flow chart 2: Algorithm for evaluation of microscopic hematuria**Flow chart 3:** Algorithm for evaluation of macroscopic hematuria

CONCLUSION

Hematuria in children is usually a frightening symptom not only for the child but also for the doctor attending on the child. A good detailed history and adequate clinical examination will direct us towards the cause of hematuria. Algorithmic approach of evaluation will help us to come to your conclusion on the etiology. Once the diagnosis is made the treatment is essentially based on it. If no diagnosis is made initially with the available clinical picture and evaluation it is always better to keep the child under surveillance as at a later date the presentation may direct us towards the correct diagnosis. If we follow the simple approach that usually macroscopic hematuria has a pathological background and microscopic hematuria in a significant number of children can be benign and needs only a follow-up, we can face the symptom with ease. Once again remember that not in all children of hematuria can a diagnosis be arrived at initially. Please note that the two important nonpostinfective causes of hematuria are IgA GN and hypercalciuric syndromes. Early detection and appropriate timely interventions delay the progression to end stage renal disease in them. Proper importance should be given to meticulous follow-up.

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Systemic Arterial Hypertension in Children and Adolescents

S Srinivasan

Systemic arterial hypertension (SAH) in children and adolescents is one of the increasingly observed and investigated clinical entities in the last two decades. Specific guidelines from various nations around the globe regarding its definition, recognition, causal identification with investigative work up, treatment and preventive modalities are brought about to facilitate the treating pediatricians.¹⁻⁷ Universally among pediatricians there is a heightened awareness of the increasing incidence of hypertension in children and adolescents, more so in obese children. They are also keen to know the emerging data on pediatric hypertension with regard to the possibility of early and progressive hypertensive target organ damage in those with untreated or poorly controlled hypertension and the potential preventive role they have to play in reducing the emerging burden of early hypertension related cardiovascular and renal morbidities.

The objectives of a rational clinical approach to SAH in children and adolescents are:

1. To ensure without an element of doubt its presence by accurate and repeated measurements using reliable BP apparatus and appropriate cuff size and approved and available regional or national BP centile charts (from neonatal period to completion of adolescence) for males and females.
2. To recognize hypertensive urgencies/emergencies and institute prompt, effective and safe treatment.
3. To identify its nature—Acute/chronic; transient/sustained (persistent)/paroxysmal; systolic/diastolic/both.
4. To identify presence of risk factors for hypertension by clinical history and examination.
5. To identify presence of clinical pointers or markers for identifiable causes of secondary hypertension.
6. To identify without undue delay the specific cause of secondary hypertension by institution of rational, cost

—effective, meaningful and stepwise/staged investigative plan.

7. To institute appropriate and effective therapeutic modalities to treat and remove the cause of secondary hypertension.
8. To evaluate and recognize the absence or presence of any early target organ damage so as to prevent, reverse or minimize this effect.
9. To incorporate educational inputs to affected children and family members to ensure compliance and adherence to management strategies.
10. To monitor the immediate and long-term therapeutic response, adverse effects of drugs, compliance and markers of target organ response.

Epidemiological Considerations⁸⁻¹¹

Recommendations of the task force on hypertension in children and adolescents in US gave impetus to many epidemiological and screening studies in childhood populations of various ethnic groups in that nation. They give enough evidence to indicate a perceptible trend of increasing incidence of hypertension in these age groups. While mid 1970 studies reported an incidence of 1 to 2 percent in healthy, school attending children, studies in this decade report an incidence of 3 to 5 percent. Recent survey in USA has reported a prevalence of prehypertension in children to be 10 percent and hypertension to be around 4 percent. Another important aspect of childhood hypertension in USA is the recent revelation from 4 studies that the levels of both systolic and diastolic BP are slowly rising in a few ethnic American boys and girls over the years.

Pathogenesis and Pathophysiology of Hypertension in Children and Adolescents¹²⁻²²

In majority of neonates, infants and children with hypertension, hypertension is secondary to an underlying renal,

renovascular, cardiovascular, endocrinal, postinfective or systemic vasculitides disorders.

Genetics has a more definitive role in primary hypertension than in secondary hypertension. Of 192 children and adolescents with primary hypertension, 49 percent had parents with primary hypertension and 10 percent had parents with secondary hypertension; and 24 percent and 46 percent of 84 children and adolescents with secondary hypertension had parents with primary and secondary hypertension respectively. Genetic factors also have a role in the development of some causes of secondary hypertension.

A detailed discussion on pathophysiology and pathogenesis of both forms of hypertension, e.g. primary or essential and secondary, is beyond the scope of this article. Evolution of hypertension involves a complex interplay of genetic and environmental factors that trigger and modulate various neural (central, peripheral and autonomic), hormonal renin-angiotensin II–aldosterone system (RAAS) and vascular (endothelium, endothelin, nitric oxide and other vasoactive substances) mechanisms and feedback loops. The interested readers may read the article written by Mukesh Singh et al on pathogenesis and clinical physiology of hypertension in *Cardiology Clinics* 2010 issue.

Low Birth Weight IUGR Babies and Association with Hypertension¹⁷⁻¹⁹

In a study of 95 children with new onset hypertension, Feig et al observed essential hypertension in low birth weight children than controls. On follow-up of 144 children with IUGR and 372 normal birth weight children at 6 years of age, Shankaran et al recorded hypertension in 24 percent of IUGR children and 16 percent of non – IUGR children. Franco et al on recording BP in 118 children between 8 and 13 years of age, observed hypertension in 38.1 percent of children born with low birth weight and in only 2.8 percent of children with normal birth weight. 9.5 percent of children born with low birth weight had prehypertension.

Obstructive Sleep Apnea and Hypertension in Children^{21,22}

Studies in children with obstructive sleep apnea (OSA) have documented intermittent increase in systemic and pulmonary vascular resistance and subsequent elevation of systemic and pulmonary pressures with remodeling and abnormal ventricular geometry and hypertrophy of the left and right ventricles (LV, RV).

Obesity and Hypertension in Children²³

Obesity in children and adolescents is associated with cardiovascular disease including hypertension, dyslipidemia, insulin resistance, glucose intolerance, type 2 diabetes mellitus and left ventricular hypertrophy. Reduction in

weight has been shown to result in lowering of both systolic and diastolic BPs.

Evaluation of BP in Children^{1-7,32-37}

The earliest recommended age for recording BP in children is 3 years. Before 3 years of age, BP recording on routine examination has technical difficulties. Application of cuff is difficult and measurements often are inaccurate. The cost of an accurate instrument to be used in this age group is another reason. BP measurement is essential below 3 years of age, if the child has a history of prematurity, IUGR, or any cardiac or renal problems. BP must be recorded twice in children over 3 years during every medical consultation.

The recommended instrument is conventional sphygmomanometer and the recommended method is the conventional auscultatory method over the brachials. The onset of the tapping Korotkoff (K1) sounds on auscultation indicates systolic BP and the disappearance of these sounds (K5) is now recognized as indicative of diastolic BP. In infants and young children less than 3 years, automated oscillometric BP instruments or the Doppler devices are often employed. Both systolic and diastolic BP must be recorded.

Techniques of BP Measurement

The ideal site for noninvasive external measurement of BP is brachial artery. Measurement devices applied over wrist and fingers are available, but the problem is the fact that systolic pressure increases and the diastolic pressure decreases in the distal arteries.

There are four measurement techniques:

1. The auscultatory method
2. The oscillometric method
3. The ultrasound technique and
4. The finger cuff method of Penaz.

The auscultatory method of listening to Korotkoff sounds using mercury sphygmomanometer is still considered the gold standard for BP measurement in office settings. As there is an official ban in the use of mercury in many developed nations, the mercury device used in auscultatory method is getting phased out in these nations. The available aneroid manometers are less accurate and they need frequent calibrations. New devices combining the features of both electronic and auscultatory devices known as “hybrid” sphygmomanometers have been developed where the mercury column is replaced by an electronic pressure gauge similar to oscillometric devices but the readings are obtained using a stethoscope and listening for the Korotkoff sounds.

First demonstrated by Marey in 1876, the oscillometric technique records the oscillations of pressure in a sphygmomanometer cuff during gradual deflation, where the point of maximal oscillation corresponds to the mean

intra-arterial pressure. It must be remembered that the oscillations begin at approximately systolic pressure and continue below diastolic and both these pressures are derived using an empirical algorithm, which is different for different commercial brands. However, there has been good agreement in the estimated BP levels when compared with intra-arterial evaluation and auscultatory Korotkoff sound methods. This method is better suited for ambulatory monitoring and home monitoring devices as there is no placement of a transducer over brachial artery, but its main drawback is its total unreliability during physical activities.

With ultrasound devices, when sphygmomanometer cuff with an ultrasound transmitter and receiver kept inside is deflated after placement over the brachial artery, systolic pressure gets recorded when there is a Doppler phase shift arising due to the movement of the arterial wall and the diastolic pressure at the point of diminution of arterial motion. This method with minor modification is helpful in recording systolic pressure in infants and young children.

In the Photo-Plethysmograph Finger Cuff Method of Penaz, arterial pulsation in a finger is recognized by the plethysmograph under a pressure cuff. The oscillations of pressure in the cuff are measured and they resemble the intra-arterial pressure wave. Finometer and portapres recorders are commercially available and their systolic and diastolic estimates have been validated against intra-arterial pressures in many reports.

Blood Pressure Measurement

Though there is no consensus regarding the position in which BP is to be taken, most of the guidelines on BP measurement recommend evaluation of BP in the sitting position. In adults, there are a few studies that indicate a higher diastolic pressure of 10 mm Hg in the sitting position in younger subjects. This difference between sitting and supine readings is only 2 mm Hg in older individuals around 70 years of age.

The position of the arm in which the cuff is applied is also important. BP reading is higher by 5 mm Hg when the arm is kept vertically down than when it is kept in the horizontal position. The subject must be sitting with a support behind as in an individual sitting bolt upright without a back support the diastolic reading is noted to be higher by 6.5 mm Hg.

Choice of BP Cuff (Table 1)

Choosing the appropriate sized cuff is vital to record accurate BP in children. Inappropriately small sized cuff gives abnormal elevated readings whereas bigger sized cuffs give low inaccurate readings. The inflatable bladder inside the cuff should have an ideal width of at least 40 percent

Table 1: Recommended dimensions for blood pressure cuff bladder sizes

Age range	Bladder width (cm)	Bladder length (cm)	Max. arm circumference (cm)*
Newborn	3–4	6–8	<6–10
Infant	5–6	12–15	15
Child	8–9	18–21	16–22
Smalladult	10	24	22–26
Adult	13	30	27–34
Largeadult	16	38	35–44
Thigh	20	42	45–52

* Calculated so that the largest arm would still allow bladder to encircle arm by at least 80 percent

of the midarm circumference and a cuff length that is 80 percent to 100 percent of the arm circumference.

The American Heart Association, National High Blood Pressure Education Program (NHBPEP) and fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents recommend cuffs of different sizes standardized to the arm circumference (Table 1).

Specific Recommendations for Office BP Measurement in Children and Adolescents

- The recommended method is auscultatory
- Use K1 for systolic BP and K5 for diastolic BP
- If the oscillometric method is used, the monitor needs to be validated
- If hypertension is detected by the oscillometric method, it needs to be confirmed using the auscultatory method
- Use the appropriate cuff size according to arm width (40% of the arm circumference) and length (4–8 cm, 6–12 cm, 9–18 cm, 10–24 cm, to cover 80–100 percent of the individual's arm circumference).
- Children above 3 years of age who are seen in a medical setting should have their BP measured. In younger children, BP should be measured under special circumstances that increase the risk for hypertension: under neonatal conditions requiring intensive care, congenital heart disease, renal disease, treatment with drugs known to raise BP and evidence of elevated intracranial pressure.

Classification of Blood Pressure (Table 2)

As body size is one of the known essential determinants of blood pressure in children, besides age and sex of the child, the height percentile chart is to be referred to determine if BP is normal. Classification of blood pressure was constructed from large epidemiologic studies that considered age, gender, height, and body weight.

Table 2: Classification of elevated blood pressure in children and adolescents ≤ 17 years of age

Classification	<i>Blood pressure value as percentile for age, sex and height taken at different visits</i>
Normal	<90th percentile
Prehypertensive	≥ 90 th and <95th percentiles (consistently recorded on three visits)
Hypertensive	≥ 95 th percentile
Stage 1 hypertension	95th to 99th percentile +5 mm Hg
Stage 2 hypertension	≥ 99 th percentile +5 mm Hg

Table 3: Age related causes of hypertension in children and adolescents

Age group	Common causes of hypertension
Neonate	Renal artery thrombosis or stenosis, renal malformations, coarctation of the aorta, bronchopulmonary dysplasia
Infants to 6 years	Renal parenchymal diseases, coarctation of the aorta, renal artery stenosis
6–10 years	Renal parenchymal diseases, renal artery stenosis, essential hypertension
Adolescence	Essential hypertension, obesity, renal parenchymal diseases, renal artery stenosis

Table 4: Causes of acute and chronic sustained systemic arterial hypertension*Causes of pediatric hypertension*

<i>Acute</i>	<i>Chronic sustained</i>
<i>Renal</i>	
Acute poststreptococcal glomerulonephritis	Chronic nephritis/renal parenchymatous disease (many causes)
Hemolytic uremic syndrome	Obstructive uropathy
Acute nephritis (many causes)	Chronic pyelonephritis
Interstitial nephritis	Reflux nephropathy
Acute pyelonephritis	Polycystic kidney disease
Acute kidney injury	Multicystic dysplastic, hypoplastic kidneys
Urinary tract obstruction	
<i>Vascular</i>	
Renal artery thrombosis	Renal artery stenosis–fibromuscular, atheromatous
Renal vein thrombosis	Extrinsic compression of renal vessels
Patent ductus arteriosus	Aortic coarctation
Vasculitis syndromes	Vasculitis syndromes
<i>Endocrine</i>	
Cushing syndrome	Congenital adrenal hyperplasia: 11 β - or 17 α -hydroxylase deficiency
	Cushing's syndrome -
	Hyper-/hypothyroidism
	Mineralocorticoid excess
	Glucocorticoid remediable aldosteronism
	Liddle's syndrome
<i>Tumors</i>	
	Pheochromocytoma, Neuroblastoma (catecholamine –secreting tumors)
	Juxtaglomerular cell tumors
	Mesoblastic nephroma
	Adrenal tumors- aldosterone-producing adenomas, adrenal carcinoma
<i>Genetic syndromes or inherited disorders</i>	
Williams syndrome	Williams syndrome
<i>Acute neurological conditions</i>	Tuberous sclerosis
Encephalitis	Neurofibromatosis
Meningitis	
Raised intracranial pressure	
Guillain-Barre syndrome	
Familial dysautonomia	
Postseizure	
Severe emotional stress	
After intracranial surgery	
Intracranial trauma	
Poliomyelitis	

Contd...

Contd...

Metabolic

Hypercalcemia
Hypernatremia
Acute intermittent porphyria

Drugs/Ingestions/Toxic

Ingestions
Prescription medications
Sympathomimetic amine containing drugs:
Decongestants, eye drops
Eating foods with a high tyramine content (aged cheese, pickled herring, beer, red wine) while taking monamine oxidase inhibitors
Over-the-counter medications
Steroids - contraceptive pills with estrogen, anabolic steroids, therapeutic
Illicit drugs: Cocaine,
Amphetamines, phencyclidine
Heavy metals: Mercury, lead
Licorice
Hypervitaminosis A or D

Prescription medications –steroids, contraceptives
Over-the-counter medications
Sex hormones testosterone, anabolic steroids
Excess licorice ingestion,
Ketoconazole administration
Herbal therapies
Dietary supplements
Illicit drugs

Miscellaneous

Bronchopulmonary dysplasia
Pre-eclampsia
Stevens-Johnson syndrome
Leukemia
Burns
Prolonged bedrest and traction
Pseudoxanthoma elasticum
Genitourinary tract surgery
Closure of abdominal wall defects
Orthopedic limb lengthening
Familial chloride-losing enteropathy
Cyclic vomiting
Extracorporeal membrane oxygenation
Surgical/trauma/injury
Intravascular volume overload

The diagnosis of hypertension is made only after recording of two further high readings above the 95th percentile at different visits after the initial abnormal reading. The causes of hypertension in children are given in Tables 3 and 4.

Ambulatory Blood Pressure Monitoring in Children and Adolescents²³⁻²⁵

Another recent advance in the field of pediatric hypertension is the increasing use of ambulatory blood pressure monitoring (ABPM) in children and adolescents to identify those hypertensive children who otherwise escape being recognized as hypertensives because of repeatedly and randomly recorded apparently normal BP readings using conventional devices and techniques at office or home. As BP gets affected in children over 24 hours by factors like physical activity, emotional changes, posture,

time of day, level of wakefulness and others, in recent years considerable interest and efforts have been put into record BP continuously round the clock by developing newer measurement devices that can record the ambulatory BP. ABPM data published in recent years have identified children with elevated blood pressures who would have otherwise been passed off as normotensive children. The masked hypertension is a condition in which subjects classified as normotensive by conventional office or clinic measurement are hypertensive with ambulatory BP monitoring or self-measurement. This entity of masked hypertension is a new subentity which is different from white coat hypertension and can be identified only with 24-hour BP record patterns. Ongoing researches in “unmasking” the hidden or occult hypertension in children by ABPM will help to formulate normative data and percentile charts and to establish investigative and therapeutic guidelines

to abolish or minimize the risk of target organ damage. It is hoped that ABPM when indicated will help in fine tuning and establishing a correct therapeutic approach in further reducing the risk of target organ damage. Definite indications for ABPM are being developed.

Clinical Evaluation of Children with Systemic Arterial Hypertension^{1-7,32,37} (Tables 5 to 8)

Evaluation of children and adolescents identified as having hypertension always starts with history and physical examination. History sheet must record all the following details. History and physical examination must try to find an identifiable cause, target organ involvement. The following recommendations are made by the European Society of Hypertension in 2009.

Assessment of Hypertensive children for Comorbidities (Table 9)

In all hypertensive children and more so in those with obesity, family history of hypercholesterolemia or hypertriglyceridemias, fasting blood lipid panel and sugar, glucose tolerance test or glycosylated hemoglobin (HgbA1C) must be estimated.

*Uric Acid—Role in New Onset Pediatric Essential Hypertension^{17,20}

There are scientific evidences to correlate elevated uric acid levels in serum with new onset primary essential hypertension in children and adolescents. Uric acid is postulated to cause hypertension in two phases—firstly it predominantly causes peripheral vasoconstriction. In the

Table 5: Clinical history sheet-data to be recorded in pediatric hypertension
(European Society of Hypertension Recommendations – J Hypertension 2009;27:1719-42)

Symptoms suggestive of target organ damage	Headache, epistaxis, vertigo, visual impairment Facial palsy, fits, strokes Dyspnea
Symptoms suggestive of secondary hypertension	Dysuria, thirst/polyuria, nocturia, hematuria Edema, weight loss, failure to thrive Palpitations, sweating, fever, pallor, flushing Cold extremities, intermittent claudication Virilization, male pseudohermaphroditism and primary amenorrhea Sleep history Snoring, apnea, daytime somnolence
Risk factors to be identified	Physical exercise Dietary habits Smoking, alcohol Drug intake: Anti-hypertensives, steroids, cyclosporine, tacrolimus or other tricyclic antidepressants, atypical antipsychotics, decongestants Oral contraceptives, illegal drugs Pregnancy
Perinatal history	Birth weight, gestational age, oligohydramnios, anoxia, umbilical artery catheterization
Previous history	Hypertension Urinary tract infection, renal or urological disease Cardiac, endocrine (including diabetes) or neurological disease Growth retardation
Family history	Hypertension Cardiovascular and cerebrovascular disease Diabetes mellitus Dyslipidemia Obesity Hereditary renal disease (Polycystic kidney disease) Hereditary endocrine disease (pheochromocytoma, glucocorticoid-remediable aldosteronism, multiple endocrine neoplasia type 2, von Hippel-Lindau) Syndromes associated with hypertension (neurofibromatosis)

Table 6: History suggestive of a secondary cause of childhood hypertension

<i>Positive history</i>	<i>Possible cause/s</i>
Past history of UTI, symptoms of recent/current UTI	Reflux nephropathy, chronic and acute pyelonephritis
Acute onset of hematuria	Glomerulonephritis, renal vein thrombosis
Pyoderma, sore throat preceding onset of oliguria, hematuria, pedal edema, puffiness of eyelids	Poststreptococcal glomerulonephritis
Fever –recurrent, arthralgias/arthritis, rash	Vasculitis, SLE
Abdominal or Renal trauma	Renal artery stenosis, renal infarction
Mouth breathing, excessive snoring	Obstructive sleep apnea disorder associated hypertension
Recurrent and frequent spells of facial flushings, pallor, sweating, palpitations	Pheochromocytoma
Sweating, heat intolerance, tremors, weight loss	Hyperthyroidism
Precocious puberty	Adrenal disorder
Renal transplant	Transplant renal artery stenosis
Muscle cramping, constipation	Hyperaldosteronism
Abdominal radiation	Radiation nephritis, Renal Artery Stenosis
Abdominal mass or distension	Polycystic kidneys, hydronephrosis, renal and urinary tract obstructive disorders, Wilms' tumor, neuroblastoma, pheochromocytoma (rare)
Drugs: Medications - steroids, sympathomimetics, contraceptive pills	Drug induced hypertension
Substance abuse	Anabolic steroids, cocaine, amphetamines, phencyclidine
Toxins: Lead exposure	Lead induced hypertension
Positive family history	
Hypertension	Essential hypertension
Renal disease	Many congenital renal disorders

Table 7: Physical examination—Data to be recorded
(European Society of Hypertension Recommendations) – J Hypertension 2009;27:1719-42)

<i>General</i>	<i>Age, Sex, height, weight, body mass index</i>
External features of syndromes/conditions associated with hypertension	Neurofibromatosis, Klippel-Trenaunay-Weber, Feuerstein-Mims, von Hippel-Lindau, multiple endocrine neoplasia, pseudoxanthoma elasticum, Turner, William, Marfan, Cushing, hyperthyroidism, lupus, vasculitis, congenital adrenal hyperplasia
Cardiovascular examination	Pulse and BP measurement in both arms and legs Bruits/murmurs– heart, abdomen, flanks, back, neck, head Signs of left ventricular hypertrophy or cardiac failure
Abdomen	Masses – Wilms, neuroblastoma, pheochromocytoma, autosomal dominant and recessive polycystic kidney disease, multicystic kidney dysplasia, obstructive uropathy Hepatosplenomegaly – autosomal recessive polycystic kidney disease
Neurological examination	Fundoscopy for hypertensive changes and retinal hamartoma (von Hippel-Lindau) Evidence of VIII nerve palsy Other neurological defects including stroke

Table 8: Physical findings as indicators of the possibility of presence of a secondary cause of childhood hypertension

<i>Region</i>	<i>Physical findings on clinical examination</i>	<i>Possible cause/s</i>
Height/weight	Growth retardation	Chronic renal failure
	Obesity (high BMI)	Primary hypertension
	Truncal obesity	Cushing syndrome, insulin resistance syndrome
Vital signs	Tachycardia	Hyperthyroidism, pheochromocytoma neuroblastoma, primary hypertension
	Decreased lower extremity pulses; Drop in BP from upper to lower extremities	Coarctation of the aorta
Eyes	Retinal changes	Severe hypertension, more likely to be associated with secondary hypertension
Ear, nose and throat (ENT)	Adenotonsillar hypertrophy	Possible association with sleep-disordered breathing (sleep apnea), snoring
Head and neck	Moon facies	Cushing's syndrome
	Elfin facies	Williams syndrome
	Webbed neck	Turner syndrome
	Thyromegaly	Hyperthyroidism
Skin	Pallor, flushing, diaphoresis	Pheochromocytoma
	Acne, hirsutism, striae	Cushing syndrome, anabolic steroid abuse
	Café-au-lait spots	Neurofibromatosis
	Adenoma sebaceum	Tuberous sclerosis
	Malar rash	Systemic lupus erythematosus
	Acanthosis nigricans	Type 2 diabetes
	Widely spaced nipples	Turner syndrome
Chest	Heart murmur	Coarctation of aorta
	Friction rub	SLE and collagen vascular diseases (pericarditis), end stage renal disease
	Apical heave	Left ventricular hypertrophy, chronic hypertension
Abdomen	Truncal obesity, Striae	Cushings, exogenous steroids
	Mass	Wilms tumor, neuroblastoma, pheochromocytoma
	Palpable kidneys	Polycystic kidney disease, hydronephrosis, multicystic- dysplastic kidney, mass
	Epigastric/flank bruit	Renal artery stenosis
Genitalia	Ambiguous/virilization/hypogonadism	Congenital adrenal hyperplasia
Extremities	Joint swelling	SLE and collagen vascular diseases
	Muscle weakness	Hyperaldosteronism, Liddle syndrome

second phase, it induces renal afferent arteriosclerosis and subsequent altered pressure natriuresis leading to sodium dependent hypertension. Studies with allopurinol treatment are under way to find out the BP response to lowering of uric acid levels as preliminary data have suggested such a positive response.

Birth weight was noticed by Feig et al to have an inverse relationship with uric acid levels. Hence, there is considerable speculation that raised uric acid levels may signal early onset of hypertension in those who were born underweight.

Target Organ Damage²⁶⁻³¹

Pediatricians have always been aware of the target organ complications like acute encephalopathy, left ventricular failure with pulmonary edema and acute renal failure arising as a result of abrupt and acute elevations of blood pressure of brief durations in children. In developing countries, many children below 8 years of age present with seizures, altered sensorium, acute pulmonary edema secondary to hypertension of poststreptococcal glomerulonephritis.

Table 9: Investigative work up (Recommended by guidelines)^{1-7,32-37}*Routine tests in all hypertensive children*

- Full blood count
- Urinalysis
- Plasma sodium, potassium and calcium, urea, creatinine
- Serum uric acid – primary essential hypertension*
- Fasting plasma glucose
- Serum lipids (cholesterol, LDL cholesterol, HDL cholesterol)
- Fasting serum triglycerides
- Chest X-ray, ECG and 2-D echocardiography
- Renal ultrasound for renal parenchymatous diseases, anomalies, hydronephrosis, Wilms tumor, neuroblastoma

Next line of Investigations

Dimercaptosuccinic acid (DMSA) scan	Chronic pyelonephritis
Renal Doppler ultrasound, MRI	Renal artery stenosis
Digital subtraction angiography	
Markers for target organ damage	Left ventricular hypertrophy- LV mass
Plasma renin concentration	Increased in renal artery stenosis; decreased in primary hyperaldosteronism, dexamethasone-suppressible hypertension
Plasma aldosterone concentration	Increased in renal artery stenosis, primary hyperaldosteronism, dexamethasone-suppressible hypertension
Plasma deoxycorticosterone	Increased in congenital adrenal hyperplasia
Urinary steroids	Mineralocorticoid excess, congenital adrenal hyperplasia

Sophisticated investigations following the initial work up

Color Doppler ultrasonography	Estimation of carotid wall intima-media thickness
Urinary catecholamines, metanephrines, VMA	Pheochromocytoma, neuroblastoma
Pheochromocytoma	
Urinary normetanephrine with a reported sensitivity of 96.9%, platelet norepinephrine –Sn. of 93.8%, urinary norepinephrine –Sn. of 77.7%	
Renal arteriogram	Renal artery stenosis
Captopril primed MAG3 labeled isotope renal scan	Renal artery stenosis
Renal vein renin estimation	
CT scan, MRI	Tumors
Radioisotopic ¹³¹ I-metaiodobenzyl guanidine scanning	Pheochromocytoma Sn – 83.7% (False positives in neuroblastoma and carcinoids)
Molecular genetic studies	Apparent mineralocorticoid excess, Liddle's syndrome, etc.

The effects of long and sustained hypertension on arterial vessels, heart, kidneys, brain and retina causing significant morbidity and mortality in adults are well studied and documented. The risks for target organ damage have been worked out by elegant and robust studies in adult hypertension. Besides hemodynamic alterations, varied factors like duration and severity of hypertension, family and hereditary predisposition, ethnicity play significant role in determining the degree of target organ damage. The importance of prevention and early treatment of hypertension in preventing or reversing these target organ damages by appropriate measures has been adequately proved.

In children and adolescents with hypertension, these questions are yet to be answered. The need for very early identification of target organ damage in hypertensive children and adolescents has become a recent priority in advanced countries. Recently published studies in children with hypertension have focused their attention in this direction. A definitive and conclusive evidence of onset of target organ damage in early childhood hypertension will help the pediatric community and specialists to take a rational decision regarding initiation of antihypertensive drug treatment without delay with the sole objective of reducing the risk of target organ damage and improving their quality of life in future. Moreover, monitoring

of the trends of these recognized markers of organ damage during drug therapy will also indicate the therapeutic response and the need for change or addition of drugs.

In adults, the two markers of cardiac damage secondary to hypertension are left ventricular mass (LVM) and carotid wall intima-media thickness. Studies now are in progress to determine the left ventricular mass in various age groups in children and adolescents and to correlate the same with weight, lean body mass, and other growth and maturation parameters of these children and in hypertensive children. Adiposity has correlation with increased left ventricular mass. Sustained ambulatory BP elevations in adolescents are reported to have increased LVM when compared to normotensive adolescents. Concentric left ventricular hypertrophy (LVH) is considered indicative of end organ damage in childhood hypertension. Echocardiatic measurement of LVM and its (LVMI) correlated to height of the child have shown increased values in 41.1 percent and 15.5 percent of hypertensive children.

Carotid wall and femoral intima-media thickness (c-IMT and f-IMT) are being assessed in children in all stages of hypertension as markers of cardiac endovascular and organ damage. Studies by Litwin et al have shown increased c-IMT (more than 2 S.D) in 38.8 percent and f-IMT (more than 2 S.D) in 17.5 percent of hypertensive children and also their good correlation with 24 hours SBP and pulse pressure. They also demonstrated functional carotid vascular changes like arterial distensibility, elasticity and compliance in hypertensive children. Meyer et al made two observations: (1) Increased c-IMT had association with increased BP in children and (2) a significant increase in c-IMT in obese children as compared to controls. However, c-IMT is not currently recommended in the fourth report of National High Blood Pressure Education Program (NHBPEP) working group as a screening procedure in childhood hypertension.

In adults with hypertension and diabetes, microalbuminuria and urinary albumin excretion (UAE) are routinely evaluated as they correlate well with renal and cardiovascular morbidity. Current and future studies in pediatric age group will be able to define the importance of these markers in predicting target organ damage.

TREATMENT OF HYPERTENSION³²⁻³⁷

Principles of Treatment of Hypertension in Children

1. Treatment of the primary cause of secondary hypertension.
2. Non-pharmacological measures (lifestyle modifications).
3. Pharmacological or drug treatment.
4. Treatment of hypertensive urgencies and emergencies.

Non-Pharmacological Measures (Lifestyle Modifications) (Table 10)

In all children with primary or essential hypertension, a trial of non-pharmacological measures is warranted to bring down BP. When the repeatedly recorded BP levels in a child fall between 90th and 95th percentile for that age (prehypertension), lifestyle changes are recommended and the compliance ensured. These activities are also applicable to children who have established hypertension with BP recordings more than 95th percentile.

Table 10: Dietary and certain life style modifications in lowering BP – Currently available evidence from literature

Persuasive evidence

- Dietary sodium intake 2.3 g (<100 mmol) per day*
- Dietary potassium intake 4.7 g (>120 mmol) per day
- Increased Omega-3 polyunsaturated fat from natural sources
- Indian vegetarian diet, DASH diet (USA), Mediterranean diet (Europe), Ornish diet (USA)
- Moderation of alcohol intake in those who take alcohol to <2 drinks/day in adolescent boys and young men and <1 drink/day in women
- Stress management

Suggestive evidence

- High fiber diet
- Carbohydrate
- Exercise at least 30 minutes of moderate activity most days of the week

Limited or equivocal evidence

- Increased dietary calcium and magnesium intake through natural sources
- Low saturated fat diet
- Omega-6 unsaturated fat, Monounsaturated fat
- Low cholesterol diet
- Increased vegetable protein instead of carbohydrates
- Yoga, meditation and other relaxation techniques

* Children and adolescents are reported to be less responsive than adults to salt restriction.

Weight reduction: Demonstrable fall in BP has been documented in those overweight children who shed more than 4 to 7 kg of their original weight and maintained the weight loss in a determined manner. Altered sympathetic tone, reversal of endothelial dysfunction and improved metabolic responsiveness to insulin have been incriminated in bringing about this BP lowering effect.

Exercise: Four times a week regular exercise and physical activities for a duration of 30 to 40 minutes have shown perceptible improvement in BP. Yoga and biofeedback as

Table 11: Indications for drug therapy in pediatric and adolescent hypertension

- Stage 2 hypertension
- Symptomatic hypertension
- Secondary hypertension
- Hypertensive target-organ damage
- Diabetes (types 1 and 2)
- Persistent hypertension despite nonpharmacologic measure

stress reduction techniques have effect in lowering BP in highly motivated, compliant children and adolescents.

Pharmacological or Drug Treatment (Table 11)

Before the initiation of drug treatment of hypertension in children without a remediable cause, 2-weekly BP response to a trial of closely supervised nonpharmacological measures for a period of 3 to 6 months must be evaluated. When the predetermined BP goals are not achieved, the drug treatment is initiated with a single drug at its recommended lowest therapeutic dosage. Its effect on lowering of BP is monitored on alternate days in the first 2 weeks and then every 2 weeks. The dosage of medications is stepped up to the maximum recommended dosage once in 2 weeks and occurrence of any adverse effects is noted and taken into account.

As there are no evidence based data on the long term benefits of pharmacologic therapy of childhood hypertension in preventing the development or occurrence of strokes, cardiovascular diseases and progressive renal damage, pediatricians must weigh the benefits of treatment against the adverse effects of long term use of antihypertensive drugs on growth and development of children and adolescents.

Antihypertensive therapy with a single drug or more than one is recommended in children and adolescents with:

1. Symptomatic hypertension when symptoms such as headaches or seizures are related to elevated blood pressure.
2. Secondary hypertension.
3. Stage 2 hypertension, defined as blood pressure levels that are 5 mm Hg greater than the 99th percentile.
4. Stage 1 hypertension persisting after four to six months of nonpharmacologic therapy.
5. Stage 1 hypertension in patients with diabetes mellitus or other conditions that increase the risk of heart disease or stroke, such as high cholesterol or lipids.
6. Prehypertension with more than one additional risk factor for heart disease or stroke.
7. Physical signs of hypertension, such as a thickened wall of the left ventricular chamber of the heart.

From the various classes of available antihypertensive drugs, the most appropriate drug in terms of therapeutic efficacy, safety, cost and above all the acceptance and tolerance of the child is chosen. The drug that is so individualized is started with the initial recommended dose with monitoring of the BP response to this drug. If there are no adverse effects to this drug and if BP is not adequately brought down to normal levels, the dose is stepped up every third or fourth day till optimum BP control is achieved or till the maximum recommended dose for that drug is reached. If no desired effect is seen, another drug with complementary action is added and the above process is repeated. The subsequent steps are given in the table. This stepped care approach recommended by NHBPEP is still followed. Before increasing the dose or adding another drug, enough attention must be given to the drug compliance and adherence to the management protocol.

Angiotensin-Converting Enzyme Inhibitors (ACEIs) (Table 12)

Among the available ACEIs, Captopril was the first orally available drug to be used since in early 1980S to treat

Table 12: Pharmacological choices for treatment of hypertension in children and adolescents

Class of drugs: Angiotensin converting enzyme inhibitors (ACEIs)

Drugs	Initial dose	Maximum dose	Interval	Side effects and remarks
Captopril	0.3-0.5 mg/kg/day	6.0 mg/kg/day	bid-tid	CI: children with bilateral RAS
Enalapril	0.04 mg/kg/day-up to 5 mg/day	0.6 mg/kg/day up to 40 mg/day	qd	Hyperkalemia, cough, angioedema, decrease in GFR, loss of taste, thrombocytopenia
Lisinopril	0.07 mg/kg/day-up to 5 mg/day	0.6 mg/kg/day up to 40 mg/day	qd	
Benazepril	0.2 mg/kg/day-up to 10 mg/day	0.6 mg/kg/day up to 40 mg /day	qd	
Fosinopril		0.6 mg/kg/day up to 40 mg/day	qd	Periodic monitoring of serum chemistries
Quinapril	5-10 mg/day	up to 80 mg/day	qd	
Ramipril	2.5 mg/day	20 mg/day	qd	

children including neonates with hypertension. Captopril has been employed successfully for a number of years in the proper control of both neonatal and childhood hypertension. Though found to be safe and effective, it has to be administered three times a day because of its shorter duration of action. Cough is an often reported side effect. It should not be used, if there is any suspicion of presence of bilateral renal artery stenosis.

Longer acting ACEIs - enalapril and lisinopril, being nonsulphydryl containing ACEIs, cause lesser incidence of side effects than captopril. While enalapril gets activated to enalaprilat by hydrolysis after gastrointestinal absorption, lisinopril needs no bioactivation. Its absorption is slower than enalapril. Enalapril and lisinopril are safe and effective in lowering BP in controlled trials. Enalapril has been effectively employed in hypertensive treatment of neonates and children. Ramipril has proved its safety and efficacy in lowering BP and reducing proteinuria in children with hypertensive chronic renal failure. Fosinopril and quinapril have been tried less often and used only in a few smaller trials.

Angiotensin II Receptor Blockers (ARBs) (Table 13)

Currently many trials are under way evaluating the usefulness of ARBs in childhood hypertension. A few studies with losartan, irbesartan, candesartan and valsartan have shown promise. With losartan treatment, significant

reductions in DBP were reported in children with estimated GFRs 30 ml/min per 1.73 m² or more. Smaller trials have reported the efficacy of other ARBs like irbesartan (75-150 mg/kg/day) and candesartan in childhood hypertension. Both of these agents reduced BP and proteinuria seen in some of the treated children. valsartan has been reported to effectively lower both SBP and DBP compared with placebo in 1 to 5 years old children. The drugs are currently very costly.

Calcium Channel Blockers (CCBs) (Table 14)

Calcium channel blockers (CCBs) by inhibiting calcium entry into the vascular smooth-muscle cell via a voltage-gated channel causes direct vasodilatation. They are widely used precisely because of their generally recognized safety profile. Among the available three categories of CCBs-dihydropyridines (e.g. nifedipine), phenylalkylamines (e.g. verapamil) and benzothiazepines (e.g. diltiazem), the most widely used drugs in this class are the dihydropyridines. Amlodipine, because of its enhanced binding to the calcium channel, has prolonged elimination half-life (30 hours) and extended duration of action. In a dose of 0.05 to 0.5 mg/kg per day, it is given in once daily dosage and hence considered by most pediatricians as an optimal CCB agent for use in children. As no liquid formulation is available for use, it is only prescribed for children who can swallow tablets. Flushing, headaches, migraines,

Table 13: Pharmacological choices for treatment of hypertension in children and adolescents

<i>Class of drugs: Angiotensin II receptor blockers (ARBs)</i>				
<i>Drugs</i>	<i>Initial dose</i>	<i>Maximum dose</i>	<i>Interval</i>	<i>Side effects and remarks</i>
Losartan	0.75 mg/kg/day up to 50 mg/day	1.4 mg/kg/day up to 100 mg/day	qd	CI: children with bilateral RAS, pregnancy
Irbesartan	6-12 yrs: 75 mg 6-12 yrs: 150 mg qd	>12 yrs: 150 mg >12 yrs: 300 mg		Dizziness, drowsiness, headache, nausea, dry mouth, abdominal pain loss of taste, hyperkalemia, thrombocytopenia
Valsartan	1.3 mg/kg/day up to 40 mg/day	2.7mg/kg/day up to 160 mg/day	qd	
Candesartan	4-8 mg/day	32 mg/day	qd	
Olmesartan	2.5 mg/day	40 mg/day	qd	

Table 14: Pharmacological choices for treatment of hypertension in children and adolescents

<i>Class of drugs : Calcium channel blockers (CCBs)</i>				
Amlodipine	0.05 mg/kg/day 6-7 yrs: 2.5 mg/day	0.5 mg/kg/day up to 10 mg/day	qd	Headache, dizziness, flushing, nausea, gingival hyperplasia, mild tachycardia, swelling of the lower legs or feet
Nicardipine				
Isradipine	0.05 - 0.15 mg/kg/day	0.8 mg/kg/day up to 20 mg/day	tid - qd	
Nifedipine –extended release	0.25 -0.5 mg/kg/day	3 mg/kg/day	bid - qd	
Felodipine	2.5 mg/day	10 mg/day	qd	

peripheral edema are common side effects than gingival hyperplasia, nausea and vomiting and chest pain.

Beta-Adrenergic Blockers (β -ABs) – Selective and Nonselective and α - and β - Adrenergic Blocking Agents (Table 15)

Beta adrenergic blockers (β -ABs) alter central and peripheral sympathetic activity, inhibit renin release, lower blood pressure via a number of mechanisms, reduce cardiac output, and potentiate the action of natriuretic peptides thereby lowering BP in hypertensive subjects. Earlier introduced β -ABs like propranolol have been in use for many years but its non-selectivity is associated with a potential risk of precipitating bronchospasm. Pediatric hypertension has been treated for many years with propranolol. It

is contraindicated in asthma and heart failure. Propranolol may cause hypoglycemia and night terrors. It impairs glucose tolerance and alters lipid profile adversely by lowering HDLP-cholesterol and raising plasma triglycerides. It reduces the ability to perform physical activity.

The reported adverse drug reactions of β -blockers are fatigue, depression, dizziness, and light headedness, bradycardia, postural hypotension, cold extremities and nausea. Nowadays, β -adrenergic blockers are not as widely advocated for treatment of pediatric hypertension as calcium channel blockers or ACE inhibitors. This may be due to questions regarding long-term effects of β -blockers on growth and lipid profiles, and their tendency to cause drowsiness. They are used only when CCBs and ACEIs prove ineffective.

Table 15: Pharmacological choices for treatment of hypertension in children and adolescents

Class of drugs: Beta-adrenergic blockers (BABs)				
Selective β -Blockers				Bradycardia, bronchospasm, congestive cardiac failure, hypoglycemia, hyperkalemia, nightmares, confusion
Metoprolol	1-2 mg/kg/day	6 mg/kg/day	bid	
Atenolol	0.5-1 mg/kg/day	2 mg/kg/day up to 100 mg/day	qd -bid	
Nonselective β -Blockers				Hyperkalemia, nightmares, confusion, depression, altered serum lipoprotein concentrations
Propranolol	1 mg/kg/day	16 mg/kg/day up to 640 mg/day	bid-tid	
Metoprolol	1 mg/kg/day	5 mg/kg/day		
Atenolol	1 mg/kg/day	8 mg/kg/day	qd -bid	
Nadolol	0.5 mg/kg/day	4 mg/kg/day		
Prazosin	Prazosin	Prazosin	Prazosin	Hypotension, tachycardia, fluid retention
Doxazosin	Doxazosin	Doxazosin	Doxazosin	
Terazosin	Terazosin	Terazosin	Terazosin	
Phentolamine	Phentolamine	Phentolamine	Phentolamine	
Phenoxybenzamine	Phenoxybenzamine	Phenoxybenzamine	Phenoxybenzamine	
Class of drugs: α - and β - adrenergic blocking agents				
Labetalol	2-3 mg/kg/day	10-12 mg/kg/day up to 1.2 g/day	bid	CI: Asthma, CHF and diabetes, carvedilol not CI in CHF
Carvedilol	0.1 mg/kg/dose up to 12.5 mg	0.5 mg/kg/dose up to 25 mg	bid	
Class of Drugs: Central α - adrenergic antagonists				
Clonidine	5-10 mcg/kg/day	25 mcg/kg/day	Bid tid	Rebound hypertension with sudden withdrawal of clonidine
Dry mouth, sedation				
α -Methyldopa	5-10 mg/kg/day	40 mg/kg/day	tid, bid	
Class of drugs: Peripheral α -adrenergic antagonists				
Prazosin	0.05 mg/kg/day	0.5 mg/kg/day	tid	All cause first dose hypotension
Doxazosin	1 mg/day	4 mg/day	qd	
Terazosin	1 mg/day	20 mg/day	qd	
Phentolamine	0.2 mg/kg/day	1.0 mg/kg/day		
Phenoxybenzamine	1 mg/kg/day	5 mg/kg/day		

In adult trials, β -ABs do not protect against heart attack more than other classes and are reported to be associated with a 14 percent increase in the risk of stroke. The use of cardioselective β -ABs such as atenolol and metoprolol do not cause this problem. They are effective as single agents or in combination with diuretic and/or ACEIs.

Labetalol and carvedilol with its additional peripheral α 1-adrenergic blocking action besides β -blocking action enhance blood pressure-lowering property. Labetalol is one of the most commonly prescribed agent for treating pediatric hypertensive emergencies.

Diuretics in Systemic Arterial Hypertension (Table 16)

Diuretics cause a decrease in systemic arterial pressure by reducing blood volume and decreasing peripheral vascular resistance in a sustained manner. They have been found to be most useful in hypertensive children with

renal diseases. The three commonly used diuretic groups of drugs are thiazides or thiazide like diuretics, loop diuretics and potassium sparing ones. Frusemide, commonly used loop diuretic, is employed in hypertensive children with less than 50 percent of residual renal function. Hypokalemia is its major disadvantage. Frusemide when given by rapid intravenous push may cause ototoxicity. In preterms, frusemide administration may be associated with nephrocalcinosis. Spironolactone being an aldosterone antagonist has its use in those children with secondary hyperaldosteronism.

All diuretics are employed as add on therapy with one of the above classes of primary antihypertensive agents.

The responsibilities of treating pediatricians do not end with appropriate selection and institution of drug therapy in hypertensive children (Table 17). They need to periodically monitor on a long-term basis these children

Table 16: Class of drugs: Diuretics in systemic arterial hypertension

Chlorothiazide	10 mg/kg/day	20 mg/kg/day	bid	Hyperuricemia, hypokalemia, decreased urinary calcium excretion, hypovolemia, hypokalemia
Hydro chlorothiazide	0.5-1 mg/kg/day	2 mg/kg/day	qd	
Chlorthalidone	0.3 mg/kg/day	2 mg/kg/day up to 50 mg/day	qd	
Bumetanide	0.02-0.3 mg/kg/day	0.3 mg/kg/day		
Amiloride	5-10 mg/day	20 mg/day	qd	
Loop diuretics				
Furosemide	0.05-1 mg/kg/day	6 mg/kg/day		
<i>Aldosterone antagonists</i>				
Spironolactone	1-2 mg/kg/day	3.5 mg/kg/day up to 100 mg/day	qd/bid	Hyperkalemia
Eplerenone	25-50 mg per day	100 mg/day	qd/bid	
Triamterene	1-2 mg/kg/day	3-4 mg/kg/day up to 300 mg/day	bid	

Table 17: Drug options for initial therapy for hypertension in children

<i>Class of drugs</i>	<i>Patients' characteristics</i>	
ACE-Is/ARBs	First-line therapy	High plasma renin activity, unilateral renovascular hypertension, renal parenchymal disease, renal proteinuria, congestive heart failure, diabetes mellitus, gout, hyperlipidemia, reactive airway disease
	Avoid in	Pregnancy, bilateral RAS
CCBs	First-line therapy	Emergency hypertension (nifedipine), black race, diabetes mellitus, chronic obstructive lung disease, bronchopulmonary dysplasia, gout, hyperlipidemia, peripheral vascular disease. Renal transplant, therapy with anticalcinurin
	Avoid in	Contracted intravascular volume, high plasma renin activity, hyperdynamic circulation, anxiety, migraine (propranolol, nadolol), hyperthyroidism, neuroadrenergic tumors
β -blockers	Avoid in	Avoid in athletes and people with diabetes
	Adjunct second-line drug	Volume-dependent, low plasma renin activity, black race, oral contraceptive therapy, congestive heart failure
Diuretics	Avoid in	Avoid in athletes

ACE-I—angiotensin converting enzyme inhibitor; ARB—angiotensin receptor blocker; CCB—calcium channel blocker

Table 18: Individualized stepped care approach recommended for medical drug therapy for control of hypertension in children and adolescents

<i>Step 1:</i>	Start with the recommended initial therapeutic dose of the first selected drug If desired BP control is not achieved
<i>Step 2:</i>	Increase the dose of the first selected drug until the target BP is attained or maximum therapeutic dose is reached If desired BP control is not achieved
<i>Step 3:</i>	Add a second medication with complementary mechanism of action Increase gradually to its highest recommended therapeutic dose if necessary If desired BP control is not achieved
<i>Step 4:</i>	Add a third antihypertensive drug of a different class or consult a pediatrician with expertise in treating childhood and adolescent hypertension

for the adequate control of BP, occurrence of any adverse drug effects, electrolyte and other metabolic disturbances, compliance of drug therapy and non pharmacological measures and for any evidence of onset of target organ damage. Besides these, the need for periodic counseling regarding risk factors needs adequate stress in the management plan (Table 18).

Some children and adolescents with a good BP control for years with drugs and life style modifications, especially those who were obese to start with, may be considered for “step down” therapy. The drug dosage is gradually reduced over a period of months and if BP continues to remain normal even after this reduced dosage, a final attempt is made to totally withdraw the drug treatment in children. Once the drugs are totally withdrawn, these children must be encouraged to comply with the non-pharmacological measures and their BP status needs to be periodically checked.

Surgical options are considered for those children with secondary hypertension like renovascular hypertension, coarctation of aorta, tumors and surgically treatable endocrinal causes. They are appropriately referred.

Acute Hypertensive Crisis in Children^{38,39}

Hypertensive crises in children are pediatric emergencies that carry significant mortality and morbidity if recognized and treated late. It refers to clinical states in children with suddenly elevated blood pressure usually exceeding stage II hypertension levels in severity and requiring prompt institution of safe and appropriate rapidly acting antihypertensive drugs to normalize blood pressure in a stepwise manner so as to prevent or to revert impending or already existing effects on end organs like brain, kidneys and heart.

Table 19: Features of severe hypertension

Blood pressure	Above the 99.9th percentile or increasing rapidly
Target organs	Clinical features
Neurologic	Focal or generalized seizures, localizing signs, isolated facial nerve palsy, headaches
Cardiac	Pulmonary edema, left ventricular hypertrophy
Renal	Severe back or abdominal pain, abdominal or renal masses or bruits, decreasing renal function
Visual	Blurred vision, papilledema, retinal hemorrhages and exudates, constriction of retinal arteries

Acute hypertensive crisis is further classified into hypertensive emergencies and hypertensive crisis.

Hypertensive urgency refers to rapid, sudden elevation of high blood pressure in children without signs and symptoms of end-organ dysfunction. Hypertensive emergencies are defined as states of markedly elevated blood pressure associated with any one of the symptoms and signs of end-organ dysfunction such as seizures, headache with vomiting, altered sensorium and irritability, encephalopathy, facial palsy, intracerebral hemorrhage, breathlessness and cough with evidence of left heart failure and acute renal dysfunction (Table 19).

As evidence based treatment guidelines for hypertensive crisis from randomized control trials are not available, the selection of safe and rapidly acting effective first and second line drugs are based on pediatric observational studies of small sample size and extrapolated data from adult studies. Because of this limitation, it is essential that pediatricians have adequate knowledge of the current recommendations of expert groups in the selection of the most relevant, safe, speedy drugs, its dosage, route and frequency of administration so as to safeguard the child from adverse effects of hypertension on the target organs as well as from the undesirable side effects of the chosen drugs.

Pediatric emergency guidelines and institutional protocols call for controlled and stepwise reduction of highly raised BP over 48 hours and recommend the use of safe, effective and rapidly acting therapeutic agents often given parenterally. A 20 to 25 percent reduction of BP in the first 8 hours is ideal to prevent permanent end organ damage. Subsequent reduction in BP is gradually and carefully done with constant or regular, periodic monitoring over the next 40 hours and the target BP is aimed to be below 95th percentile in children without end organ damage or co-existing morbidities like diabetes mellitus or chronic renal failure and to be below 90th percentile in those without these above mentioned conditions.

The clinical features of hypertensive emergency are symptoms pertaining to target organ dysfunction. Invariably the parents are unaware of the gravity of the initial

symptoms like headache, vomiting, visual disturbances, cough with shortness of breath. Younger children cannot express these. Only when the child develops sudden seizures, altered sensorium, marked breathlessness, the parents seek medical attention. The pediatrician must always record the BP with appropriate sized cuff and reliable instrument in any child presenting with any of the symptoms pertaining to the target organs – CNS, CVS, kidneys or eyes. One of the commonest causes of hypertensive encephalopathy in children of tropical and developing countries is poststreptococcal glomerulonephritis secondary to pyoderma or pharyngitis. They present with a few days of oliguria, puffiness of upper eyelids in the mornings, mild pitting edema of feet preceding the onset of seizures or shock due left ventricular failure or marked breathlessness due to pulmonary edema. Other well documented precipitating causes are hypertensive reflux nephropathy, coarctation of aorta, vasculitides, renovascular thromboembolic events, renal artery stenosis, acute renal tubular necrosis and hemolytic uremic syndrome. Other features that may be seen are intracerebral hemorrhage, facial palsy, retinopathy, acute renal failure, hematuria and arrhythmias.

The pathogenesis of hypertensive crisis involves interplay of several complex neurohormonal and haemodynamic pathways, e.g. activation of renin-angiotensin-aldosterone system (RAAS), oxidative and mechanical microvascular damage, endothelial dysfunction, sympathetic neuronal overactivity, fluid overload, etc.

SUMMARY

The prevalence of systemic arterial hypertension is steadily increasing in children and adolescents. The need for accurate, frequent and sometimes 24-hour ambulatory measurement of BP is stressed. Secondary hypertension, especially secondary to renal parenchymal and renovascular disorders, accounts for majority of hypertensive children and needs extensive work-up. The increased risks of essential hypertension developing in children with obesity, sleep obstructive disorders and low birth weight are getting more attention and understanding.

Currently accumulating epidemiological data on childhood and adolescent hypertension emphasizes the need to recognize its presence early and treat effectively with appropriately chosen drugs (Table 20) and non-pharmacological measures to prevent and minimize the target organ damage

Table 20: Drugs used in the treatment of hypertensive emergencies

<i>Drug</i>	<i>Class</i>	<i>Route</i>	<i>Dose</i>	<i>Onset of action</i>	<i>Comments</i>
Sodium nitroprusside	Direct vasodilator	IV infusion	0.5-8 mg/kg/min	Within 30 seconds	Thiocyanate toxicity; inactivated by light
Labetolol	A and BB	V infusion	0.25-3 mg/kg/hr	5-10 minutes	CI: Asthma, CHF; may cause bradycardia
Nicardipine	CCB	IV infusion	1-3 mg/kg/min	Within minutes	Reflex tachycardia
Clonidine	Central alpha agonist	IV bolus	2-6 mg/kg/min	10 minutes	Sedation, dry mouth; rebound hypertension
Esmolol	Selective B1B	IV infusion	100-500 mg/kg/min	Within seconds	CI: Asthma, CHF; May cause bradycardia
Enalaprilat	ACEI	IV bolus	0.05-0.1 mg/kg/dose	15 minutes	CI: suspected bilateral RAS
Captopril	ACEI	oral	0.1 -0.2 mg/kg/dose	10-20 minutes	
Nifedipine	CCB	oral	0.25 mg/kg/dose	20-30 minutes	Reflex tachycardia; may cause unpredictable hypotension
Furosemide	Loop diuretic	IV bolus	0.5-2 mg/kg/dose	Within minutes	Hypokalemia
Minoxidil	Direct arteriolar vasodilator	oral	0.1-0.2 mg/kg/dose	5-10 minutes	Hypotension, fluid retention,
Hydralazine		IV	0.1-0.5 mg/kg	Within 30 minutes	
Diazoxide		IV	0.1-0.5 mg/kg	Within 30 minutes	Tachycardia, hypotension, flushing

A and BB—alpha and beta blocker; CCB—calcium channel blocker; BB—beta blocker; ACEI—angiotensin converting enzyme inhibitor; CI—contraindicated; RAS—renal artery stenosis

in heart, vessels and kidneys. There are emerging evidences to show childhood onset of end organ damage in hypertensive children such as left ventricular hypertrophy and arterial wall (intima-media) thickening in children with essential hypertension. Current research priorities are identification of biomarkers of target organ damage, genetic susceptibility and pharmacogenomics that determine therapy.

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INTRODUCTION

Proteinuria is common in children and detection of abnormal amounts or types of protein in the urine is frequently the first sign of significant renal or systemic disease. Normally, a small amount of protein is present in the ultrafiltrate which is produced by the glomerulus and majority of it is absorbed by the tubules. At a normal GFR, approximately 1.4 kg of plasma proteins would be lost in the urine each day, if the kidneys were not capable of efficiently preventing the transglomerular trafficking of plasma proteins. The ability of the kidneys to retain proteins is essential for life. Normal urine contains not more than 150 mg of proteins per day.¹ Urinary protein excretion in excess of 100 mg/sq m/day or 4 mg/sq m/hr is considered abnormal in children. Approximately, 60 percent of urine proteins are derived from plasma whereas the remainder is produced by the kidney and the lower urinary tract. Physiological proteinuria means excretion of small amounts of protein in urine (less than 150 mg/day). Protein excretion is highest in infants, which decreases with age until late adolescence. This relatively high protein excretion observed in newborns represents tubular proteinuria, reflecting the immaturity of their renal function² (Table 1). Asymptomatic or isolated proteinuria is defined as proteinuria not associated with any signs or symptoms of renal disease.

MECHANISM OF PROTEINURIA

The glomerular capillary wall and the adjacent structures constitute the main barriers to the passage of macromolecules, including globulin and albumin. The barrier consists of the endothelial cells lining the capillary loops, the glomerular basement membrane and the visceral epithelial cells. The passage of macromolecules across the glomerular capillary wall is inversely proportional to their size. In addition to the size barrier, the glomerular capillary wall also contains negative charges, because of presence

of heparan sulphate proteoglycans. The negative charges repel negatively charged macromolecules, such as albumin (molecular weight 60,000 daltons).^{3,4} Most inflammatory glomerular diseases result in alteration of the size barrier and loss of anionic charges, leading to proteinuria. Low molecular weight proteins (molecular weight less than 60,000 daltons) are freely filtered through the glomerulus and are subsequently absorbed and catabolized by the proximal tubule. They include beta 2 microglobulin, retinol binding protein, alpha 1 microglobulin, and hormones such as vasopressin, insulin and parathyroid hormone.^{5,6} Injury to the proximal tubular epithelium leads to inability of the tubule to reabsorb low molecular weight proteins and to their loss in urine.⁵

Hemodynamic alterations in glomerular blood flow can also result in proteinuria. A decreased glomerular blood flow increases albumin penetration of the glomerular barrier and entry of albumin into the urinary space. This effect is functional and not pathological since restoration of blood flow promptly restores the leaky state of the glomerular capillary wall. A reduced number of functioning nephrons, as occurs in chronic kidney disease leads to increased filtration of proteins in remaining nephrons and to proteinuria. Other conditions that cause proteinuria by altering glomerular hemodynamics⁷ include exercise, fever, seizures, epinephrine use and emotional stress. Overflow proteinuria occurs when the plasma concentration of certain small proteins exceeds the capacity of the tubules to reabsorb the filtered protein, examples include presence of immunoglobulin light chains in the urine in multiple myeloma, hemoglobinuria in intravascular hemolysis, myoglobinuria in rhabdomyolysis and amylasuria in acute pancreatitis.⁸

The positive reaction to protein associated with hematuria is due to plasma albumin that accompanies the red blood cells into the urine. However, high grades of proteinuria detected in dipstick testing of grossly bloody urine

should not be ignored because the finding may reflect an underlying glomerulopathy.

MEASUREMENT OF PROTEINURIA

Qualitative Methods

The dipstick method provides an estimate of urinary protein concentration and is widely used. Proteins in solution cause a change in the color of a reagent strip impregnated with tetrabromophenol blue. Because tetrabromophenol is a pH indicator, the dipstick is buffered to prevent the influence of normal variations in urine pH on color change. False-positive results can be obtained when the urine is alkaline (pH greater than 7) or when it contains large amounts of mucus, blood, pus, semen or vaginal secretions. False-positive results can also occur in the presence of radiographic contrast material and in samples from children receiving high dosages of penicillin, cephalosporins or sulfonamides. The strips react preferentially with albumin and are relatively insensitive to other proteins such as gamma globulins. The amount of protein in the urine is assessed as 1+ (30 mg per dL), 2+ (100 mg per dL), 3+ (300 mg per dL) or 4+ (1,000 mg per dL). It is common practice in many hospital laboratories to verify the results of a positive dipstick test using sulfosalicylic acid test. In this test, three drops of a 20 percent solution of sulfosalicylic acid are added to 5 mL of urine to cause acidic pH and precipitation of proteins. The turbidity of the urine is noted by visual inspection. This test is more accurate than the dipstick method because all classes of proteins are detected. Because both dipstick and sulfosalicylic acid tests are sensitive to the concentration of protein in the urine, they can underestimate proteinuria or give false-negative results in the presence of a dilute urine (i.e. specific gravity less than 1.010). Urine with a specific gravity greater than 1.015 is necessary for reliable results.

Quantitative Methods

Several colorimetric laboratory methods are available to quantitate protein concentration in urine.⁹ Urinary protein electrophoresis and direct measurements of low-molecular-weight proteins such as β_2 microglobulin may be performed in special circumstances but are not part of the routine evaluation of a child with proteinuria. In adults, a protein excretion of less than 150 mg per 24 hours is considered normal. In children, however, physiologic proteinuria varies with age and the size of the child (Table 1). After the first year of life, daily protein excretion in children, expressed in mg/m²/24 hours, is relatively constant. The traditional way of quantitating urinary protein excretion has been to measure protein in a urine sample collected over a 12 or 24-hour period.

The patient is instructed to void after waking up in the morning and to discard that first urine and mark the time. The urine from each subsequent voiding is then collected

Table 1: Normal urinary protein excretion in infants and children

Age group	Total protein (mg per 24 hours)	Total protein (mg per m ² per 24 hours)
5 to 30 days (premature)	29	182
7 to 30 days (full term)	32	145
2 to 12 months (infant)	38	109
2 to 4 years (child)	49	91
4 to 10 years	71	85
10 to 16 years	83	63

for the next 24 hours; the final urine sample is to be voided precisely 24 hours after the timed collection had begun. Timed urine collections are difficult in young children and impossible in infants without subjecting them to bladder catheterization.

Determining the amount of excreted creatinine in the same 24-hour urine sample may be helpful in evaluating the accuracy of the collection. Steady-state daily creatinine excretion is 20 mg/kg in children from one to 12 years of age and 22 to 25 mg/kg in older children, with the lower value corresponding with creatinine excretion in girls.

A strong correlation has been found between the urine protein-to-creatinine ratio (UPr/Cr),¹⁰ obtained in random urine samples, and the 24-hour urinary protein excretion, corrected for body-surface area. Other studies have confirmed this observation.¹¹ The usefulness of urinary protein-to-creatinine ratios has been documented in normal children¹² and in children with renal disease.¹³

In adults and children over two years of age, a UPr/Cr of less than 0.2 on a random urine specimen is considered normal. In children aged six months to two years, the upper limit of normal should be extended to 0.512. A UPr/Cr above 2.0 is consistent with nephrotic-range proteinuria.

The ratio is not valid in children with severe malnutrition, as serum and urine concentrations of creatinine depends on muscle mass. In the presence of significant reductions in the glomerular filtration rate, tubular secretion of creatinine increases, and this may result in artificially low UPr/Cr values. The UPr/Cr ratio is considered by some investigators to be more reliable than 24-hour urinary protein measurements. A collection error was found in 57 percent of 24-hour urine samples, as assessed by high or low urinary creatinine content. The actual 24-hour protein excretion can be calculated from the UPr/Cr ratio at all levels of proteinuria, using a formula derived by log-log regression analysis.¹³

$$\text{Total urine protein (g/m}^2\text{/day)} = 0.63 \times (\text{UPr/Cr})$$

This method avoids the need for urine collection, and the results are obtained more expeditiously. Serial UPr/Cr ratios can be obtained over time to monitor the progression of proteinuria.

PREVALENCE OF PROTEINURIA

The prevalence of isolated asymptomatic proteinuria in children has been estimated to be between 0.6 to 6.3 percent.¹⁴⁻¹⁷ Proteinuria is usually transient and intermittent, so that much higher prevalence is observed when a single urine specimen is tested. Most children who test positive for proteinuria on initial evaluation lose the proteinuria at follow up, and only about 10 percent of the children have persistent proteinuria after 6 to 12 months.

ETIOLOGY OF PROTEINURIA

Transient or functional proteinuria: As many as 30 to 50 percent of children with proteinuria may have transient non-repetitive proteinuria⁶. Transient proteinuria can occur with strenuous exercise, emotional stress, exposure to extreme cold, epinephrine administration, abdominal surgery or congestive heart failure. It is also known to occur during febrile illnesses and after seizures. In all these circumstances proteinuria resolves spontaneously after the cessation of causal factor and an extensive workup is usually not recommended.

Intermittent proteinuria: Intermittent proteinuria indicates that protein is detectable in only some of the urine samples. This form of proteinuria may be related to posture (postural proteinuria). Some of the factors known to be associated with intermittent proteinuria are shown in (Table 2).

Persistent proteinuria: Persistent proteinuria indicates that protein is found in every urine sample. If these patients have associated evidence of renal disease such as microscopic hematuria, there are very high chances of having significant pathology in the urinary tract. Such patients should be identified and thorough diagnostic evaluation should be undertaken.

Causes of persistent proteinuria: In vast majority of cases persistent proteinuria is of glomerular origin. However, non-glomerular mechanisms can cause proteinuria too. Thus, proteinuria can be classified according to the pathophysiological mechanism responsible as shown in (Table 2).

Glomerular Mechanisms

Any disease, which damages the glomerular basement membrane, increases glomerular permeability to plasma proteins results in proteinuria. The whole of increased filtered load of proteins cannot be reabsorbed and the majority will appear in the urine. Acute and chronic glomerulonephritis are thought to produce proteinuria by this mechanism. These diseases cause severe histological damage to the glomeruli including abnormalities in the glomerular basement membrane. Such injury increases the effective pore size in the glomeruli. This increases the permeability of the mechanical barrier to the filtration of proteins and permits an increase, not only in the filtration of albumin but also of larger proteins such as globulin.

A second major mechanism for glomerular proteinuria is loss or reduction of the glomerular charge barriers and this results primarily in albuminuria. There is little or no increase in glomerular permeability to globulins, so this proteinuria is highly selective. The classical cause for this kind of proteinuria is minimal change nephrotic syndrome (MCNS).

A reduction in nephron mass results in increased glomerular permeability and increased proteinuria from the residual nephrons. This mechanism is responsible for proteinuria in renal transplant donors and in patients of cystic kidney disease.

Any increase in filtration fraction will increase plasma protein concentrations at the distal end of the glomerular capillaries to a level above the threshold. This explains the proteinuria due to stress and that associated with high levels of angiotensin.

Nonglomerular Mechanisms

The proximal convoluted tubule mainly reabsorbs most of the filtered protein and any damage to this segment of the nephron can result in proteinuria. Causes of tubular proteinuria are shown in (Table 2).

Overflow proteinuria results when the plasma level of a protein exceeds the renal threshold of that protein.

Table 2: Causes of proteinuria classified by type and mechanism

Intermittent proteinuria

- Postural
- Nonpostural
 - Contamination of urine
 - False positive (penicillin, radio contrast agent, sulfonamide administration)
 - Nonrenal cause, e.g. fever, exercise
 - Obstruction of urinary tract

Persistent proteinuria

- Glomerular causes
- Damage to glomerular basement membrane, e.g. acute and chronic glomerulonephritis
- Loss of glomerular polyanion, e.g. minimal change nephrotic syndrome
- Increased permeability in residual nephrons, e.g. end stage renal disease
- Hemodynamic alterations, e.g. hyperreninemia and early stages of diabetes
- Cause unknown, e.g. asymptomatic proteinuria

Nonglomerular causes

- Decreased tubular reabsorption—Fanconi's syndrome
- Overflow proteinuria
- Normal renal function—repeated albumin transfusions, myeloma or macroglobulinemia
- Decreased renal threshold—albumin infusions in nephrotic syndrome
- Secretory proteinuria—Tamm-Horsfall proteinuria, analgesic nephropathy

This can occur even when the kidney function is normal. Plasma concentration of albumin may increase sufficiently to cause proteinuria after repeated transfusions of either albumin or whole blood. Alternatively in multiple myeloma the appearance in the plasma of Bence Jones protein will result in loss of this protein in the urine and hence, clinically detectable proteinuria. Similarly, the release of free hemoglobin into the plasma causes the rapid appearance of this protein in the urine.

The increased excretion of tissue proteins into the urine may result in proteinuria too and is referred to as secretory proteinuria. Some of the proteinuria observed with renal stones and urinary tract infection may result from irritation of the lower urinary tract and the increase of tissue proteins.

Orthostatic (Postural Proteinuria)

The presence of increased amounts of proteins in urine formed when the patient is in upright position, but not in the urine formed when the patient is supine is referred to as postural proteinuria. In only 15 percent of the cases the postural proteinuria is fixed and reproducible, in remaining patients it is referred to as variable since not every orthostatic challenge results in proteinuria. It accounts for up to 60 percent of all cases of asymptomatic proteinuria¹⁸ reported in children. If all laboratory tests are normal except for persistently elevated protein excretion the possibility of postural proteinuria should be considered, this is best done by using the so-called orthostatic test. The patient is instructed to urinate just before going to bed at night and to discard the urine. He or she must remain supine all night and urinate the next morning immediately after arising. This urine sample is kept separate and labeled 'supine' or 'recumbent.' Additional urine samples are then collected and pooled during the next 12 to 16 hours, while the patient maintains normal daily activity. The final sample should preferably be collected in the evening, just before the patient goes to bed; this pooled sample should be labeled as 'active' urine. The duration of collection time for the latter sample can be shortened to 12 hours or less. In patients with orthostatic proteinuria, the supine sample will be free of protein, but the active sample will contain protein.⁸

Children with orthostatic proteinuria excrete less than 1 g of protein in 24 hours (UPr/Cr less than 1.0). The long-term prognosis for young adults with orthostatic proteinuria is excellent, even after 20 years of follow-up,^{19,20} but similar data is not available for children. However, it is believed that the prognosis in children and adolescents is equally good. Long-term follow up is necessary (unless proteinuria resolves) in order to monitor the child for evidence of renal disease (hematuria, hypertension, diminished renal function or proteinuria exceeding 1 gm/day).²¹ Yearly follow-up is recommended for children diagnosed with this condition.

EVALUATION OF A PATIENT OF PROTEINURIA

A positive dipstick for protein on random analysis is common in children. General screening of normal school age children with a urine dipstick (proteinuria >1+) will be seen in 5 to 10 percent. However, only 0.1 percent of children have persistent proteinuria.

In evaluation it is important to exclude false positive cases (Common causes for false positive results are shown in [Table 3]).

If the test is found to be positive due to these reasons then a repeat test should be done and shown to be negative.

Further evaluation of proteinuria should include a complete history, including a family history of renal disease, recent upper respiratory infections, gross hematuria, changes in weight and changes in urine output. The physical examination should include measurements of height, weight and blood pressure, identification of edema, ascites, skin pallor and palpation of the kidneys in newborn infants. A urinalysis should be performed and blood obtained for determination of electrolytes, blood urea nitrogen, creatinine, total protein and albumin levels, as well as a complete blood cell count and C3 complement level. A quantitative assessment of urinary protein excretion should be made, using either a 24-hour collection or a random urine sample for the UPr/Cr ratio. Clinical correlations for proteinuria have been listed in (Table 4).

A good clinical history, examination, and investigations are required to determine whether proteinuria is transient, orthostatic or persistent in type. Transient proteinuria, which is often associated with fever, stress, dehydration or exercise is not considered to be indicative of underlying renal disease.²²

Table 3: Causes for misleading screening tests for proteinuria

False positive results

- Dipstick method
 - Highly concentrated urine
 - Alkaline urine (ph > 8)
 - Gross hematuria, pyuria, bacteriuria
 - Dipstick left in urine too long
 - Contamination and drugs:
 - Antiseptics, chlorhexidine, benzalkonium
 - Phenazopyridine

Protein precipitation methods

- Highly concentrated urine
- Gross hematuria, pyuria, bacteriuria
- Drugs
 - Radiocontrast agents
 - Penicillin, cephalosporin
 - Metabolites of tolbutamide and sulfonamide

False negative results

- Very dilute urine
- Acidic urine (pH 4.5)
- Nonalbumin proteinuria

Table 4: Clinical correlations for proteinuria

<i>Likely diagnosis</i>	<i>History/physical examination</i>	<i>Creatinine</i>	<i>Albumin</i>	<i>C3 complement</i>	<i>UPr/Cr</i>	<i>Other associations</i>
Orthostatic proteinuria	>10 years of age	Normal	Normal	Normal	<1.0	–
Minimal change disease	Edema <6 years of age	Normal	Low	Normal	>2.0	Increased cholesterol
Acute glomerulonephritis	Edema, gross hematuria	Normal or high	Normal or low	Low	<1.0	Increased ASO titer
FSGS, MGN, MPGN	BP normal or high	Normal or high	Normal or low	Normal or low	<1.0	Hematuria
Henoch-Schönlein purpura nephritis	Purpuric rash on thigh and buttocks	Normal	Normal or low	Normal	Variable	Hematuria
Lupus nephritis	Butterfly rash, arthritis	Normal or high	Normal or low	Low	Variable	Increased ANA, hematuria
Tubulointerstitial disease	UTIs, polyuria	Normal or high	Normal	Normal	<1.0	–

If orthostatic proteinuria is diagnosed, the child should be followed with annual visits, including determination of a UPr/Cr ratio. If fixed isolated proteinuria is ascertained, the workup depends on the degree of proteinuria. If total protein excretion is less than 1 g per 24 hours (or the UPr/Cr is less than 1.0), twice-yearly visits, later extended to annual visits, with determination of the UPr/Cr ratio are sufficient. If proteinuria persists beyond one year, renal biopsy should be considered. If the total protein excretion is more than 1 g per 24 hours (or the UPr/Cr is greater than 1.0), a urinalysis should be performed and blood obtained for determination of electrolytes, blood urea, creatinine, total protein and albumin levels, C3 complement level and a complete blood cell count.

In young children (under six years of age), renal ultrasonography may be helpful to detect anatomic or congenital abnormalities such as polycystic kidneys. If the laboratory test results are abnormal, for example, if the patient has increased creatinine levels or hypocomplementemia or hematuria, a chronic glomerular disease may be present. Renal biopsy is indicated in these patients, and referral to a pediatric nephrologist is recommended.

The existence of an antecedent streptococcal infection may be investigated by measuring antistreptolysin-O and anti-deoxyribonuclease B titers. Postinfectious glomerulonephritis is usually self-limited, and a renal biopsy is not indicated. However, except in very mild cases, the patient should be referred to a pediatric nephrologist. If urinary protein excretion is in the nephrotic range (UPr/Cr greater than 2.0), even in the absence of edema and the patient is younger than six years of age, idiopathic nephrotic syndrome is likely, and a trial of corticosteroid therapy is warranted.

Renal biopsy is not indicated unless the patient has other abnormal laboratory test results, such as hematuria,

increased blood urea nitrogen and creatinine levels or hypocomplementemia. If urinary protein excretion is in the nephrotic range and the patient is older than six years of age, idiopathic nephrotic syndrome is less likely, and referral to a pediatric nephrologist is recommended. Renal biopsy will identify the type of glomerular disease responsible for the nephrotic syndrome (Table 2).

TREATMENT CONSIDERATIONS

Proteinuria is a marker of parenchymal injury in kidney disorders of diverse etiologies. Primary treatment of most disorders by immunomodulator medications is empiric. Treatment aimed at the mechanism of disorder, often immune mediated, also treats proteinuria.

Excessive restrictions on the child's lifestyle and physical activity are not necessary. Dietary protein supplementation to replace the loss of protein is not recommended and may be harmful. Most children with protein excretion under 1 g per 24 hours do not develop edema. Avoiding excessive salt intake is desirable, and more rigorous salt restriction may be necessary if edema develops. Therapy with an angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) can bring about a significant reduction of proteinuria.²³ The antiproteinuric effect appears to be connected to their diverse effects including control of hypertension. The explanation for the mechanism of anti-proteinuric effect is selective vasodilatation of the efferent arteriole which lowers the filtration pressure and hence the amount of protein in the ultrafiltrate. The use of ACE inhibitors in the treatment of renal disease may cause a reduction in glomerular filtration rate and hyperkalemia and therefore, if ACE inhibitors are used, renal function should be closely followed with periodic measurement of blood urea nitrogen, creatinine and potassium levels.

PROGNOSIS

While patients with orthostatic proteinuria have an excellent prognosis, the long-term prognosis for children with isolated fixed proteinuria remains unknown. It is generally believed that children with isolated proteinuria not exceeding 1 g per 24 hours have a better prognosis than those with higher amounts of protein in their urine. In a six-year retrospective study of 31 children with proteinuria of 10 months duration, renal biopsies were performed in 17 children.²⁴ Of these children, 12 had pathologic findings on biopsy, including eight with focal and segmental glomerulosclerosis. Among 12 of the 14 patients who were not biopsied and four of the five patients with normal histology, proteinuria completely resolved.

In a study²⁵ of 53 Japanese children with asymptomatic proteinuria, significant glomerular changes were observed on renal biopsy in 25 patients (47 percent). Fifteen of them had focal glomerulosclerosis. Seven patients with abnormal glomerular histology developed renal insufficiency; none of the patients with normal glomerular histology developed renal insufficiency. In a survey of pediatric nephrologists,²⁶ 36 percent of the physicians surveyed would perform a renal biopsy in a nine-year-old child with moderate proteinuria (600 mg per day). Until more information is available, the decision to perform a renal biopsy in a child with isolated proteinuria will depend on factors such as parental or physician anxiety and the availability of effective therapy.

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Routine antenatal ultrasonography has focused our attention to urological abnormalities that occur in babies. This review aims to outline a logical approach to this problem through the gestational period into the neonatal period emphasizing what needs to be done and when; and, more importantly, what need not be done.

What is the Magnitude of the Problem?

It is estimated that some degree of dilatation of the fetal renal collecting system is identified in 1 to 5 percent of all pregnancies,¹ but in only one-fifth of these is the dilatation significant.² It must be understood at the outset that the term hydronephrosis simply denotes dilatation of the upper urinary tract and does not necessarily imply the presence of an obstructive lesion or a significant functional abnormality of any kind. In fact, only 3 percent of babies with a renal pelvis diameter <10 mm had a significant abnormality needing surgery. The usual causes of antenatal hydronephrosis include:

- *Functional dilatation:* Minor degree of dilatation that usually spontaneously resolves later in gestation or early infancy.
- *Obstruction:* Usually at the pelviureteric junction, at the ureterovesical junction, or in the urethra (as in posterior urethral valves)
- Vesicoureteral reflux
- Renal dysplasia including multicystic dysplastic kidneys
- Uncommon conditions like duplex collecting system or Prune-belly syndrome, etc.

What is Significant Dilatation?

In order to standardize data, the Society of Fetal Urology (SFU) has adopted a grading system for hydronephrosis (Table 1).¹ An alternate method is to measure the renal pelvis anteroposterior diameter.^{3,4}

A renal pelvis anteroposterior (AP) diameter of >10 mm after 24 to 26 weeks of gestation is generally accepted as a reasonable criteria to denote significant dilatation.^{3,5} The presence of caliectasis or calyceal dilatation is considered an additional factor indicative of significant hydronephrosis.^{1,6} More recently, there is evidence to suggest that milder degrees of dilatation may also be significant in that such babies may have vesicoureteral reflux (VUR) rather than obstruction.⁷⁻⁹ Currently, a renal pelvis diameter of at least 4 mm before 33 weeks and 7 mm after 33 weeks is considered significant.¹⁰ Antenatal hydronephrosis can be classified as mild, moderate or severe for prognostic purposes (Table 2).¹ A large systematic review suggests that the risk of significant postnatal pathology is 11.9 percent for mild, 45.1 percent for moderate and 88.3 percent for severe hydronephrosis.¹¹

Table 1: Grading of hydronephrosis¹

Grade	Pattern of renal sinus splitting
0	No splitting
1	Urine in pelvis barely splits sinus
2	Urine fills intrarenal pelvis
2	Urine fills extrarenal pelvis, major calyces dilated
3	SFU Grade 2 and minor calyces dilated and parenchyma preserved
4	SFU Grade 3 and parenchyma thin

Table 2: Definition of antenatal hydronephrosis (ANH) by anteroposterior diameter¹

Degree of ANH	Second trimester	Third trimester
Mild	4 to <7 mm	7 to <9 mm
Moderate	7 to <10 mm	9 to <15 mm
Severe	>10 mm	>15 mm

What Information is Sought on an Antenatal Ultrasound Scan?

While assessing the significance of the antenatal renal dilatation, particularly with a view to identifying a possible cause and whether it is worth continuing pregnancy, the US must be done carefully and must give the following information:

- Estimated fetal size and weight, and its comparison with normal for that gestational age
- Amniotic fluid volume (AFV)
- Whether dilatation is unilateral or bilateral, and whether ureters are dilated or not
- Degree of dilatation (SFU grading) and dilatation of calyces
- Bladder fullness, thickness and emptying
- Appearance of external genitalia
- Any other associated malformation.

The initial study is usually done at 16 to 20 weeks gestation using a 5 MHz transducer. There are no specific guidelines on how frequently to image the fetus. It would be reasonable to do the US every 4 weeks till 32 weeks and two weekly thereafter, mainly to assess the AFV.

What is the Current Status of Fetal Intervention?

The rationale for fetal urinary decompression is that those with severe obstruction early in gestation have significant impairment of both renal and pulmonary development. It has been recognized that if the AFV is adequate up to 27 weeks gestation, then severe pulmonary hypoplasia is unlikely to occur.¹² Percutaneous shunting of the bladder into the amniotic space is technically feasible with some morbidity. However, its role is extremely limited.

There is no place for any fetal intervention in unilateral hydronephrosis. Even with bilateral pelviureteric junction obstruction (PUJO), if the AFV is normal, percutaneous drainage of the fetal kidneys or early delivery are not warranted. For babies with posterior urethral valves (PUV), poor prognostic criteria include:

- Early severe oligohydramnios
- Renal cortical cysts suggesting renal dysplasia
- Bladder urine with sodium >100 mEq/L, chloride >90 mEq/L, osmolality >210 mOsm/L, increased β_2 -microglobulin
- Evidence of pulmonary hypoplasia.

What is the Natural History of Antenatal Hydronephrosis?

Spontaneous resolution of prenatally detected hydronephrosis occurs in 50 to 70 percent of all fetuses. This regression may be noted on serial antenatal ultrasound scans or in the postnatal life up to 3 years.^{3,13-17} Furthermore, in a substantial number, even if the hydronephrosis does not resolve completely, the renal function does not deteriorate despite persistence of pelvic dilatation.¹⁶ On

the other hand, 15 to 33 percent of patients show progressive renal deterioration during observation.¹⁸⁻²⁰ It has been noted that increasing degrees of hydronephrosis correlated with increased risk of urological pathologies that may need surgical intervention.^{21,22}

Postnatal Evaluation of Antenatal Hydronephrosis

Immediately after birth, the following must be recorded:

- Sex of the baby; in males PUV is an important diagnosis to be considered, requiring early intervention
- Palpable kidney—common causes are PUJO (more commonly unilateral), multicystic dysplastic kidney (unilateral), PUV (unilateral or bilateral)
- Palpable bladder—indicative of PUV in boys.

If the diagnosis of PUV is suspected, all further investigations need to be done urgently as the baby requires early surgical intervention. These babies need renal function tests, US scan, voiding cystourethrogram (VCUG) within a day or two after birth so that surgical ablation of the valves may be done at the earliest.

In all other situations, there is no great haste to perform investigations. The initial study to be done is the US scan that must preferably not be done in the first 2 to 3 days. However, if the mother is being discharged earlier, it is practical to send the baby with the US scan results.

Following the US scan, a VCUG is done. There is no doubt that the conventional VCUG is preferred to a direct radionuclide cystogram (DRCG) because the latter does not give a good delineation of the bladder and urethral anatomy and that reflux, if present, cannot be accurately graded. Controversy surrounds two aspects of VCUG:

- Should VCUG be done in all babies?
- When should it be done?

Should VCUG be Done in all Babies?

VCUG is an invasive procedure, and some studies have quoted a 6 percent rate of UTI following VCUG. This has made most clinicians reluctant to ask for a VCUG in newborn babies. However, if properly performed under antibiotic cover, the procedure is safe with no risk of UTI (personal experience²³). There are some recent reports that claim that routine VCUGs may not be indicated in all babies with antenatally detected hydronephrosis.²⁴⁻²⁸ These studies recommend VCUG for those babies with:

- Bilateral hydronephrosis
- Dilated ureters
- Presence of UTI.

This literature against routine use of VCUG is far from convincing. Most large centres recommend that this test must be done in all babies with antenatal hydronephrosis even if the postnatal US scan is normal.^{1,4,29} VUR has been recorded in 15 to 30 percent babies born with an antenatal diagnosis of hydronephrosis.^{4,11,30} Tibballs³¹ reported that among 255 renal units with reflux, the postnatal US

was normal in 177 (70%). Furthermore, some studies have shown that the postnatal US may be normal even with the higher grades of VUR (12% of grade V and 31 percent with grade IV).³²⁻³⁴

When Should it be Done?

Some authors recommend that a VCUG should be done at 4 to 6 weeks postnatal age. Though, again, it would be more practical to do it before the baby leaves hospital. Either way, till the VCUG has been done and VUR excluded the baby needs to be on low dose antibiotics using amoxycillin (15 mg/kg/day) or cephalexin (50 mg/kg/day). Trimethoprim (2 mg/kg/day) may be used safely in babies after 4 to 6 weeks of age. Neonates who do not have VUR do not need further antibiotic chemoprophylaxis.

When is a Radionuclide Study Indicated?

In most babies, the US scan is repeated at 4 to 6 weeks of age. In most situations, a diuretic renogram is done at about 4 weeks of age to evaluate renal functional status and presence of obstruction. Renograms performed immediately after birth may be difficult to interpret due to the immature function of the kidneys and their handling of the radioisotope. Diuretic renogram is indicated in all kidneys with grade 3 or 4, and occasionally grade 2 hydronephrosis;^{35,36} there is bilateral PUJ or ureterovesical junction obstruction; if there is a solitary kidney; or the kidney is palpable and tense.

The renal scan is superior to the IVP for many reasons. It is safer (contrast reactions and radiation are less), there is better visualization of the collecting system and, objective and quantitative assessment of relative function of each kidney is possible. The ideal radionuclide is MAG3, but a cheaper, though less accurate option is the DTPA (not DMSA) scan. In lower grades of hydronephrosis, if VUR has been excluded no further workup with renal scans may be necessary. These babies need observation with 3-monthly ultrasounds to ensure that the degree of hydronephrosis is static and not worsening.

Follow-up Evaluation

Currently, no single test can reliably predict whether a hydronephrotic kidney will improve or deteriorate. Most people agree that nearly all infants with unilateral PUJ obstruction are initially managed conservatively if the diuretic renogram shows at least 35 to 40 percent differential renal function.^{35,37} Exception are infants with renal infection, tense renal lump,^{35,36} or pelvis AP diameter >50 mm.²⁰ Follow-up US scan and diuretic renography is repeated at 3 to 6 months and if there is a deterioration in differential renal function, pyeloplasty is indicated.^{18-20,35} Nearly 20 percent infants will show deterioration on follow-up requiring pyeloplasty. This usually happens in the first year of life.^{16,18,19}

Children with lesser degree of hydronephrosis (up to pelvis AP diameter of <20 mm) need to be followed up with an US scan at 3 m, 1 year; then 2, 5, and 10 years. Radionuclide study is done at 3 m, 1 year and if required at 2, 5, and 10 years. If the renal function or degree of dilatation improves, there is no further need for the isotope study.²⁰

Vesicoureteral Reflux in Neonates

VUR may be seen in 20 to 35 percent neonates with antenatal hydronephrosis.^{1,29,38-41} Nearly 80 percent of such patients are boys. The presence of a large, thin walled bladder, normal renal architecture and AFV in a male fetus most likely signifies massive VUR designated as megacystis-megaureter syndrome.⁴² Neonates with reflux should undergo a baseline DMSA renal scan, (not DTPA) to identify scarring, which may be present in 40 percent cases.³⁵

Most such neonates are initially managed medically with antibiotic prophylaxis (initially amoxycillin or cephalexin for 2 months, later trimethoprim or nitrofurantoin). Circumcision may be recommended in these boys to reduce the risk of UTI.

Urine examinations are indicated if the baby is febrile, not feeding well, sluggish, not gaining weight or having loose stools. Follow-up is done with US scan, which is repeated at 3 m, 6 m, and 1 year. VCUG, but if available a radionuclide cystogram (DRCG), is preferred at 1 year and 2 years to reevaluate the status of reflux. If two consecutive studies show absence of VUR, antibiotic prophylaxis may be discontinued.

Surgery for the correction of reflux may be indicated in babies who have breakthrough UTI or progression of renal scarring.

Posterior Urethral Valves

PUV is the most common cause of severe obstructive uropathy in neonates. It presents as a spectrum of clinical manifestations. On the one hand, there may be a neonate who voids near-normally, the bladder may be empty, renal function is normal, yet the only evidence is bilateral hydroureteronephrosis. The other end of the spectrum is a preterm baby with severely deranged renal function and acidosis, evidence of pulmonary hypoplasia with severe obstructive uropathy. Approximately one-third of all babies born with PUV finally develop chronic renal insufficiency. Prognosis is worse when the prenatal US detected the anomaly prior to 24 weeks gestation. Favorable prognostic criteria include:

- S. creatinine that falls to below 1 mg/dl after bladder decompression
- Unilateral reflux into a nonfunctioning kidney (the "pop-off" effect) with normal contralateral kidney
- Urinary ascites (this results in natural decompression)
- Maintenance of corticomedullary differentiation on renal US.

The initial treatment of such babies is bladder decompression using a fine infant feeding tube and biochemical stabilization. Following bladder decompression, these babies pass large volumes of urine and lose a lot of electrolytes in the urine. Both, volume and electrolytes need to be adequately replaced. A VCUG must be done immediately. Frequent catheter changes are a potent source of urosepsis that can be disastrous in these critically balanced babies.

Definitive treatment in the form of endoscopic transurethral valve ablation is usually possible in most neonates and must be done at the earliest. In case the equipment is not available or does not negotiate the urethra, a poor second choice is a vesicostomy. Vesicostomy may also be indicated if the s. creatinine levels remain very high after valve ablation or there is persistent infection. In the current scenario, supravescical diversion in the form of cutaneous pyelostomy or ureterostomy is rarely necessary.

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Management of Difficult Nephrotic Syndrome

PK Pruthi, Kanav Anand

BACKGROUND

Nephrotic syndrome is a renal disease which occurs due to increased permeability across the glomerular filtration barrier. It is classically characterized by proteinuria (>1 gm/m²/day), hypoalbuminemia (<2.5 gm/dl), edema and hyperlipidemia (serum cholesterol >200 mg/dl).¹⁻⁴ Proteinuria sets in motion, a series of homeostatic and compensatory mechanisms that result in clinical features of nephrotic syndrome.^{1,2}

Management of nephrotic syndrome focuses on:

- Treatment of the causative disease (minimal change nephrotic syndrome (MCNS), focal segmental glomerulosclerosis (FSGS), membranoproliferative glomerulonephritis (MPGN) and membranous glomerulonephritis) with steroids or other immunosuppressive agents.
- Treatment of complications of nephrotic syndrome.

In treatment of nephrotic syndrome difficulties may be encountered in either of these two management issues.

DIFFICULTY IN MANAGEMENT OF CAUSATIVE DISEASE

Frequent Relapser or Steroid Dependent Nephrotic Syndrome (SDNS)

Patients having frequent relapses or those who are steroid dependant require repeated courses of prednisolone and often develop steroid toxicity. Important side effects include development of severe cushingoid features, hirsutism, hypertension, impaired glucose tolerance, posterior subcapsular cataract, growth retardation and emotional problems.⁵ Serious complications of steroid toxicity should not be allowed to develop in such cases. Following treatment of relapse, the dose of prednisolone is tapered gradually to maintain the patient in a state of remission on alternate day dose of

0.5 to 0.7 mg/kg or lower. Alternate day prednisolone may be administered for 9 to 18 months.⁶ A close monitoring of growth, blood pressure and evaluation for features of steroid toxicity is essential. If the prednisolone threshold to maintain remission is higher or there is development of steroid toxicity then the following immunosuppressive agents are recommended. Instead of prednisolone, deflazacort can also be used as an alternative in view of its much better side effect profile.⁷

Levamisole⁶⁻⁹

Levamisole is an immunomodulatory agent without any anti-inflammatory effect and has been successfully employed in patients with frequent relapses and steroid dependence. This can be administered in a dose of 2 to 2.5 mg/kg on alternate days for 12 to 24 months or even longer. It has been found to be effective in about 50 to 60 percent of cases with a marked reduction in the relapse rate. This drug acts as a steroid sparing agent. Treatment with prednisolone in a dose of 1.5 mg/kg on alternate days is continued and gradually reduced by 0.15 to 0.25 mg/kg every 4 weeks to a maintenance dose of 0.25 mg/kg, which may be continued for 6 months. In 20 to 30 percent of cases prednisolone can be stopped and levamisole alone is sufficient. There is a strong tendency for relapse to recur when levamisole is discontinued. The chief side effects of treatment with levamisole are leucopenia, flu like symptoms and skin rash. Total count should be monitored every 4 to 8 weeks. The reduction in neutrophils is usually transient and reversible on withdrawal of the drug.

Alkylating Agents¹⁰⁻¹²

Alkylating agents chiefly cyclophosphamide may induce long lasting or rarely permanent remission in children with frequent relapsing or steroid dependent nephrotic

syndrome. This drug is administered after inducing remission with standard prednisolone treatment. Cyclophosphamide (CMP) may be administered orally in a dose of 2 mg/kg along with alternate day prednisolone as 1-1.5 mg/kg for 12 weeks. This results in a prolonged remission in majority of cases. The results are better in older children. Only a single course of the drug is usually recommended. Total leucocyte count needs to be monitored every 2 weeks. Treatment is discontinued if the total counts falls below 4000 mm³. Gonadal toxicity is an important consideration with pubertal and post pubertal patients being most vulnerable, especially the male sex. Hemorrhagic cystitis is an uncommon complication and increasing fluid intake and frequent voiding help in preventing this. Treatment with CMP may rarely cause alopecia, nausea or vomiting. A standard course of cyclophosphamide up to a cumulative dose of 168 mg/kg is reasonably safe. CMP may also be used as monthly pulses for six months, but it is unclear whether intravenous cyclophosphamide is as effective as oral cyclophosphamide in sustaining remission. One study, for example, reported that intravenous cyclophosphamide was not effective in preventing relapse in steroid-dependent patients.¹³ In contrast, a randomized trial of 47 patients found that the risk of relapse at six months was lower with intravenous cyclophosphamide (six monthly doses) than with a 12-week course of oral cyclophosphamide, although the benefit did not persist at two year follow up.¹⁴ The use of this subset of drugs should be reserved for those patients who cannot be managed with long term low dose alternate day steroids or levamisole. Therefore, treatment with CMP may be considered in patients showing:

- a. Significant steroid toxicity.
- b. Severe relapses with hypovolemia and thrombosis.
- c. Poor compliance on follow-up.

Calcineurin Inhibitors

Cyclosporine^{11,15,16}

Cyclosporine(CsA) is a calcineurin inhibitor which acts by inhibiting the T helper cells and inhibiting the production and release of lymphokines. It is administered in a dose of 4-5 mg/kg in two divided doses for 12 to 24 months. Therapy is continued with alternate day prednisolone for 12 to 24 weeks and then tapered off gradually. Side effects such as hypertension, gum hypertrophy and hirsutism may occur in which case dose may be reduced to 3 mg/kg per day. Patients who continue to have relapses after a course of cyclophosphamide can be considered for treatment with cyclosporine. A renal biopsy is essential before starting this drug. A wider use of CsA is precluded by its nephrotoxicity. Blood levels of urea, creatinine, transaminases, cholesterol and CsA should be measured every 4-6 months. Blood levels of CsA should be kept between 100 and 150 ng/ml. It becomes essential to monitor the blood levels of CsA in patients who are nonresponders, non-compliant or who develop an elevated serum creatinine

while on treatment with this drug. Cyclosporine is recommended in patients that continue to be steroid-dependant or frequent relapser despite a course of levamisole or CMP.

Tacrolimus

It has a similar mechanism of action as cyclosporine and is administered in a dose of 0.1-0.2 mg/kg/day in two divided doses. Alternate day prednisolone is also be continued. The main advantage of tacrolimus over CsA is lack of cosmetic side effects. Tremors, blood glucose abnormalities and diarrhea are few of the common side effects. Its trough levels should be maintained between 4 and 8ng/ml.

Mycophenolate Mofetil

Mycophenolate mofetil (MMF)¹⁷⁻¹⁹ is a potent reversible inhibitor of inosine monophosphate dehydrogenase, an enzyme required for purine synthesis. Mycophenolate mofetil (MMF) has shown benefit in reducing relapse rates and steroid requirements in patients with frequent relapses or steroid dependant cases. Long term treatment with this drug appears to be promising in patients with difficult nephrotic syndrome with no risk of nephrotoxicity, hepatotoxicity or neurotoxicity. The major side effects of this drug are gastrointestinal (abdominal pain, diarrhea) and hematological. The dose of MMF is 30 mg/kg/day (600-750 mg/m²/day) in two divided doses. It can be continued for a period of 1-2 years, while keeping a watch on the leucocyte counts and serum transaminases levels. Treatment is temporarily held if leucocyte counts fall below 4000 mm³.

Rituximab

Rituximab (RTX), a chimeric anti-CD20 monoclonal antibody, which is a drug used in treatment of rheumatoid arthritis and B cell lymphomas, has been found useful in reducing the relapse rates in children who are frequent relapsers or have steroid dependence, thus reducing the steroid usage. It is also a treatment of choice for children who are refractory to all other immunosuppressants mentioned above. It can be given as 1-2 doses of 375 mg/m² (IV infusion), at weekly intervals. The response to rituximab appears to be better if the patient is in remission at the time of the infusion. Therefore, rituximab should not be administered during a relapse but after remission has been induced by increased doses of steroids.²⁰⁻²³

Relapses during and following treatment with levamisole, CMP, CsA, tacrolimus or MMF are treated with standard regimen. The benefits of using these immunosuppressive agents should be weighed against their toxicity before initiating them.

Steroid Resistant Nephrotic Syndrome

Steroid resistance is defined as absence of remission despite therapy with daily prednisolone at a dose of 2 mg/kg/day for 4 weeks.²⁴ Such a child need to be biopsied (Table 1) and he can have any of the below mentioned

Table 1: Indications for kidney biopsy in nephrotic syndrome*At Onset*

- Age of onset <1 year
- Gross hematuria, persistent microscopic hematuria or low serum C3
- Sustained hypertension
- Renal failure not attributable to hypovolemia
- Suspected secondary causes of nephrotic syndrome

After Initial Treatment

- Proteinuria persisting despite 4-weeks of daily corticosteroid therapy
- Before treatment with cyclosporine A or tacrolimus

histological patterns on renal biopsy: minimal change nephrotic syndrome (MCNS), mesangial proliferative glomerulonephritis (MesPGN), focal segmental glomerulosclerosis (FSGS), membranoproliferative glomerulonephritis (MPGN) and membranous nephropathy.

Steroid Resistant Minimal Change Nephrotic Syndrome

A very small proportion of minimal change nephrotic syndrome (MCNS)²⁵ have initial steroid resistance. Of these almost 30 percent respond to treatment with a 12 weeks course of cyclophosphamide. Those who subsequently relapse respond to steroids. Intravenous administration of high dose methylprednisolone or dexamethasone has been used in some patients of MCNS who are oral prednisolone resistant. Cyclosporine in combination with alternate day prednisolone may induce remission in 60 to 70 percent of patients of steroid resistant MCNS. Most patients who respond, do so within 3 months of therapy. The treatment is carried out for 2 to 3 years. Tacrolimus may also be used in place of cyclosporine, in case the child develops side effects. Rituximab (anti-CD20 monoclonal antibody) may be tried in case other therapies fail.

Focal Segmental Glomerulosclerosis

Focal segmental glomerulosclerosis (FSGS)²⁶⁻²⁸ is the most frequently encountered progressive glomerular disease. About 70 to 80 percent patients with focal segmental glomerulosclerosis (FSGS) will have initial or late steroid resistance. Idiopathic FSGS should be distinguished from secondary FSGS that can occur in conditions like HIV infection, reflux nephropathy, sickle cell disease and hyperfiltration injury. The initial treatment of FSGS is similar to that of MCNS. Some of the patients who give a positive response to steroids will relapse. Guidelines for treatment of this group of patients are similar to those of relapsing MCNS. A repeat course of steroids may again induce a remission if steroids were earlier given more than 6 months back. However in those who relapse earlier repeated high dose steroid therapy may result in

unacceptable cumulative toxicity. Therefore alternative forms of treatment such as CMP or CsA may be useful. In patients with glomerular tip lesion variant of FSGS, a trial of steroids is appropriate because many patients show a decline in protein excretion with steroids.

Prednisolone resistant FSGS has been successfully treated with pulse methylprednisolone. Pulse methylprednisolone has been used in a dose of 30 mg/kg three times a week for 2 weeks, once a week for 8 weeks, once in 2 weeks for another 8 weeks and then once a month for 6 to 12 months. The results of this regimen are good, demonstrating sustained remission in 60 percent of patients with steroid resistant FSGS. Some patients have also been given alkylating agents along with alternate day steroids and about 70 percent of children have shown benefit. Patients resistant to prednisolone may be induced into remission by using calcineurin inhibitors (cyclosporine/tacrolimus). A combination of CsA and prednisolone is reported to cause partial to complete remission in about 50 percent of patients. Long-term therapy with CsA may arrest progression of FSGS by reducing proteinuria. Plasmapheresis has also been used in some cases to good effect. Rituximab is nowadays being used as rescue therapy for patients who are refractory to all other drugs.

Membrano Proliferative Glomerulonephritis (MPGN)²⁵

Corticosteroids, immunosuppressive agents and anti-platelet therapy have been used with variable benefits. Early administration of relatively high doses of prednisolone (1-1.5 mg/kg) on alternate days for prolonged periods (3-5 years) may have a favorable effect in children. Patients should be screened for hepatitis B and C infection before initiating steroid therapy. Hypertension should be controlled with appropriate medications. ACE inhibitors may be a preferred class of drug as they will also help in decreasing the proteinuria.

Membranous Nephropathy

The condition is rare in children and most cases are secondary. Hepatitis B is the most frequent cause of membranous glomerulonephritis (MGN)²⁵ in children. Other causes include hepatitis C, SLE and exposure to gold, penicillamine and non-steroidal anti-inflammatory drugs. Children with hepatitis B associated MGN typically go into spontaneous remission with the development of antibodies. Such patients may be treated with lamivudine and/or other antiviral agents. In idiopathic MGN with persistent nephrotic syndrome, prednisolone and alkylating agents or calcineurin inhibitors may be judiciously used.

MANAGEMENT OF COMPLICATIONS**Edema**

Early treatment of relapse and judicious use of diuretics will ensure that the child does not develop massive

edema. Furosemide and bumetanide are very potent diuretics. These loop diuretics are organic anions mostly bound to plasma protein and very little of the diuretic reaches tubules through glomerular filtration. They are secreted into the lumen of the proximal tubule by the organic anion transport system and act on the luminal side of thick ascending limb of loop of henle. Patients with massive edema are usually resistant to the action of these diuretics.²⁹⁻³¹ In such cases up to 70 percent of the drug within the tubular lumen may be bound to the filtered protein and large doses of loop diuretics may be required. Mild edema can be treated with salt restriction (2 mEq/kg/ day). For more significant edema furosemide 1-3 mg/kg is used in 2 to 3 divided doses. Occasionally continuous intravenous infusion of furosemide as 4-10 mg/kg over 24 hours may be necessary to achieve adequate diuresis. If furosemide is used for more than 3 days then a potassium sparing diuretic spironolactone may be added to the treatment in a dose of 1-3 mg/kg/day (Table 2). Use of large doses can be hazardous and should be accompanied with careful monitoring of serum electrolytes. Metalazone in the dose of 0.1-0.5 mg/kg/day may also be used in refractory cases.

Table 2: Management of nephrotic edema

Furosemide (1-2 mg/kg/dose) oral or intravenous
↓
No response (no diuresis in 1-2 days)
↓
Double dose of furosemide (can go up to 10 mg/kg/day)
↓
Add spironolactone (1-3mg/kg/dose) if furosemide being used for more than 3 days
↓
No response
↓
Add metalazone (0.1-0.5 mg/kg/day)
↓
No response
↓
Change to intravenous furosemide or infusion form
↓
No response
↓
Intravenous albumin 20 percent (1 gm/kg/day)
↓
No response, try head out water immersion
↓
Ultrafiltration

Use of Albumin^{31,32}

In some cases edema is extremely pronounced with serum albumin levels below 1 gm/dl and associated hypovolemia. Diuretics are ineffective unless blood volume is expanded. 1 gm/kg salt free 20 percent albumin can be given slowly over 60 to 120 minutes with monitoring of pulse and blood pressure. Intravenous furosemide in a dose of 1 to 2 mg/kg is administered at the end of albumin infusion.

Head Out Water Immersion^{33,34}

Head out water immersion therapy, 2-4 hours each day for few days, is quite feasible in older children with parental cooperation. The procedure leads to movement of edema fluid from the interstitial to intravascular compartment. The procedure also leads to release of atrial natriuretic peptide (ANP), which inhibits sodium and water absorption from the medullary collecting duct.

Ultrafiltration

In patients with decreased GFR and heavy proteinuria ultrafiltration may be employed to remove fluid but may lead to acute renal failure if pursued too vigorously.

Hyperlipidemia^{35,36}

A host of abnormalities of lipid metabolism exist in patients with nephrotic syndrome. These include elevations in total plasma cholesterol, very low density lipoproteins, intermediate density lipoproteins, low density lipoproteins and lipoprotein A. Triglyceride levels may also be elevated. Levels of high-density lipoproteins are variable.

In steroid responsive nephrotic syndrome raised lipids fall after remission but high levels may persist in patients with heavy proteinuria or those having resistant nephrotic syndrome. Hyperlipidemia may play an important role in the development of glomerulosclerosis and progressive renal injury. The diet should contain less than 30 percent fat and low cholesterol (<200 mg/day). If dietary restrictions are not effective, then cholesterol-lowering agents may be considered. Lipid lowering drugs like atorvastatin (HMG-CoA reductase inhibitor) can be used in the dose of 0.1-0.3 mg/kg/day.

Thromboembolic complications^{37,38}

A number of abnormalities present in the nephrotic state predispose to thrombosis. These include hemoconcentration from hypovolemia, increase in blood viscosity and fibrinogen concentration, and several other abnormalities like low level of antithrombin III and protein S activity. Platelet hyperaggregability also increases the chances of thrombosis. Diuretics should be used judiciously and dehydration should be avoided. Sepsis should be treated promptly. Arterial thrombosis occurs less frequently than venous thrombosis. When the diagnosis of thrombosis is

established a loading dose of heparin 75 units/kg is given IV over 10 minutes followed by a maintenance dose of 20 units/kg/hr. Monitoring of APTT is required while patient is receiving heparin. Low molecular weight heparin (enoxaparin) can also be used in a dose of 1mg/kg/dose given twice a day. On follow up, warfarin can be given orally in dose of 0.2 mg/kg, which is continued for a period of 3-6 months. Warfarin dosage is adjusted according to INR values.

Infection^{39,40}

A number of immunological abnormalities have been documented in patients with nephrotic syndrome which predispose them to infections. These include decreased serum immunoglobulin levels due to urinary losses, impaired antibody generation, defective opsonization due to depressed level of complement factor B and abnormalities of cell mediated immunity. Infection with encapsulated organisms such as *Streptococcus*, *Haemophilus* or *Klebsiella* species is common. Aggressive antibiotic therapy should be instituted at the first suspicion of infection (Table 3).

Abnormalities of Calcium Homeostasis^{41,42}

Hypocalcemia (both total and ionized) and secondary hyperparathyroidism have been variably described in nephrotic syndrome. Potential mechanisms include reduced intestinal absorption of calcium, blunted calcemic response to parathyroid hormone, reduced levels of 25 hydroxycholecalciferol and vitamin D binding globulin (due to loss in the urine). Treatment with oral vitamin D should be prescribed in patients with evidence of hyperparathyroidism, patients with persistently low serum ionized calcium levels and in patients with unremitting or frequently relapsing nephrotic syndrome. Measurement of bone mineral density should be considered in children with persistent nephrotic syndrome

particularly if they have received large doses of steroids over long periods of time.

REDUCTION OF PROTEINURIA⁴³⁻⁴⁵

Persistent heavy proteinuria can cause progressive renal injury. In cases of steroids and immunosuppressant failure some other drugs may be used that can reduce proteinuria and retard the progression of renal disease. Indomethacin and meclofenamate can reduce proteinuria by reducing glomerular filtration and altering the capillary wall permeability, however these drugs are too toxic to be used for long time. Angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB) reduce the amount of filtered protein by causing efferent arteriolar dilation and reducing glomerular filtration pressure. Enalapril in a dose of 0.2 to 0.5 mg/kg/day in 2 divided doses can cause reduction in proteinuria by 30 to 40 percent, increase in serum albumin and reduction in serum cholesterol levels. A combination of ACE inhibitor and ARB enhances the anti proteinuric effect. There are no significant side effects and long-term therapy is safe. Regular monitoring of serum creatinine and electrolytes is necessary.

Recently there has been evidence regarding use of aliskiren (anti renin drug), spironolactone (aldosterone receptor antagonist) and vitamin D and its analogs for anti proteinuric action.

CONGENITAL NEPHROTIC SYNDROME

Congenital nephrotic syndrome starts within the first three months of life or may be present at the time of birth. Finnish type (autosomal recessive) is the most common type of congenital nephrotic syndrome. Some other causes include diffuse mesangial sclerosis, primary FSGS and congenital infections like syphilis, cytomegalovirus, rubella, hepatitis B and toxoplasmosis.

The management is difficult since there is no specific treatment and mostly patients are resistant to steroids and immunosuppressive drugs. Infants with syphilis or toxoplasmosis can be initiated on specific antimicrobials. Treatment is mainly symptomatic. Edema is treated with diuretics (loop and thiazide) and albumin infusions. Dietary management in the form of high protein (3-4 gm/kg/day) and high carbohydrate diet with calcium and vitamin supplements is done. Thyroxine supplements are needed in most of the cases. ACE inhibitors and non-steroidal anti-inflammatory agents can be used to reduce GFR and proteinuria. Unilateral nephrectomy is advised in case of refractory proteinuria. Renal transplantation can be done when the child is little older or is more than 10 kgs in weight.

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Table 3: Management of infections

Site	Common organism	Antibiotic
Peritonitis	<i>E. coli</i> , <i>S. pneumoniae</i> , <i>S. aureus</i>	Ampicillin and aminoglycoside or 3rd generation cephalosporin
Cellulitis	<i>H. influenzae</i> , Grp <i>A streptococcus</i> , β hemolytic <i>streptococcus</i>	Ampicillin and aminoglycoside, coamoxycylav, cefotaxime, ceftriaxone
Urinary tract infections	Gram negative organisms	Cephalexin, amoxycillin, amikacin, coamoxycylav
Pneumonia	<i>S. pneumoniae</i> , <i>H. influenzae</i>	Ampicillin, cephalexin Ampicillin and aminoglycoside Cefotaxime, ceftriaxone

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Renal Replacement Therapy

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INTRODUCTION

The normal kidneys have several functions and play various roles in the normal physiological state in humans. Renal replacement therapy is a form of treatment that intends to replace some or all the functions of the kidney. The best form of renal replacement therapy is a renal transplant, wherein all the functions of the kidney are performed by the transplanted organ. Dialysis is an important form of renal replacement therapy both in acute kidney injury and chronic kidney disease.

Dialysis aims at performing two major functions of the kidney – solute removal—removal of urea, creatinine, middle molecules, acid and thus maintaining acid-base and electrolyte balance and fluid removal.

Renal Replacement Therapy in Acute Kidney Injury

The indications for renal replacement therapy in acute kidney injury (AKI) are:

- Symptoms of uremia
- Fluid overload
- Refractory hyperkalemia
- Refractory acidosis
- Hypercatabolic states
- Requirement of fluids/blood/blood products with oligoanuria.

Note: The degree of reduction in glomerular filtration rate or the degree of rise in creatinine value solely is not considered an indicator for RRT.

Modalities for renal replacement therapy:

- Acute peritoneal dialysis (PD)
- Intermittent hemodialysis (IHD)
- Continuous renal replacement (continuous venovenous hemofiltration [CVVH] hemodiafiltration [CVVHDF])

The choice of modality depends on the clinical condition of the patient, the availability of expertise in the

<i>Modality</i>	<i>In hemodynamic instability</i>	<i>Efficiency</i>	<i>Fluid removal</i>	<i>Anti-coagulation</i>	<i>Easy to perform</i>
Acute PD	Yes	Moderate	Moderate, uncontrolled	No	Easy
IHD	No	High	Moderate, controlled	Yes	Moderate
CVVH	Yes	Moderate	High, controlled	Yes	Moderate
CVV HDF	Yes	High	High, controlled	Yes	Difficult

hospital. The advantages and disadvantages of each of the above modalities is listed in Table 1.

ACUTE PERITONEAL DIALYSIS

Acute peritoneal dialysis is performed by insertion of a stiff polyurethane catheter or a flexible Cook's catheter percutaneously into the peritoneal cavity under local anesthesia and sedation.

The catheters are available in neonatal, pediatric and adult sizes.

Procedure for insertion of PD catheter:

- Procedure is done under sedation and local anesthesia with continuous monitoring
- Empty bladder by catheterization
- Site of insertion: infraumbilical or paraumbilical
- Create artificial ascites by instilling 10 to 20 ml/kg PD fluid into the peritoneal cavity using a 14 to 16 gauge needle
- Using a scalpel make a nick into the skin and subcutaneous tissue up to the rectus sheath
- Insert the PD catheter with stylet into the abdominal wall by a screwing motion till a loss of resistance is felt

- Withdraw stylet for 1 to 2 cm and push the catheter, directing towards left iliac fossa
- Remove stylet after ensuring that all the holes of the catheter are within the peritoneal cavity
- Connect to a 3 way connector-one end serves as inlet and other as outlet for the fluid.

Dialysis Fluid Composition

Dextrose	1.7 g/dl
Sodium	130 mEq/L
Potassium	0
Chloride	100 mEq/L
Acetate/lactate	35 meq/L
Magnesium	1.5 mEq/L
Calcium	3 mEq/L
Osmolality	355 mOsm/kg

The most commonly available PD fluid contains acetate/lactate which is converted in the liver to bicarbonate. Bicarbonate based fluid is more biocompatible and are ideal for PD. Bicarbonate based fluid is preferred in situations with liver dysfunction, lactic acidosis and inborn errors of metabolism.

Bicarbonate based fluid can be prepared using the following formula:

Solution A: 440 ml of 5 percent dextrose + 60 ml sodium bicarbonate.

Solution B: 500 ml of normal saline.

500 ml of solution B + 250 ml of solution A are mixed to obtain a fluid with sodium 140 mEq/L, bicarbonate 40 mEq/L and dextrose 1.5g/dl

Prescription

Initially four to five rapid cycles with a dwell time of 5 minutes can be done to ensure patency of the catheter.

Fill volume	20-40 ml/kg
Solution	1.7%
Fill time (inflow)	5 minutes
Dwell time	30-40 minutes (15-20 minutes in neonate)
Drain time (outflow)	10 minutes

Monitoring

Vitals	Every 30 minutes. Look for signs of respiratory compromise
Random blood sugar	Every 2 hours
Serum electrolytes, ABG	Every 4-6 hours
Serum creatinine, calcium, magnesium	Every 24 hours

Additives to PD

Heparin: 500 to 1000 U/L if PD fluid is hemorrhagic

Potassium: 4 mEq/L if serum potassium is <3.5 mEq/L

Insulin: In case of hyperglycemia.

All the above additives must be added with strict aseptic precautions to reduce the chance of infections.

Contraindications for Peritoneal Dialysis

- Abdominal wall abnormalities – omphalocele
- Diaphragmatic hernia
- Recent abdominal surgery
- Peritonitis.

Trouble Shooting

Obstruction during inflow: Consider blood clot and fibrin clot obstructing the lumen. This can be relieved by flushing the catheter and adding heparin if the fluid is blood stained.

Obstruction during outflow: Consider omentum wrapping around the catheter tip and obstructing outflow – catheter can be repositioned with all aseptic precautions.

Fluid overload: This can be handled by reducing the dwell time or increasing the concentration of dextrose in the PD fluid both of which will increase the ultrafiltration.

Hyperkalemia: Rapid cycles will facilitate removal of potassium. Reduce dwell time to 15 minutes.

Blood stained fluid: Add heparin to the fluid to prevent formation of clots.

Complications of PD

- Mechanical complications: Obstruction of the lumen by blood or fibrin clot, obstruction due to wrapping of omentum
- During insertion of catheter: Bleeding, perforation of bowel, bladder
- Infection: Cellulitis of the abdominal wall, peritonitis
- During removal of catheter: Extrusion of the omentum
- Electrolyte and metabolic abnormalities: Hyponatremia, hypokalemia, hyperglycemia, metabolic alkalosis
- Respiratory embarrassment.

INTERMITTENT HEMODIALYSIS

Intermittent hemodialysis is an effective modality of RRT in children who are hemodynamically stable.

The major advantages are:

- Short duration of therapy
- Effective for rapid treatment of fluid overload, refractory hyperkalemia and refractory acidosis.

The disadvantages are:

- Need for vascular access and anticoagulation
- Needs expertise and equipment along with trained nursing staff.

CONTINUOUS RENAL REPLACEMENT THERAPY

Continuous renal replacement therapy (CRRT) is a very effective modality of renal replacement therapy in acute kidney injury. Continuous veno-venous hemofiltration (CVVH) or hemodialysis (CVVHD) or hemodiafiltration (CVVHDF) are used based on the need for fluid removal alone, predominant solute removal or both respectively.

The major advantages of CRRT are:

- It is a continuous slow mode of RRT, hence suitable in patients with hemodynamic instability.
- It is a preferred mode of RRT in acute poisoning and inborn error of metabolism due to its continuous nature.
- It is the preferred mode of RRT in children with raised intracranial pressure.
- It allows for provision of parenteral nutrition

The major drawbacks are:

- Need for vascular access and anticoagulation
- The lack of expertise, infrastructure in all hospitals
- This therapy is expensive and requires trained nursing staff to conduct it.

RENAL REPLACEMENT THERAPIES IN END-STAGE RENAL DISEASE

- Chronic peritoneal dialysis:
 - Continuous ambulatory peritoneal dialysis (CAPD): This involves cycles of 4 to 8 hours dwell of dialysis fluid in the peritoneal cavity every day
 - Automated peritoneal dialysis (APD): This involves cycles at night time using a machine called the “cycler” and patient may or may not carry fluid in the cavity during the day.
- Hemodialysis and
- Renal transplantation.

Indicators to Initiate Dialysis in Chronic Kidney Disease

- *Laboratory criteria:* GFR <14 ml/min/m², refractory hyperkalemia, hyperphosphatemia and metabolic acidosis.
- *Clinical criteria:* Children with symptoms of nausea, vomiting, malnutrition, growth retardation, fluid overload, hypertension and uremia.

Strengths and limitations of chronic peritoneal and hemodialysis.

RENAL TRANSPLANTATION

Renal transplantation is the best option for children with end-stage renal disease and chronic dialysis should be considered only as a bridge to transplantation. Children are not miniature adults and have issues characteristic to transplantation in terms of the spectrum of native kidney

disease, dynamic phase of growth, pre-transplant work-up, immunization status, nutritional demands, technical expertise and psychosocial support. Children are fortunate to have donors as parents for a better graft survival and need to be on life-long immunosuppression.

Pretransplant Issues

Evaluation of lower urinary tract in children with abnormal urinary tract with deranged bladder function by a pediatric urologist is essential. Interventions to maximize bladder function like augmentation surgery may be required before transplant. Pretransplant native nephrectomy may be considered in patients with massive proteinuria, at risk for pyelonephritis, uncontrolled hypertension or those requiring more than three antihypertensive and to accommodate large donor kidneys in small children.

Operative Skills

Transplantation is usually considered when the weight of the child is above 10 kg. For children less than 15 kg, the transplant is performed through a midline incision and larger vessels like aorta and inferior vena cava are used for anastomosis with donor kidney blood vessels. The transplantation technique for children with body weight greater than 15 kg is similar to adults. Vascular thrombosis and infections are important post-transplant complications in children.

CONCLUSION

Renal replacement therapies form a crucial treatment modality for both acute kidney injury and end-stage renal disease. The responsibility of offering the best suitable and feasible option of renal replacement therapy lies in the hands of the clinician.

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INTRODUCTION

Chronic kidney disease (CKD) refers to a state of irreversible kidney damage and/or reduction of kidney function which can be progressive. The term chronic kidney disease has replaced the clinical terms like chronic renal failure (CRF) and chronic renal insufficiency (CRI) which describe kidney dysfunction of varying degrees from severe to mild in nature. CKD more clearly defines kidney dysfunction as a continuum, rather than a discrete change in kidney function.

DEFINITIONS AND CLASSIFICATIONS

The definition and classification of chronic kidney disease (CKD) was introduced by the National Kidney Foundation (NKF) and Kidney Disease Outcomes Quality Initiative (K/DOQI) in 2002, and were subsequently adopted with minor modifications by the international guideline group Kidney Disease Improving Global Outcomes (KDIGO) in 2004.¹⁻³

The K/DOQI workgroup defined CKD as follows:

- The presence of markers of kidney damage for ≥ 3 months, as defined by structural or functional abnormalities of the kidney with or without a decreased glomerular filtration rate (GFR), that is manifested by either pathological abnormalities or other markers of kidney damage, including abnormalities in the blood, urine, or in imaging tests.

OR

- GFR < 60 ml/min per 1.73 m^2 for ≥ 3 months, with or without kidney damage.

The K/DOQI workgroup developed a classification system for patients greater than two years of age based upon the level of kidney function, which is independent of the primary renal diagnosis. This staging system was aimed at promoting early detection and treatment of CKD. The

stages and their definitions based upon estimated GFR are as follows:

- *Stage 1 disease:* Normal GFR (≥ 90 ml/min per 1.73 m^2)
- *Stage 2 disease:* GFR between 60 to 89 ml/min per 1.73 m^2
- *Stage 3 disease:* GFR between 30 and 59 ml/min per 1.73 m^2
- *Stage 4 disease:* GFR between 15 and 29 ml/min per 1.73 m^2
- *Stage 5 disease:* GFR of less than 15 ml/min per 1.73 m^2 or end stage renal disease (ESRD).

Normal levels of GFR vary with age, gender, and body size. GFR increases with maturation from infancy and approaches adult mean value by two years of age.^{4,5} Children under two years of age do not fit within the K/DOQI classification system because their GFR is normally lower than the GFR of older patients. Thus, the GFR of young children and infants would incorrectly place them in a stage of disease characterized by greater renal impairment than their actual renal function.

In 2004, the Kidney Disease Improving Global Outcomes (KDIGO) group modified the K/DOQI classification system for adults by adding urinary albumin excretion as an additional staging factor to the various levels of GFR. The KDIGO classification system is currently being reviewed for its relevance to pediatric CKD. Currently, the classification of CKD in children remains based on the original K/DOQI system that uses estimated GFR.

EPIDEMIOLOGY

The prevalence of CKD among children is 1.5 to 3 per 1 lakh child population. The incidence and prevalence of CKD is greater in males than females. The increased risk of CKD in males is due to the higher incidence of congenital anomalies of the kidney and urinary tract (CAKUT),

including obstructive uropathy, renal dysplasia, renal hypoplasia, and prune belly syndrome.

In the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) chronic renal insufficiency (CRI) database, which contains over 7000 patients, the age distribution at presentation was as follows:

- Below 2 years of age — 20.1 percent
- 2 years of age to below 6 years of age — 15.9 percent
- 6 years of age to below 13 years of age — 32.1 percent
- 13 years of age to below 18 years of age — 28.2 percent
- 18 to 21 years of age — 3.7 percent.

ETIOLOGY

CKD in children is the result of a heterogeneous group of disorders.

Congenital causes account for almost 60 percent of cases of CKD.⁶⁻⁸ The following distribution of causes is based upon the NAPRTCS CRI database of over 7000 patients who were registered from 1994 to 2008⁷. The distribution of causes varies with age.

- Congenital renal anomalies were present in 57 percent of cases. These anomalies included obstructive uropathy (21 percent), renal aplasia/hypoplasia/dysplasia (18 percent), reflux nephropathy (8 percent), and polycystic kidney disease (4 percent).
- Glomerular disease was present in 17 percent of patients. It was more common in older children, accounting for approximately 45 percent of cases in patients greater than 12 years of age.
- Focal segmental glomerulosclerosis (FSGS) was the most common glomerular disorder occurring in 9 percent of all CKD cases. African-American children were three times more likely to develop FSGS than Caucasian patients (18 versus 6 percent), and FSGS was the cause of CKD in one-third of African-American adolescent patients.
- Other causes accounted for approximately 25 percent of cases. In 18 percent of all cases of CKD, the underlying primary diagnosis was not identified (15 percent) or was unknown (3 percent). Other more uncommon causes of CKD in children included hemolytic-uremic syndrome, genetic disorders (e.g. cystinosis, oxalosis, and hereditary nephritis (also referred to as Alport's syndrome)), and interstitial nephritis. Unlike adults, diabetic nephropathy and hypertension were rare causes of CKD in children.

NATURAL HISTORY AND PROGRESSION OF CHRONIC KIDNEY DISEASE

The natural history of renal disease is variable and, at times, unpredictable. The initial injury to the kidney may result in a variety of clinical manifestations. In some cases, individuals may fully recover and suffer little or no sequel,

like patients with post streptococcal glomerulonephritis or in most children with hemolytic-uremic syndrome.

In children with CKD, the persistent deterioration of renal function may be a result of repeated and chronic insults to the renal parenchyma leading to permanent damage and/ or to the adaptive hyperfiltration response of the kidney, which compensates for the loss of nephrons from the initial injury.⁹

Over time, however, the enhanced transglomerular ultrafiltration and glomerular pressure leads to glomerular damage and leakage of protein resulting in interstitial inflammation and fibrosis. This long-term injury is characterized histologically by glomerulosclerosis, vascular sclerosis, and tubulointerstitial fibrosis,¹⁰⁻¹² and clinically by proteinuria and progressive renal insufficiency (Fig. 1).

The rate of progression of CKD is usually greatest during the two periods of rapid growth, infancy and puberty, when the sudden increase in body mass results in a rise in the filtration demands of the remaining nephrons. As a result, children with CKD should be closely monitored during these two periods for an accelerated progression of CKD. In addition to the increase in body mass, hormonal changes during puberty may also contribute to the rapid decline in renal function seen in adolescence.

The rate of progression to ESRD in childhood is inversely proportional to the baseline creatinine clearance (CrCl) at presentation. In addition, genetic, familial or ethnic predisposition may influence the rate of renal decline. Other factors associated with an increase in the rate of CKD progression include primary disease, hypertension, proteinuria, anemia, hyperphosphatemia and hypocalcemia.¹³

Despite the high mortality rates of very young children with ESRD, good long-term outcomes can be achieved.

CLINICAL PRESENTATION

The clinical presentation of CKD is dependent upon the severity of renal impairment and the underlying disorder.

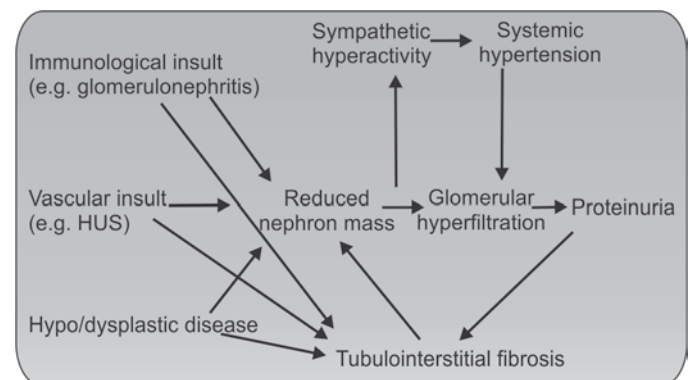


Fig. 1: Mechanism of progression of chronic kidney disease

Patients presenting during the early stages of CKD (e.g. stages 1 and 2) are typically asymptomatic. As CKD progresses and renal function deteriorates, patients become increasingly symptomatic.

In view of the heterogeneity of causes for pediatric chronic kidney injury, signs and symptoms vary and include different amounts of urine output (polyuria, oliguria, or anuria), edema, hypertension, and/or discolored urine. Patients with glomerular disease may present with hematuria, proteinuria, hypertension, and edema in the early stages of CKD, which may persist into later stages.

Patients with renal disease may present in a variety of ways:

- Polyuria may be an early presenting finding because many congenital anomalies of the kidney and urinary tract (e.g. obstructive uropathy), inherited disorders (e.g. nephronophthisis), and tubulointerstitial disorders are associated with reduced concentrating ability (i.e. nephrogenic diabetes insipidus). In these conditions, the impairment in renal concentration generally precedes a significant reduction in GFR.
- Elevation in the serum creatinine concentration and/or abnormalities on urinalysis.
- Proteinuria is a strongly-associated biomarker of CKD and is a possible sign of underlying glomerular disease or tubular dysfunction. Persistent (≥ 3 months) increased excretion of urinary protein in a nonorthostatic pattern is indicative of CKD.¹⁴
- Detection of congenital or structural anomalies by imaging studies, particularly prenatal ultrasonography.
- Poor growth is a common manifestation of CKD in children.
- Symptoms and/or signs of severe renal impairment or renal failure begin to appear in some patients with stage 3 disease and are present in those with stages 4 and 5 disease. These symptoms (referred to as symptoms of uremia) include anorexia, and vomiting, weakness and easy fatigability. Other findings attributable to the uremic state include pericarditis, deficits in neurocognitive function and osteodystrophy.
- Systemic symptoms and findings like fever, arthralgias/ arthritis, rash or pulmonary symptoms, depending upon the concurrent systemic disease that affects renal function resulting in CKD, such as lupus nephritis or Wegener's granulomatosis.

COMPLICATIONS OF CHRONIC KIDNEY DISEASE

A moderate to severe loss of GFR (i.e. stage 3 to 5 disease), is associated with a number of complications due to impairment of the many functions performed by the kidney. These complications may be the presenting sign or symptom of CKD and include:

- Disorders of fluid and electrolytes—hyponatremia or hypernatremia, hypokalemia or hyperkalemia, metabolic acidosis, fluid overload
- Disorders of mineral metabolism and renal osteodystrophy
- Anemia
- Hypertension
- Dyslipidemia
- Endocrine abnormalities—abnormalities of thyroid hormone, growth hormone and gonadal hormones metabolism
- Growth impairment
- Decreased clearance of renally excreted substances from the body (uremia).

EVALUATION AT PRESENTATION

The evaluation of a child with CKD begins with a history and physical examination. Imaging and laboratory evaluation are useful to determine the underlying cause of CKD, severity of renal impairment and whether any associated complications of CKD are present.

Clinical Evaluation

History

The history should include documentation of the age at onset of symptoms, duration of symptoms, type of symptoms due to uremia (weakness, fatigue, anorexia, or vomiting), systemic diseases (fever, rash, or arthralgias/ arthritis), or specific renal disorders (e.g. glomerulonephritis with hematuria and/or edema).

The history is focused on signs of CKD or factors that increase the risk of CKD, the list of which should include the following:

- Family history of renal disease or hypertension
- Growth history, particularly poor linear growth
- Polyuria, polydipsia or enuresis
- Elevated blood pressure
- Antenatally diagnosed congenital anomaly of the kidney or urinary tract (CAKUT)
- Orthopedic or urologic abnormalities
- Recurrent urinary tract infection
- Unexplained anemia
- Seizures
- Fluid and electrolyte disorders.

Physical Examination

The physical examination of any child suspected of having CKD should include:

- Measurement of growth parameters (height, weight, and for patients ≤ 5 years of age, head circumference), as these children are at risk for poor growth.
- Blood pressure measurement, as hypertension often occurs in children with CKD due to underlying renal

pathology, hypervolemia due to impaired water excretion or certain medications.

- Pallor as an indication of anemia should be assessed.
- Examination of the extremities for any deformity as an indication of chronic kidney disease—metabolic bone disease (CKD-MBD) or edema as an indication of nephrotic syndrome. The site and type of deformity of the extremities depend upon the age of the child and the weight-bearing patterns in the limbs, and are similar to those found in children with rickets. Thus, deformities of the forearms and posterior bowing of the distal tibia are found more commonly in the infant, whereas an exaggeration of the normal physiological bowing of the legs (genu varum) is a characteristic finding in the toddler who has started to walk. In the older child, valgus deformities of the legs or a windswept deformity (valgus deformity of one leg and varus deformity of the other) may be apparent.
- Assessment for any sign of hypervolemia by noting the presence/absence of edema, rales, hepatic enlargement/tenderness, or cardiac gallop.
- Cardiac auscultation to detect a pericardial rub due to pericarditis or diminished heart sounds secondary to a pericardial effusion.

Imaging

Imaging may be useful in identifying the underlying cause of CKD and assessing a decrease in renal parenchyma.

Ultrasonography (US) is the most widely used modality and is a noninvasive procedure. It assesses the growth and the structure of the kidneys. The ultrasound examination should compare the measured length of each kidney to normative age-appropriate values.¹⁵⁻¹⁷ Kidneys that are smaller than normal indicate a decrease in renal mass due to congenital maldevelopment (e.g. renal hypoplasia), poor growth, or loss of nephrons due to an underlying disorder or injury.

Other imaging studies include voiding cystourethrogram (VCUG), computed tomography (CT), and magnetic resonance imaging (MRI), which are used in specific clinical settings, or when better resolution or visualization is required than that provided by ultrasonography.

Laboratory Testing

Depending on the type of kidney disease, blood and urine studies are often used to support the diagnosis of CKD.

- *Serum creatinine:* To know the degree of renal damage and for calculation of GFR.
- *Electrolytes:* To detect electrolyte abnormalities, particularly hyperkalemia and metabolic acidosis.
- *Complete blood count:* To detect anemia.
- *Red blood cell indices:* If the red blood cell indices are not consistent with a normocytic and normochromic anemia, which usually characterizes the anemia of CKD, then another cause of anemia should be considered.

- Reticulocyte count.
- Tests to determine iron status (serum iron, total iron binding capacity, percent transferrin saturation)
- Test for occult blood.
- Serum calcium, phosphorus, 25-hydroxyvitamin D, and parathyroid hormone level to detect any abnormalities in bone mineral metabolism.
- Fasting lipid profile that includes total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG) to detect the presence of dyslipidemia.
- *Urinalysis:* Urinalysis is a useful screening test for abnormalities of the kidney and urinary tract, and as an aid in identifying the underlying cause of CKD. The urinary dipstick makes it possible to test for protein, pH, concentration, glucose, hematuria, and pyuria. Different patterns of urinary findings are associated with both acute and chronic kidney disease.
- Proteinuria is an indicator of underlying glomerular disease and/or tubular dysfunction, and is an important biomarker strongly associated with CKD. Ongoing urinary protein excretion may contribute to the progression of CKD. The severity of renal disease is generally associated with the amount and duration of proteinuria. Therefore, persistent high-grade proteinuria (2+ protein or greater) usually warrants a prompt evaluation for other signs of renal dysfunction. Lower levels of protein detected by urinary dipstick can usually be followed with repeated measurements to determine if there is resolution of proteinuria. The presence of persistent proteinuria by dipstick evaluation should be quantified by determination of the urine protein/creatinine ratio.
- *Kidney biopsy:* Tissue samples obtained via kidney biopsy are typically evaluated by light microscopy, immunofluorescence staining and electron microscopy. Data from these studies may be useful in providing a diagnosis for the cause of CKD and guiding therapeutic choices.

MANAGEMENT

General Principles

The general management of the patient with CKD includes the following components:

- Treat reversible kidney dysfunction
- Prevent or slow the progression of kidney disease
- Treat the complications of CKD
- Identify and adequately prepare the child/family in whom renal replacement therapy will be required.

The timing of implementing these components varies primarily upon the severity of CKD.

In the early stages of CKD, there is an opportunity to treat any reversible cause of kidney dysfunction, and prevent or slow the progression of kidney disease. Children with stages 1 and 2 disease are asymptomatic and should be

closely followed for deterioration of kidney function. This period should also be used to educate the child and family about CKD, highlighting awareness of risk factors that can aggravate kidney failure (e.g. nephrotoxic drugs, recurrent infections, dehydration) and of measures that may slow the progression of kidney failure (e.g., blood pressure control).

CKD-associated complications begin to appear as CKD progresses into stage 3. These include disorders of fluid and electrolytes, renal osteodystrophy, anemia, hypertension, dyslipidemia, endocrine abnormalities, growth impairment, and disorders due to the decreased clearance of substances normally excreted from the body by the kidney (uremia). In these patients, management is focused on preventing and treating these complications.

Patients who will require renal replacement therapy (RRT) should be identified well in advance of the time that RRT is required so that adequate preparation and education can be provided to both the patient and family. This generally occurs in patients with stage 4 CKD.

Reversible Kidney Dysfunction

In children with CKD, identification and treatment of reversible causes of acute or chronic kidney dysfunction may result in some recovery of kidney function, if addressed early in the course.

The most common conditions with potentially recoverable kidney function are primarily due to decreased kidney perfusion or the administration of nephrotoxic agents.

- *Decreased kidney perfusion:* Kidney hypoperfusion is produced by hypotension (e.g. septic shock), volume depletion from vomiting, diarrhoea, diuretic use, or bleeding, and the administration of drugs that lower the kidney perfusion (such as nonsteroidal anti-inflammatory drugs, angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs)).
- If significant hypovolemia accompanied by a reduction of GFR occurs, a judicious trial of fluid repletion may result in the return of kidney function to the previous baseline.
- *Administration of nephrotoxic drugs:* Common nephrotoxic drugs include nonsteroidal anti-inflammatory agents, diagnostic agents (e.g. radiographic contrast materials), and others (e.g. aminoglycosides, amphotericin B, cyclosporine, and tacrolimus). The administration of such drugs, therefore, should be avoided or used with caution in patients with underlying CKD, with the assistance of therapeutic drug level monitoring.

Slowing CKD Progression

In patients with CKD, progressive long-term kidney damage is in part due to adaptive hyperfiltration with increased intraglomerular perfusion and pressure. The kidney injury is manifested histologically by glomerular scarring (glomerulosclerosis). The progression of CKD is

greatest during the two periods of rapid growth: infancy and puberty. These events place increased demands upon the preexistent compromised kidney function.

Blood Pressure Control

In CKD, strict blood pressure control has been shown to slow the progression of kidney disease and reduce the risk of cardiovascular disease. In particular, ACE inhibitors and ARBs have been suggested as antihypertensive therapy to reduce proteinuria and control blood pressure in these patients.

Other Interventions

Additional interventions include lipid lowering therapy and correction of anemia. In relation to protein intake, the current consensus by pediatric nephrology experts is to provide children with CKD the age appropriate recommended daily allowance for protein.

CKD COMPLICATIONS

A wide range of complications result as a consequence of the loss of kidney function. These include disorders of fluid and electrolyte balance, renal osteodystrophy, hypertension, anemia, dyslipidemia, growth impairment, malnutrition and risk of poor neurodevelopmental outcome.

Sodium and Intravascular Volume

As GFR becomes severely decreased (i.e. stages 4 and 5 disease), water and sodium retention may result in volume overload. In general, a combination of dietary sodium restriction and diuretic therapy may correct the increased water balance and prevent water retention from recurring.

Diuretic therapy includes either loop diuretics such as furosemide given at a dose of 0.5 to 2 mg/kg per day or thiazide diuretics such as hydrochlorothiazide at 1 to 3 mg/kg per day. Thiazide diuretics are usually used in the early stages of CKD and a loop diuretic in the more advanced stages of disease when the thiazides are less effective. Both classes of diuretics become less effective with decreasing GFR.

Some children with obstructive uropathy and/or dysplastic kidneys have poor urinary concentrating capacity and exhibit urinary sodium wasting, resulting in a propensity for hypovolemia and hyponatremia. In these children the need for fluid replacement should be emphasized to the caretakers, especially when the child has an intercurrent illness that increases volume losses (e.g. diarrhea) or decreases fluid intake (e.g. vomiting).

Hyperkalemia

Hyperkalemia develops primarily because of inadequate potassium excretion due to a reduced GFR. Other factors that can contribute to elevated potassium levels include a high dietary potassium intake, increased tissue breakdown,

metabolic acidosis, hypoaldosteronism (due in some cases to administration of an ACE inhibitor or an ARB), or an impaired cellular uptake of potassium.

Management to prevent hyperkalemia in children with CKD consists of the following:

- Low potassium diet.
- Administration of a loop diuretic (e.g. furosemide) to increase urinary potassium loss.
- If there is metabolic acidosis, oral sodium bicarbonate to correct acidosis.
- In infants under selected circumstances, formula can be mixed with sodium polystyrene sulfonate and decanted externally to decrease the potassium content of the formula prior to feeding.¹⁸ The use of sodium polystyrene sulfonate in this manner is a common practice in many pediatric nephrology centers.

Renal replacement therapy must be considered if conservative management fails to control hyperkalemia.

Hypokalemia is uncommon in children with CKD. However, it can be observed in children in the early stages of CKD associated with Fanconi syndrome, renal tubular acidosis, or from excessive diuretic therapy.

Metabolic Acidosis

In children, overt acidosis is characteristically present when the estimated GFR is less than 30 ml/min per 1.73 m² (i.e. stage 4 disease). Acidosis is associated with growth impairment because the body utilizes bone buffering to bind some of the excess hydrogen ions.

Current guidelines by the K/DOQI working group are to maintain the serum bicarbonate level at or above 22 mEq/L.¹⁹ Sodium bicarbonate therapy is suggested in patients with metabolic acidosis to achieve this targeted goal.¹⁹ Sodium bicarbonate therapy is started at 1 to 2 mEq/kg per day in two to three divided doses, and the dose is titrated to the clinical target.

Bone Metabolism and Bone Disease

Changes in mineral metabolism and bone structure are an almost universal finding with progressive CKD due to abnormalities in the metabolism of calcium, phosphate, vitamin D, and parathyroid hormone (PTH) levels.^{19,20} If these abnormalities are not addressed, these changes result in kidney bone disease, referred to as renal osteodystrophy. Significant morbidity may be associated with renal osteodystrophy, including growth failure, avascular necrosis, skeletal fractures and deformities.

Hypertension

Strict blood pressure control is recommended in all children with CKD. Treatment of hypertension should include specification of target blood pressure levels, nonpharmacologic therapy and antihypertensive therapy.

Target Blood Pressure Goals

In children with CKD, the National High Blood Pressure Education Program Working Group (NHBPEP) has recommended a reduction in blood pressure to below the 90th percentile based upon the age, gender, and height of the patient.²¹ The K/DOQI guidelines also recommend a target systolic and diastolic blood pressures of less than 90th percentile for age, gender, and height, or less than 120/80 mm Hg, whichever is lower.

Therapeutic Interventions

Therapy includes both nonpharmacologic and pharmacologic interventions:

- *Nonpharmacologic therapy:* Treatment should be initiated with conservative measures such as weight reduction, exercise and dietary salt reduction. The current recommendation for adequate daily sodium intake is only 1.2 g/day for four to eight year olds and 1.5 g/day for older children.²¹
- *Pharmacologic therapy:* The ACE inhibitors or angiotensin II receptor blockers (ARBs) may be used for treatment of hypertension in the earlier stages of CKD. They are the preferred antihypertensive agents as they appear to be more beneficial in slowing the progression of CKD compared to other agents in patients with CKD.²²⁻²⁵ Enalapril is often started at an initial dose of 0.08 mg/kg per day (maximum of 5 mg/day), and is titrated to a maximum dose of 0.6 mg/kg per day (maximum of 40 mg/day) based upon the response of the patient's blood pressure and results of lab tests (e.g. serum potassium). Enalapril is used because its long half-life and it allows once a day dosing. Alternatively we can use other long-acting ACE inhibitors like lisinopril and ramipril.

Both ACE inhibitors and ARBs should be used cautiously if the GFR is less than 60 ml/min per 1.73 m².²⁵ Since the decline in GFR induced by an ACE inhibitor typically occurs within the first few days after the onset of therapy, the serum creatinine and potassium concentrations should be remeasured three to five days after the institution of therapy to ensure that the therapy has not adversely affected the GFR resulting in elevation of serum creatinine and/or hyperkalemia.

A diuretic is also often recommended in the early stages of CKD. The thiazide diuretics, such as hydrochlorothiazide (1–3 mg/kg per day to a maximum of 50 mg/day), become less effective as monotherapy as the GFR declines. Thus, a loop diuretic is recommended for the treatment of hypertension and edema in patients with more severe CKD. Preferred loop diuretic is furosemide at a dose of 0.5 to 2 mg/kg per day in one to two divided doses.

Anemia

Anemia due to reduced kidney erythropoietin production generally develops when the GFR is below 30 ml/min per 1.73 m². The presence of anemia in children with CKD is very common and has been associated with excessive morbidity and an increased mortality risk.²⁶

Because anemia is a common complication of children with severe CKD (i.e. stages 4 and 5), the K/DOQI work group established guidelines for the identification, evaluation, and treatment of anemia in children at all stages of CKD.²⁷ The recommendations for the management of anemia presented here are based upon these guidelines.

Screening and Evaluation of Anemia

Annual testing of hemoglobin (Hgb) should be performed in children with CKD, regardless of stage or cause.

A diagnosis of anemia is made when the observed hemoglobin result is below the fifth percentile of normal adjusted for age and sex. Once anemia is detected in a child with CKD, the following evaluation, which is focused upon eliminating causes of anemia other than CKD and determining the iron status of the patient, is recommended:

- Red blood cell indices
- Reticulocyte count
- Iron parameters (serum iron, total iron binding capacity, percent transferrin saturation (TSAT) and serum ferritin)
- Test for occult blood in stool.

Treatment of Anemia

The treatment of anemia in children with CKD often includes iron supplementation and erythropoiesis stimulating agent (ESA).

Iron therapy (elemental iron 3–4 mg/kg per day) should be initiated if iron deficiency is detected. Iron supplementation is targeted to maintain a TSAT \geq 20 percent and serum ferritin \geq 100 ng/dL in children with CKD. All patients receiving therapy with an ESA, such as recombinant human erythropoietin (rHuEPO) and darbepoetin alfa, require iron supplementation to prevent the development of iron deficiency. Once iron status is normal, it should be monitored at least every three months, or monthly following the initiation of and/or increase in ESA dosing.

Increasing the hemoglobin (Hgb) into an acceptable range in patients with anemia may ameliorate anemia-induced symptoms (e.g. fatigue and exercise intolerance), result in cardiovascular improvement and possibly decreased mortality. K/DOQI guidelines, recommend a target hemoglobin between 11 and 12 g/dL based upon consensus expert opinion.^{27,28}

The initial rHuEPO dose in older children not receiving dialysis is 80 to 120 u/kg per week, administered in two

to three divided doses. Children younger than five years of age or children receiving dialysis frequently require higher doses (300 u/kg per week). In predialysis patients and in those who receive peritoneal dialysis, rHuEPO should preferably be administered by the subcutaneous route and the site of injection should be rotated. In patients who receive hemodialysis, erythropoietin is typically administered intravenously through their vascular access.

Darbepoetin alfa is a long-acting erythropoietic agent. Its threefold longer half-life and greater biological activity compared to recombinant erythropoietin allows for less frequent dosing to effectively maintain a target Hgb. Based upon limited pediatric data, darbepoetin alfa can be given at a dose of 0.25 to 0.75 mcg/kg once weekly.^{29,30}

Dyslipidemia

Abnormal lipid metabolism is common in patients with CKD and adds to the risk for cardiovascular disease (CVD) in children with CKD. K/DOQI, the American Heart Association (AHA) and the American Academy of Pediatrics (AAP) recommend that all adolescents with CKD should be evaluated for dyslipidemia.^{19,31,32} Evaluation is performed by obtaining a fasting lipid profile that includes total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG) at presentation, and annually thereafter or two to three months following a change in treatment or subsequent to the presentation of another condition known to cause dyslipidemia.

The following treatment guidelines have been suggested by the AHA and the AAP for children with CKD and dyslipidemia based upon a literature review by an expert panel:³²

- **Fasting TG >150 mg/dL:** Interventions initially include therapeutic lifestyle changes, such as a decreased intake of simple sugars; in patients with TG >700 mg/dL consider administration of a fibric acid, such as gemfibrozil or fenofibrate.
- **HDL <35 mg/dL:** Therapeutic lifestyle changes, such as vigorous daily physical activity of greater than 60 minutes, weight loss, and dietary substitution of monounsaturated for saturated fatty acids.
- **LDL \geq 100 mg/dL:** Therapeutic lifestyle changes including a low-saturated-fat, low-cholesterol diet and a daily exercise regimen. In children greater than 8 years of age, the use of statin therapy can be considered.

Nutrition

Malnutrition is common in children with CKD because of poor appetite, decreased intestinal absorption of nutrients, and metabolic acidosis. Attention to nutrition is critical as it affects both the physical growth and neurocognitive development of children.

Energy

The initial prescribed energy (calorie) for children with CKD is based upon the estimated energy requirement (EER) for chronological age.¹⁹ Further supplementation should be considered when the initial intake fails to meet the child's energy requirements and he/she is not achieving expected rates of weight gain and/or growth. Although supplementation by the oral route is preferred, one may have to resort to tube feedings with a nasogastric tube, transpyloric tube, or gastrostomy to ensure adequate energy intake. A trial of intradialytic parental nutrition may be considered in children undergoing chronic hemodialysis therapy.

Protein

Protein intake should be between 100 and 140 percent of the Dietary Reference Intake (DRI) based upon age and gender for children with CKD stage 3 and between 100 and 120 percent for those with CKD stages 4 and 5.¹⁹ Protein restriction is not recommended in children as it has not been shown to influence the decrease in kidney function in children with CKD. Supplementation should be considered if the oral and/or enteral protein intake is inadequate.^{19,33,34}

Vitamins and Minerals

Children with CKD should receive 100 percent of the DRIs for the vitamins, thiamine (B1), riboflavin (B2), pyridoxine (B6), vitamin B12, A, C, E, K, and folic acid, and the minerals, copper and zinc.¹⁹ In children with advanced CKD (i.e. stage 5), the loss of renal clearance of vitamin A metabolites places these children at risk for developing hypervitaminosis and these children should receive a water-soluble vitamin supplement.

Growth

Growth failure has been long recognized in children with CKD. While the institution of recombinant human growth hormone (rHuGH) therapy can have a profound effect on the height velocity of children with CKD who are growing poorly, early recognition and management of malnutrition, renal osteodystrophy, acid-base abnormalities and electrolyte disturbances should take place prior to considering the institution of rHuGH.

The use of rHuGH is continued until the child reaches the 50th percentile for mid-parental height, achieves a final adult height with closed epiphyses or receives a kidney transplant. The initial dose of rHuGH in children with CKD is currently 0.05 mg/kg per day (which corresponds to 4 IU/day per m² body surface area or 1 IU/kg per week); rHuGH is given daily via subcutaneous injections.

Neurodevelopment

Uremia is associated with alterations in cognition and may impact neurodevelopment in children. Neurologic findings can range from seizures and severe intellectual disability (mental retardation) to subtle deficits resulting in poor school performance.³⁵

Neurodevelopmental impairment can be minimized by optimizing nutritional, dialysis, and anemia management. In infants and young children, frequent monitoring of head circumference and age-appropriate developmental evaluations are necessary. The cognitive disturbance in an older child may present with abnormal performance on tasks of verbal abstract ability, visual perceptual reasoning, memory, and visual motor skills. A more formal neurodevelopmental assessment is needed in older children, especially if they have poor school performance. Educational support can be obtained by referral to early intervention programs for infants and young children or special education school services.

Uremic Bleeding

An increased tendency for bleeding is present in patients with severe CKD due primarily to abnormalities in platelet adhesion and aggregation properties. In asymptomatic patients, no specific therapy is required.

However, in patients who are actively bleeding or who are about to undergo a surgical or invasive procedure (such as renal biopsy), the platelet abnormality should be addressed. A number of different treatment options can be considered in this setting. These include the following:

- Desmopressin (dDAVP), an analog of antidiuretic hormone that is the simplest and least toxic acute treatment. It is administered intravenously or subcutaneously at a dose of 0.3 mcg/kg with an onset of effect within one hour of administration; the effect lasts for six to eight hours.
- Cryoprecipitate (1–2 units/10 kg); the effect lasts for 24 to 36 hours.
- Estrogen (0.6 mg/kg per day for 5 days); the onset of effect is over 6 to 24 hours, but the effect lasts for two to three weeks.
- Correction of anemia; an improved hemoglobin (hematocrit) is believed to facilitate increased interaction between platelets and blood vessels.

Uremic Pericarditis

Uremic pericardial disease (pericarditis and pericardial effusion) is seen only in the late stages of CKD and is an indication to institute dialysis. Most patients with uremic pericarditis respond rapidly to dialysis with resolution of chest pain as well as a decrease in the size of the pericardial effusion.

Renal Replacement Therapy

Once the estimated GFR declines to less than 30 mL/min per 1.73 m² (stage 4 CKD), it is time to start preparing the child and the family for renal replacement therapy.¹ The family should be provided with information related to pre-emptive kidney transplantation, peritoneal dialysis and hemodialysis.

As in adults, some form of renal replacement therapy will generally be needed when the GFR falls below 15 mL/min per 1.73 m² (stage 5 CKD). However, renal replacement therapy is often initiated before children reach these levels for the following reasons:

- Poor total calorie intake resulting in failure to thrive
- Clinical symptoms attributable to uremia
- Delay in psychomotor development and/or educational issues from progressive CKD.

Choice of Renal Replacement Therapy

The choice of replacement therapy in children is variable. The registry of the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) reports that of patients initiating renal replacement therapy in pediatric centres:^{7, 36}

- One quarter of children underwent pre-emptive renal transplantation
- One half were started on peritoneal dialysis
- One quarter were started on hemodialysis.

The high incidence of pre-emptive renal transplantation in children is due to having parents who are a half haplotype match, who are relatively young and healthy, and are willing to donate a kidney. In addition, pediatric nephrologists frequently follow their patients from the early stages of CKD and can prepare the patient and their family for transplantation and avoid initiating dialysis.

When pre-emptive transplantation is not an option, the choice between the two forms of dialysis is generally dictated by technical, social, compliance issues and family preference. Peritoneal dialysis is much more common in infants and younger children,³⁷ in large part due to problems of vascular access; hemodialysis becomes more common in older adolescents. However, hemodialysis can be performed successfully in infants and very young children, as well.³⁸

Children who elect to receive hemodialysis will need evaluation of their vasculature for placement of an arteriovenous (AV) fistula, arteriovenous graft or cuffed double lumen catheter. The use of an AV fistula, the recommended type of vascular access in adults, is limited in children due to the size of their vessels. In the 2008 NAPRTCS annual report, vascular access for hemodialysis included external percutaneous catheter in 77.7 percent of patients, internal AV fistula in 12.3 percent, and internal and external AV shunt in 7.3 and 0.7 percent, respectively.⁷ K/DOQI has recently encouraged greater use of AV fistulas in larger children receiving hemodialysis who

are not likely to receive a transplant within 12 months, with a goal of achieving more effective dialysis with fewer complications (e.g. infection) than occurs with catheters.

Children who are to initiate peritoneal dialysis undergo abdominal surgery for placement of a peritoneal dialysis catheter. Peritoneal dialysis is more common in infants and young children than hemodialysis due to the above mentioned vascular access problem. Peritoneal dialysis can be performed by parents at home, overnight with a cycling machine. The use of a cycler potentially allows the least disruption of home life, school, and work attendance, when compared to ambulatory peritoneal dialysis, which often requires a peritoneal dialysis exchange procedure to be conducted during the daytime, or hemodialysis, which usually requires three weekly treatments of at least three to four hours (not counting travel time). In addition, access to a nearby hemodialysis centre may not be readily available to patients and their families or the centre personnel may not be trained to care for children, especially prepubertal children and infants.

Quality of Life

CKD, as is true for any chronic condition, impacts on the quality of life for both the child and family. A survey of 402 families of 2 to 16 year old children with mild to moderate CKD (median GFR 42.5 mL/min per 1.73 m²) of median duration of seven years found an overall low health related quality of life in children with CKD.³⁹ They scored lower compared to their healthy peers in all of the four domains tested: physical, school, emotional, and social.

In particular, psychological and social stresses are found in children with CKD and their families. The normal progression of the child to independence is impeded, and concerns about body composition and image are greatly magnified in children whose growth and pubertal development are delayed or altered. The prospect of a lifetime with renal replacement therapy (dialysis and/or transplant) and the potential for catastrophic complications and/or death makes it difficult to achieve normal childhood and adolescent developmental goals.^{40,41}

This difficulty continues into adulthood as demonstrated in a study of 144 adults who had childhood ESRD.⁴² Compared to age-matched population normative data, these patients were twice as likely to be unemployed (19 versus 11%), and those who were employed were at a lower occupational level.

The negative impact of chronic disease on the emotional status of the patient's siblings is also well recognized.⁴³ These siblings frequently feel "neglected" because the parents must provide substantial physical and psychological support to the sick child. Furthermore, the well child may simultaneously feel jealous of the attention provided to the sick child, as well as guilt about being well while the sibling is severely ill.

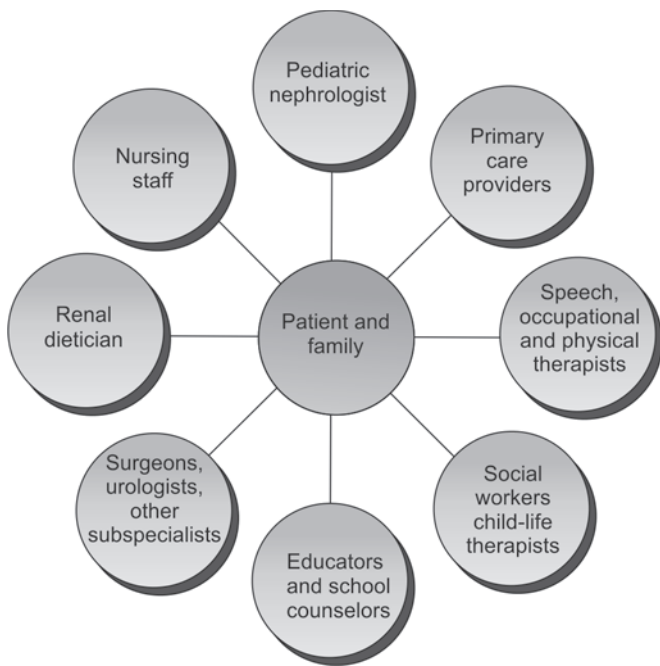


Fig. 2: Multidisciplinary care model for children with chronic kidney disease

Optimal comprehensive management of these issues involves a multidisciplinary approach that proactively addresses these concerns (Fig. 2). Key members of the team include social workers and mental health specialists.

When, on a rare occasion, parents of a child with stage 5 CKD elect conservative management and death over a lifetime of dialysis and transplantation for their child, this should be considered a choice that may, on occasion, be medically, ethically and legally acceptable. A host of factors need to be considered by the family, the healthcare providers, and often the institution's ethics committee. When a decision to forego renal replacement therapy is deemed acceptable, the family should be supported emotionally and provided with whatever care is necessary to maintain the child in a pain-free state.⁴⁴

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Voiding Disorders in Children

Madhuri Kanitkar, H Ravi Ramamurthy

INTRODUCTION

The urinary bladder is an organ interspersed between the kidneys and the external environment to ensure continence, i.e. to void at an appropriate place and time. The genitourinary system controlled by complex neural pathways ensures this function. An aberration of this mechanism, once bladder control has been achieved results in a voiding disorder. These children may present with nocturnal enuresis, altered voiding frequency, day time incontinence, urgency, hesitancy, straining, weak stream, holding maneuvers, a feeling of incomplete emptying, postmicturition dribble and genital or lower urinary tract (LUT) pain. These features may be seen in isolation or in varied combinations in a child. Such children suffer physical discomfort, psychological distress and may result in irreversible damage to the urinary system including renal failure. Recent studies have shown that untreated voiding disorders in childhood affects multiple systems, notably bowel, bladder, sexual and ejaculatory function, blood pressure, and even mood and behavior even in adult life.¹ Therefore, the usual approach of “*the child will grow out of it*” or “*they would not be wetting themselves on their wedding day*” needs to be replaced by a caring, scientific approach on part of the pediatrician with the involvement of parents and the child in treatment of this disorder.

NORMAL VOIDING AND ITS CONTROL

The main functions of the urinary bladder are storage and expulsion. At birth, micturition occurs spontaneously as a spinal cord reflex. Between one and two years of age there is a gradual increase in the bladder capacity along with neural maturation of the frontal and parietal lobe. The fully mature system has a normal bladder capacity, voluntary control of the external sphincter and an ability of the cerebral cortex to initiate and inhibit a detrusor contraction for any bladder capacity² (Fig. 1).

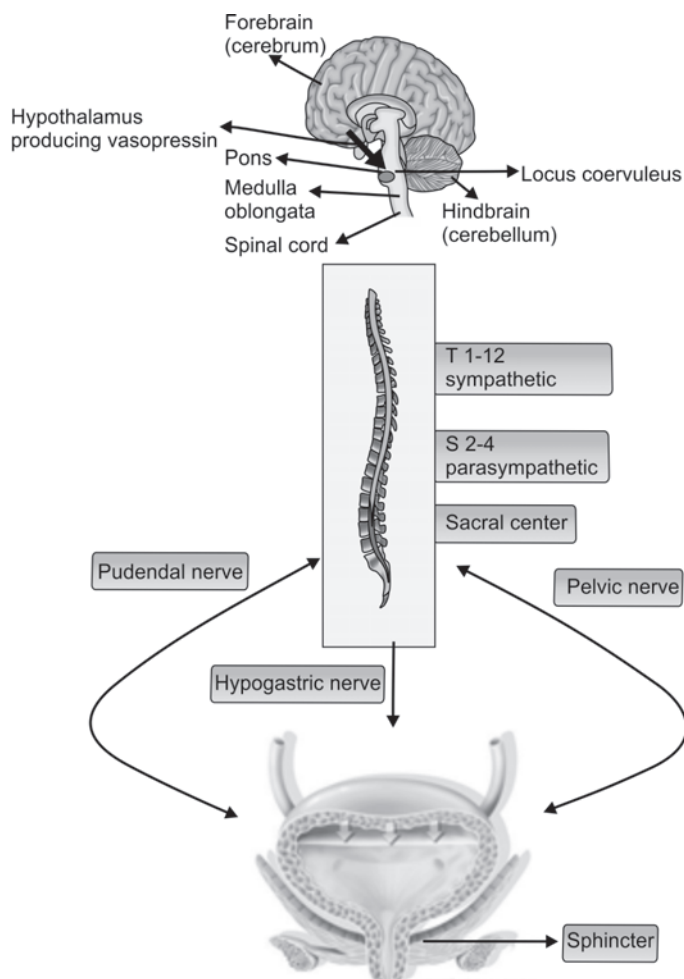


Fig. 1: The neurological control of Micturition: Coordinated contraction of detrusor muscles along with relaxation of the bladder sphincter is necessary for micturition. The sympathetic system is responsible for bladder filling and the parasympathetic system for micturition. The somatic and the central nervous system ensure cortical control of voiding, thus preventing enuresis

ETIOLOGICAL CLASSIFICATION OF VOIDING DISORDERS IN CHILDREN

- Enuresis
 - *Monosymptomatic enuresis*: Enuresis in children without any other LUT symptoms and without a history of bladder dysfunction.
 - *Non-monosymptomatic enuresis*: Enuresis along with any other LUT symptoms like nocturnal enuresis, altered voiding frequency, day time incontinence, urgency, hesitancy, straining, weak stream, intermittency, holding maneuvers, a feeling of incomplete emptying, postmicturition dribble and genital or LUT pain. This condition is broadly grouped as functional voiding disorders (FVD) and are sub classified as:
 - a. Overactive bladder (OAB) or urge incontinence: It manifests as urinary urgency and day time wetting.
 - b. Voiding postponement: Children habitually postpone micturition, often using holding maneuvers.
 - c. Dysfunctional voiding (DV): The child habitually contracts the urethral sphincter during voiding thus producing bladder sphincter dysynergia.
 - d. Underactive bladder: Children with low voiding frequency, large capacity bladder and need to strain while voiding.³
- Neurogenic bladder
- Congenital anomalies/Anatomical defects
- Others (Rare): Stress incontinence, vaginal reflux, giggle incontinence and extraordinary day time urinary frequency.

EPIDEMIOLOGY

Eighty-five percent children are dry by five years of age.⁴ But recent studies have shown that in children of around 7 years of age, the prevalence of nocturnal enuresis is 15.5 percent.⁵ Up to the age of nine years, nocturnal enuresis is twice more common in boys than girls but thereafter there is no gender difference.⁶ Among functional voiding disorders, OAB is commoner (68.2%) than DV (19.5%).⁷ Among children with voiding disorders, the common symptoms are urgency (49.7%), holding maneuvers (42.1%), diurnal incontinence (20.1%), straining (16.6%), altered urinary frequency (10.9%), dysuria (5.9%) and constipation (3.1%).⁸

PATHOPHYSIOLOGY

Monosymptomatic Enuresis

Combinations of various factors are implicated in the etiology.⁹

Developmental and Behavioral Factors

Children with delayed milestones may delay in achieving dryness. Voiding disorders are more common among chil-

dren with neuropsychiatric disturbances, such as attention deficit hyperactivity disorder (15%).¹⁰

Genetics

Genetic loci on 8q, 12q and 13q and ENURI 1 gene has been identified on the long arm of chromosome.¹³ The mode of inheritance appears to be autosomal dominant with reduced penetrance.¹¹ The odds ratios for nocturnal enuresis is 3.63 times higher in maternal and 1.85 times higher in paternal nocturnal enuresis.⁵

Nocturnal Inappropriate Antidiuretic Hormone Activity

Antidiuretic hormone (ADH) has a peak secretion between 4 and 8 AM. Lack of circadian rhythm or impaired response of the kidneys to ADH contributes to enuresis.^{9,12}

Bladder Capacity

The maximal voided volume (MVV) of the bladder is reduced in children with enuresis.¹³ The term functional bladder capacity has been replaced by MVV to avoid confusion.³ Maximal voided volume is the same as expected bladder capacity (EBC) which is obtained by the formula $EBC = (30 + (\text{age in years} \times 30))$ in ml.

Sleep Factors

Enuretic children have high arousal thresholds¹² due to underlying brainstem abnormalities, or paradoxically raised by repeated arousal stimuli of the bladder distension. The locus coeruleus (LC), a noradrenergic neuron group in the upper pons is crucial for arousal from sleep. It overlaps both functionally and anatomically with the pontine micturition center and also has axonal connections with the hypothalamic cells that produce vasopressin. Thus a disturbance in this important junction is implicated in enuresis.⁹

Obstructive Airway Disease

The constant arousal stimuli from obstructed airways cause paradoxically high arousal thresholds. Brain natriuretic peptide (BNP) levels increases with snoring and airway obstruction thus aggravating polyuria.^{9,14}

Non-monosymptomatic Enuresis or Functional Voiding Disorders

The basic abnormality in children with Functional voiding disorders (FVD) is abnormal pelvic floor and detrusor contractions.¹⁵ (Fig. 2). Additional factors that aggravate FVD are early initiation of toilet training and constipation (48%).¹⁶ The association of constipation with FVD is termed dysfunctional elimination syndrome.¹⁷ The pathophysiology and progression of FVD is depicted in Flow chart 1.³ The pathophysiology of enuresis (both mono-

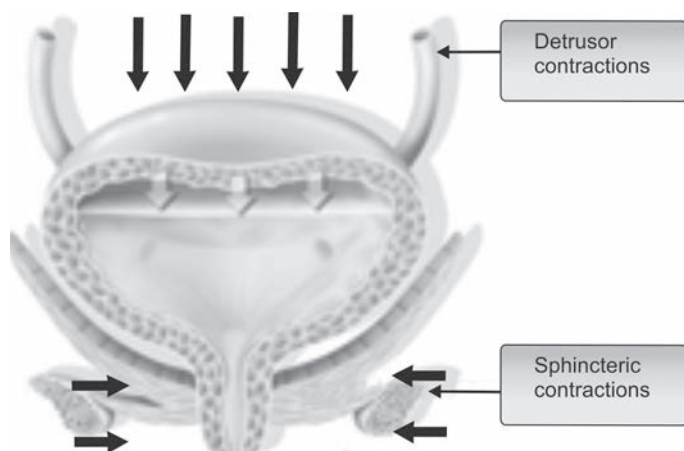
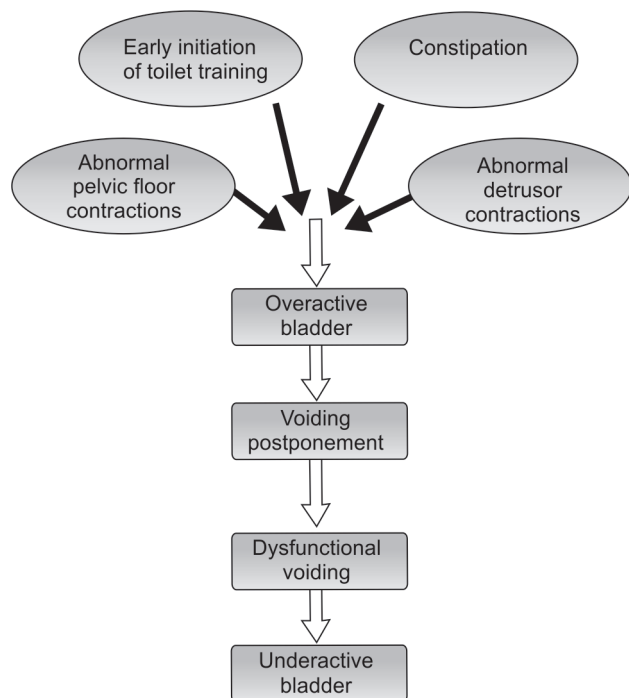


Fig. 2: Plasticity theory describes the role of abnormal pelvic floor and detrusor contraction in evolution of FVD

Flow chart 1: Pathophysiology and progression of functional voiding disorders

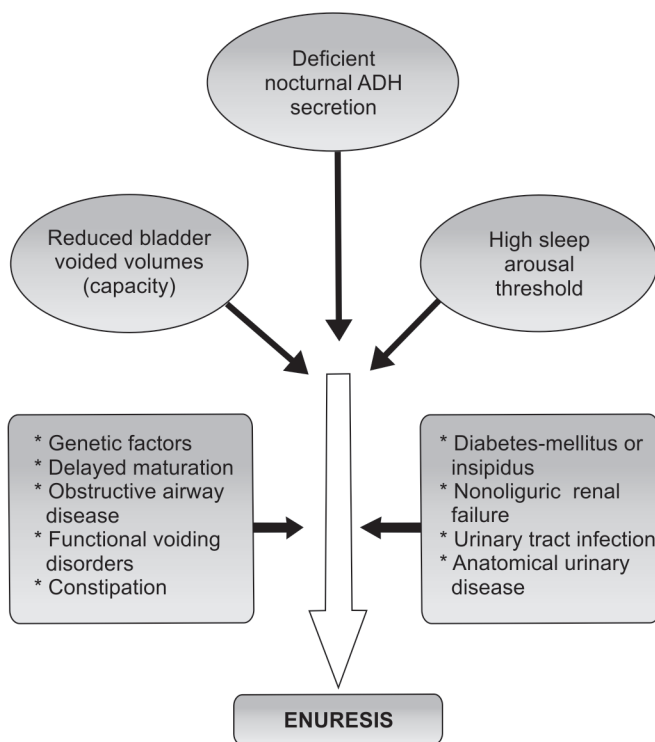


symptomatic and non-monosymptomatic) is described in Flow chart 2.

Anatomical Causes for Incontinence

Extrophy of the bladder, epispadias and urethral trauma are obvious causes for incontinence. However, ectopic ureters, urogenital sinus anomalies and posterior urethral valves require proper imaging and a cystoscopic evaluation for diagnosis. Those boys with urethral valve malformation not

Flow chart 2: Pathophysiology of monosymptomatic and non-monosymptomatic enuresis



only have a disturbed bladder function but also renal tubular damage that leads to vicious circles of polyuria, increased intravesical pressure and yet more renal damage.⁹

Neurogenic Bladder

Spinal dysraphism, closed or open menigomyelocele, sacral agenesis, autonomic neuropathy, transverse myelitis, spinal trauma, tumors or degenerative disorders of the spine may develop a neurogenic bladder.

Other causes

- Diabetes—mellitus or insipidus
- Non-oliguric renal failure
- Urinary tract infection

APPROACH TO A CHILD WITH A VOIDING DISORDER

Urinary incontinence has a strong social stigma recognized by children as the third most stressful situation in life after death of a parent and going blind.¹⁸ Therefore an understanding and a systematic approach is advised to these children.

History

A detailed history of voiding and bowel habits should be noted. The clinical features and their inference is

described in Table 1. A child may also demonstrate the Vincent’s curtsy (a typical position wherein the child bends forward or sits on the floor with the heel of a folded leg tucked into the perineum), to increase the external sphincter tone during bladder contractions. The Farhat scoring system is a reliable screening tool in the identification of FVD¹⁹ (Table 2).

Clinical Examination

It should include growth assessment, blood pressure, abdominal and genital examination. It should also include a detailed neurological evaluation, anal sphincteric tone and gait evaluation. The lower back should be examined

for tuft of hair, spinal dysraphism and scars of operated meningocele. The psychological state of the child should be noted. It is worthwhile to note that a distressed child is also motivated for therapy.

Frequency Volume Charting

A meticulous record of the number of times a child voids and the volume of each voiding is recorded for at least 48 hours.³ Abnormal patterns of voiding such as small quantity day time frequent or infrequent voiding may be noted which otherwise may not be forthcoming in the initial history. An abnormal frequency volume charting strongly suggests an underlying FVD.

Table 1: Relevant patient history to be noted in a child with a voiding disorder

Areas of interest	Relevance
General health and development	
Growth, weight loss	Poor growth in renal failure. Malaise, nausea, weight loss, etc. in diabetes or kidney disease
<i>Micturition and drinking habits</i>	
Bedwetting frequency	Prognosis poor in higher frequency enuresis
Previous dryness	Comorbidity (somatic or psychiatric) more common in secondary enuresis
Daytime incontinence: When? How often?	Neurogenic or anatomic causes gives daytime incontinence more often than isolated enuresis.
Urgency	Indicates overactive bladder
Weak stream, hesitancy, straining	Indicate dysfunctional voiding neurogenic bladder
Urinary tract infections	Indicates FVD (Overactive bladder or dysfunctional voiding)
Excessive thirst. Need to drink at night	Kidney disease, diabetes or habitual polydipsia.
Bowel habits	
Constipation	Dysfunctional elimination syndrome
Encopresis	Most commonly caused by constipation.
Psychology	
Behavioral problems	Risk for therapy-resistance and/or psychiatric comorbidity. Consider parallel psychological evaluation.
How does the child view his/her enuresis?	The child who is not bothered by the enuresis may not be motivated for labor-intensive therapy

Table 2: The investigations, the typical features and their inference in a child with a voiding disorder

Investigation	Abnormality Detected	Inference
Urine analysis		
Urine biochemistry	Glucosuria	Consider diabetes mellitus. Check blood glucose
	Proteinuria (++ or more on urine test)	Consider kidney disease
Urine microscopy	Significant pus cells positive	Take urine culture. Consider UTI

Contd...

Contd...

Ultrasonography		
Bladder	Thick bladder wall *	Underactive bladder Neurogenic bladder Bladder outflow obstruction
	Significant postvoid residue †	Incomplete voiding Vesicoureteric reflux (VUR)
Pelvic/ureteric system	Bladder wall irregularity	Recurrent UTI /Cystitis
	Hydroureteronephrosis	Obstructive uropathy /VUR
Kidneys	Anomalies (Duplication /absence)	Anatomical anomalies
	Small shrunken kidney(s)	Chronic renal disease
	Enlarged kidneys	Hydronephrosis
	Calculi/ Nephrocalcinosis	Obstructive uropathy
Micturating cystourethrogram		
Urinary bladder	Bladder wall irregularity	Overactive bladder
	Elongation of the bladder shape	Dysfunctional voiding
	Filling of the posterior urethra	Neurogenic bladder
	Spinning top configuration of the bladder	
	Small sized bladder with multiple trabeculations (Christmas tree appearance)	
Radiograph and MRI of spine		
Lumbosacral spine	Spinal dysraphism, Diastomatomyelia, Spinal trauma, tumors Degenerative disorders	Neurogenic bladder

* Upper limit for detrusor thickness of ventral wall of urinary bladder at all ages is 2.0 mm at 50% bladder fullness or 1.5 mm at a higher degree of fullness

† Bladder volumes of ≥ 20 ml, or $>10\%$ of the cystometric bladder capacity.

Investigations

The only investigation required in monosymptomatic enuresis is a urine analysis to look for Urinary tract infection (UTI), glucosuria and proteinuria. In non-monosymptomatic enuresis, suspected neurogenic bladder and anatomical anomalies, further investigation with ultrasonography of the kidneys, ureters and bladder (USS), micturating cystourethrogram (MCU) and radiograph of the spine are only required. In certain cases magnetic resonance imaging (MRI) of the spine may be required to look for neurological defects. A frequency volume chart, USS and MCU are together labeled as “Noninvasive urodynamic studies”.¹⁷

Noninvasive assessment of the urinary bladder is fairly accurate in predicting the underlying bladder dysfunction. Nocturnal enuresis with day time symptoms, holding maneuvers, small frequent voiding pattern and a small capacity bladder with insignificant residue and elongation of bladder neck in pre-micturition film on MCU predicts OAB. Straining, recurrent UTI, infrequent voiding, large capacity bladder with significant postvoid residue in the absence of a VUR and a spinning top bladder on an MCU predicts DV.⁷

Invasive urodynamic studies are indicated only in cases where the diagnosis is unclear or response to therapy is poor. The investigations, the typical features and their inference are listed in Table 2. The algorithmic approach to a child with a voiding disorder is depicted in Flow chart 3 and 4.

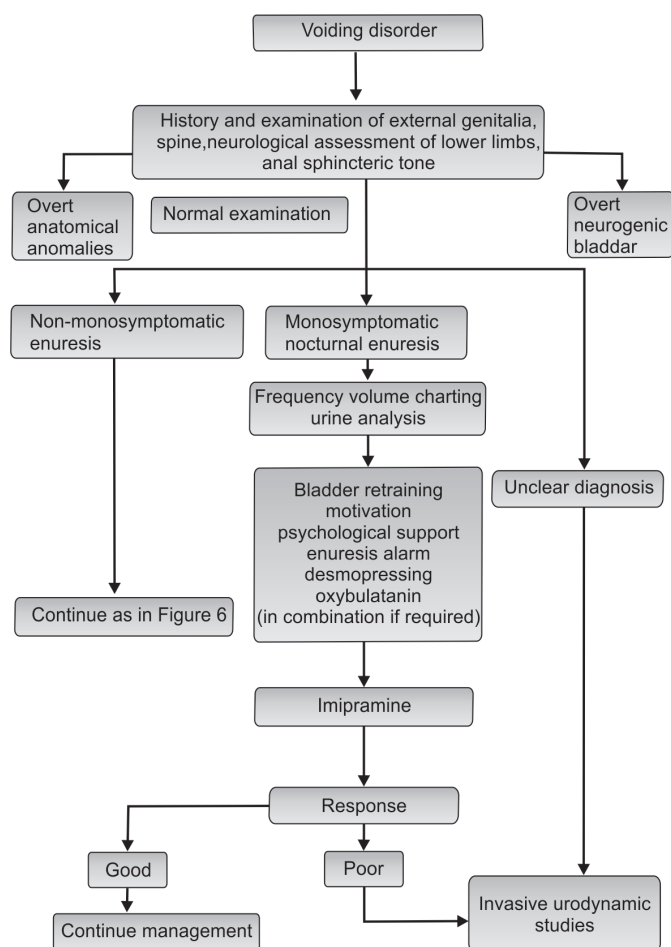
TREATMENT

The therapeutic plan needs to be discussed with the parents and individualized to the child's needs.

Monosymptomatic Enuresis

Regulated oral fluid intake: There is limited role of withholding fluids in the evening, random awakening of the child to void or punitive measures.²⁰ However, diuretic drinks like tea, coffee and sodas should be avoided in the evening.

Motivational therapy: The child is reassured, provided emotional support and every attempt is made to remove any feeling of guilt. Dry nights merit praise and encouraging words from the parents.²¹

Flow chart 3: Algorithmic approach to a child with voiding disorder

Enuresis alarm

This involves the use of an alarm device to elicit a conditioned response of awakening to the sensation of a full bladder and gradually the association with bladder distention evokes micturition. The alarm device consists of a small sensor attached to the child's underwear, or a mat under the bed-sheet and an alarm attached to the child's collar or placed at the bedside. When the child starts wetting the bed, the sensors are activated causing the alarm to sound. The therapy should continue until 14 consecutive dry nights have been achieved.

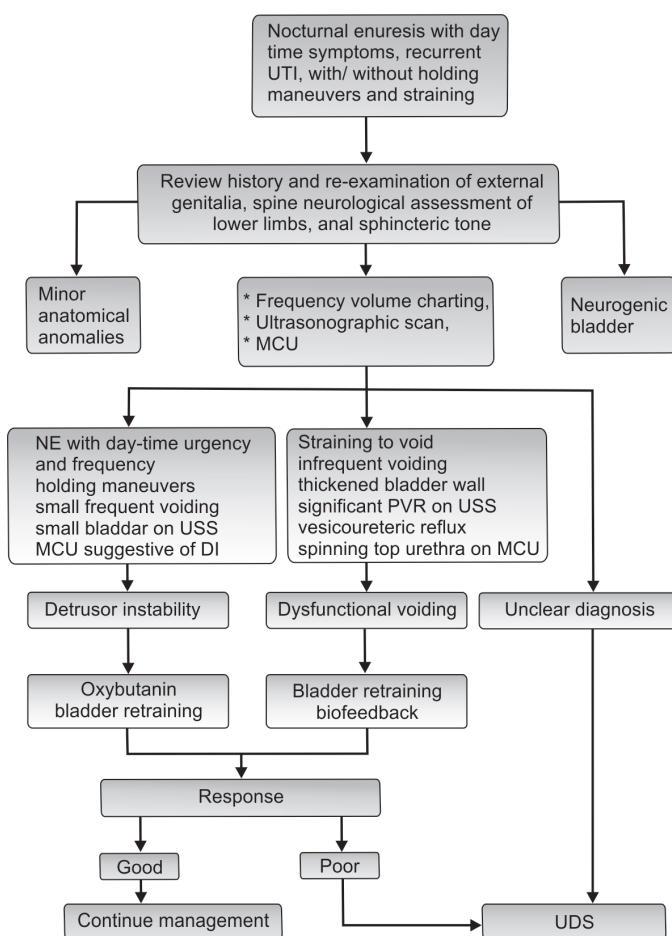
Pharmacotherapy

The common drugs used in the treatment of voiding disorders, their mechanism of action, dose and side effects are summarized in Table 3.⁹

Non-monosymptomatic Nocturnal Enuresis

Non-pharmacological therapy

Behavioral intervention: This consists of patient education, scheduled voiding regimen with gradual increasing

Flow chart 4: Algorithm to manage a case of functional voiding disorder, NE= Nocturnal Enuresis

intervals, urgency control strategies, self-monitoring and positive reinforcement. Initially the child is asked to void every two hours and gradually the voiding intervals are increased. Pelvic floor and bladder exercises with biofeedback are very useful.²²

Pharmacotherapy

Correction of constipation: Isabgol husk, lactulose and PEG-3350 (polyethylene glycol 3350) powder may be used. It is important to treat constipation consistently for 3 to 6 months.

Treatment of UTI: Judicious use of antibiotics guided by sensitivity reports is essential to control infections. Antibiotic prophylaxis may be required in children with recurrent UTI and with large postvoid residues.

Anticholinergic agents: In children with the urge syndrome and detrusor instability an anticholinergic medication like oxybutinin and tolteridone can be effective. (Table 4) Tolteridone is better tolerated than Oxybutanin.²³

Table 3: Medications used in treatment of nocturnal enuresis, their doses and side effects

Medication	Mechanism of action	Dose	Duration of use	Age group	Side effects	Precautions
<i>Desmopressin</i>	Vasopressin analog exerting ADH action	Oral – 120-240 μ g/day Nasal spray – 10-40 μ g/day	4 weeks dry and then tapered off over 3 weeks	Any	Hyponatremia, nasal stuffiness, headache, epistaxis, abdominal pain, nausea	Limit fluid intake to 200 ml from 1 hour before medication until the next morning.
<i>Oxybutanin</i>	Anticholinergic	10-20 mg/day	3-6 months	> 6 years	Dryness of mouth, facial flushing, palpitations, constipation and blurring of vision	Adequate oral fluids and prevent constipation
<i>Tolteridone</i>	Anticholinergic	2-4 mg/day 1 hour before bedtime	3-6 months	Any	Same as Oxybutanin but less intense	
<i>Imipramine</i>	Antipsychotic Anticholinergic	25-50 mg/day PO 1 hour before bedtime	3-6 months and gradually tapered	> 7 years	Anxiety, mood disturbances, personality change and palpitations	ECG to rule out long QT syndromes is mandatory. 2 weeks off medication every 3 months to prevent tolerance
<i>Doxazosin</i>	Alfa blocker	0.5-1 mg/day	3-6 months	> 6 years	Headache, fatigue, dizziness hypotension	Blood pressure monitoring

Alpha-blockers

Doxazosin (0.5 to 1 mg/day) may be used in dysfunctional voiding along with biofeedback. (Table 170.4)²⁴

Surgical intervention

In children with established dysfunctional voiding with large post void residues it is imperative to lower intravesical pressures in order to protect the upper tract. Clean intermittent catheterization (CIC) can be instituted with training.²⁵ A Mitrofanoff conduit can aid CIC especially in girls attending school.²⁶

COMPLICATIONS

The following complications in untreated children with voiding disorders are noted:

- Psychosocial complications¹⁸
- Recurrent UTI²⁷
- Hydrouretronephrosis
- Renal parenchymal damage and failure

PROGNOSIS

In monosymptomatic enuresis success rates up to 82 percent and 77.8 percent are seen with enuresis alarms and DDAVP respectively. The recurrence rates are much higher with DDAVP and imipramine.²⁸ In FVD, 94 percent show

improvement in recurrent UTI and 76 percent in voiding symptoms. The onset of VUR and renal dysfunction heralds a poorly reversible situation. The improvement in VUR and renal parameters are seen only in 63 percent and 37 percent respectively.²⁹ This fact highlights the need for timely intervention in these children.

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INTRODUCTION

The term “urolithiasis” refers to the formation of stones within the kidneys or urinary tract. “Nephrocalcinosis” is the presence of calcium deposits within the parenchyma of the kidney. Since both conditions can occur due to the same set of etiologies, they are usually discussed together.

The incidence of renal stones is thought to be rising in industrialized countries, and is estimated to occur in about 5 percent of population.¹ In children, although exact figures are unavailable particularly in the Indian subcontinent, incidence rates are only approximately 10 percent of adult rates. The reason for this much lower rate is thought to be due to the increased presence of inhibitor substances in pediatric urine.² However, several genetic and metabolic conditions typically present in the pediatric age group and require early diagnosis and treatment, to prevent multiple bilateral and recurrent stone disease or progressive nephrocalcinosis and urolithiasis which can lead to renal failure.

Calcium oxalate is the most common renal stone worldwide, and accounts for 60 to 90 percent of pediatric urolithiasis. Calcium phosphate accounts for 10 to 20 percent, uric acid for 5 to 10 percent, struvite for 1 to 18 percent of stones in developed countries, cystine for 1 to 5 percent and mixed or miscellaneous 4 percent of the pediatric stones.³

ETIOLOGICAL FACTORS

Calcifications in the urinary tract occur when there is supersaturation of solutes in urine leading to crystal deposition. This can occur due to absolute solute excess or due to reduced solvent. Urinary tract obstruction and congenital anomalies that lead to stasis and poor urinary flow are also risk factors. Urine infection can be both the precipitating cause and the sequel of renal stones. In many conditions

Table 1: Etiology of nephrocalcinosis/urolithiasis

- | | |
|----|-----------------------------------|
| 1. | <i>Increased solute</i> |
| a. | Hypercalciuria |
| b. | Hyperoxaluria |
| c. | Hyperuricosuria |
| d. | Cystinuria |
| e. | Miscellaneous |
| 2. | <i>Decreased solvent</i> |
| a. | Dehydration |
| 3. | <i>Decreased stone inhibitors</i> |
| a. | Hypocitraturia |
| b. | Hypomagnesuria |
| 4. | <i>Stasis</i> |
| a. | Obstruction |
| b. | Congenital malformation |
| c. | Immobilization |
| 5. | <i>Infection</i> |

more than one factor may be present and may be associated with a deficiency of stone inhibiting substances. The different etiopathologies of urolithiasis and nephrocalcinosis are described in brief below²⁻⁴ and tabulated in Table 1. Seventy-five percent of children have an identifiable predisposing cause of which metabolic causes are 33 percent, structural anomalies 32 percent and infection 4 percent.²

Metabolic Conditions

Hypercalciuria

The most common cause of pediatric renal stones is hypercalciuria which accounts for over 50 percent of metabolic etiologies.² This can be caused by excessive calcium and

vitamin D supplements, dietary salt and protein excess or phosphate deficiency, by drugs such as steroids and frusemide, or by prolonged immobilization. It may be associated with hypercalcemia as in hyperparathyroidism. Hypercalciuria may be transmitted in families as a polygenic or as an autosomal dominant trait. Several rare genetically transmitted renal tubular disease are associated with hypercalciuria and include familial hypomagnesemia with hypercalciuria, renal tubular acidosis, neonatal Bartter's syndrome, Dent's disease and Lowe's syndrome. Very often, however, no specific cause can be found, and it is termed "idiopathic".

Hyperoxaluria

Hyperoxaluria accounts for 2 to 20 percent of metabolic urolithiasis. Oxalate rich foods include rhubarb, beets, okra (bhindi), spinach, berries, nuts, sweet potatoes (shakarkandi), tea, chocolate and soy products. Excessive dietary intake of these substances may result in renal stones. Acute oxalate nephropathy is seen in ethylene glycol poisoning which occurs in cold countries where it is a component of car antifreeze agents. Loss of gut colonization by oxalate degrading anaerobic bacteria (e.g. *Oxalobacter*) may result in increased oxalate absorption, leading to hyperoxaluria and stone formation.⁵ Enteric hyperoxaluria occurs in gastrointestinal malabsorptive states, where excess fats in the intestine bind with calcium leaving oxalate behind for systemic absorption.

Primary or genetic hyperoxalurias are rare autosomal recessive inherited diseases that cause marked hyperoxaluria. They are due to deficiency of hepatic enzymes—alanine glyoxylate aminotransferase (AGT) or glyoxylate reductase/hydroxypyruvate (GRHPR) reductase. These conditions cause early and progressive nephrocalcinosis and recurrent stones and lead to extensive renal damage. Subsequent to renal impairment, lack of excretion leads to very high levels of oxalate in the blood—termed oxalosis, which causes damage to many body organs.

Hyperuricosuria

Increasingly, uric acid stones are occurring in obese adolescents with the metabolic syndrome and in children with high protein diets. This is a component for the growth of renal stone disease in industrialized countries. The condition may be familial or idiopathic. It may arise due to drugs such as probenecid, phenylbutazone, salicylates and pancreatic extracts used in cystic fibrosis. Severe hyperuricosuria and renal stones occur in genetic diseases such as Lesch-Nyhan syndrome and phosphoribosyl pyrophosphate synthetase superactivity. It is also seen in conditions where there is increases cell turnover like tumor lysis syndrome, lympho-or myelo-proliferative disorders.

Cystinuria

Cystinuria is the cause of 2 to 8 percent of metabolic stone disease in children. This is an autosomal recessive condition, in which renal tubular reabsorption of cystine and the dibasic amino acids, i.e. ornithine, arginine and lysine is defective, and they are lost in the urine. Cystine is poorly soluble in urine with pH of 7 or less. There are 3 disease types involving 2 genes, with type 1 being the most severe, affecting even infants. It is associated with early, bilateral and recurrent renal stones that can result in renal failure if untreated.

Deficiency of Stone Inhibitors

There are several substance that are present in urine and act as inhibitors of urinary crystallization. Hypocitraturia is present in several diseases where stone formation occurs, like renal tubular acidosis, and hypokalemic conditions. Other urinary inhibitors are magnesium (as in familial hypomagnesemia with hypercalciuria), and pyrophosphate. Other inhibitors under study include glycosaminoglycans, osteopontin, and nephrocalcin.

Environmental, Dietary and Geographic Factors

There is a great difference in incidence of renal stones depending on race, environment and diet.⁶ Urinary bladder stones are endemic in certain "stone belts"—an example being the dry north western states of India. A combination of factors, namely, hot and dry environment with scarcity of drinking water and a diet low in animal protein but rich in cereals are contributing factors. Excessively high protein diets and ketogenic diets used in epilepsy are also associated with increased risk of urolithiasis. Additionally, excessive intake of sodium, calcium and oxalate can result in renal stones.

Congenital Malformations, Stasis and Infection

Conditions interfering with the flow of urine in the renal tract are risk factors for formation of crystals due to stasis and for infection. The most common conditions are medullary sponge kidney and autosomal dominant polycystic kidney disease which are usually diagnosed in adulthood. Pediatric renal malformations can also be associated with stone formation, like hydronephrosis and horse shoe kidneys. Stasis is often associated with infection which is an additive risk factor. Bladder augmentation using intestinal mucosa is a risk factor for bladder stones.

Several bacteria (*Proteus*, *Klebsiella*, *Pseudomonas*, *Ureaplasma*, etc.) have an enzyme called urease which hydrolyses urea to form ammonium and bicarbonate ions in urine. The resulting alkaline pH causes phosphate dissociation and formation of magnesium ammonium phosphate stones which are called struvite and can result in large staghorn calculi which grow rapidly and are difficult

to remove. Xanthogranulomatous pyelonephritis which is a serious kidney infection that can lead to renal failure may be associated with staghorn calculi.

Certain Conditions which are Associated with Urolithiasis

Prematurity in itself is a risk factor for nephrocalcinosis and renal stones. This risk is compounded by treatment with steroids, frusemide and TPN. Patients with spinal dysraphism have poor bladder function and recurrent infection and this compounded by relative immobilization may be a risk for urolithiasis. Gastrointestinal diseases and obesity are also risk factors as mentioned above.

Miscellaneous

Several drugs are associated with urolithiasis and include the antiretroviral agent—idinavir, and others such as ceftriaxone, sulfonamides, etc. The treatment of gout with allopurinol can result in xanthine and hypoxanthine stones.

CLINICAL HISTORY AND EXAMINATION

The common symptoms of renal stones are colicky abdominal pain and hematuria.^{2,7} The characteristic “renal colic” that occurs in adults with pain radiating from the flanks to the groin, is rare in young children who more commonly complain of diffuse nonspecific abdominal pain. Macroscopic painful hematuria mandates a search for renal stones. Stones in the bladder or urethra can present with dysuria, frequency of urination, and urinary retention. Urethral stones may be palpable in boys. Symptoms of UTI may be present with fever. However, stones and particularly nephrocalcinosis are often silent and picked up on investigation in the presence of risk factors such as family history or congenital structural renal anomalies. They may be detected during screening of patients with associated conditions such as UTI, Fanconi’s syndromes, RTA, Dents disease and Bartter’s syndrome.

Once stones or nephrocalcinosis is detected, it is important to ask about family history since many conditions in the pediatric age group are genetically transmitted. Details of diet, drinking behavior, usual climate and history of immobilization or prematurity and UTI should be sought. Drug intake including frusemide, calcium, vitamin D analog, steroids, allopurinol may be causative factors. Any known associated renal or GIT disorder or congenital renal malformation should be investigated.

In patients with secondary renal stones there may be short stature, failure to thrive, dehydration, hyperventilation and rickets. Renal parenchymal damage may be associated with hypertension, anemia and metabolic bone disease. Characteristic stigmata may be present in syndromes such as Lesch-Nyhan syndrome and Lowe’s syndrome.

INVESTIGATIONS

The aim of the diagnostic process is not only to: (1) accurately define the presence and location of urinary stones or nephrocalcinosis, but also to (2) detect any adverse effects such as UTI, obstruction causing proximal dilatation or renal functional impairment and (3) to diagnose or exclude a treatable causative factor such as infection, stasis, obstruction, structural anomaly of the renal tract or underlying metabolic disease. Imaging modalities utilizing the minimal amount of radiation are preferred and the ultrasound scan has become the most utilized tool (Figs 1A to D). However in a few cases where stones are small and situated in the renal papillae or ureters, USS may not detect them and in such cases CT is the most sensitive (Fig. 2).

Imaging Modalities

Ultrasound (US)

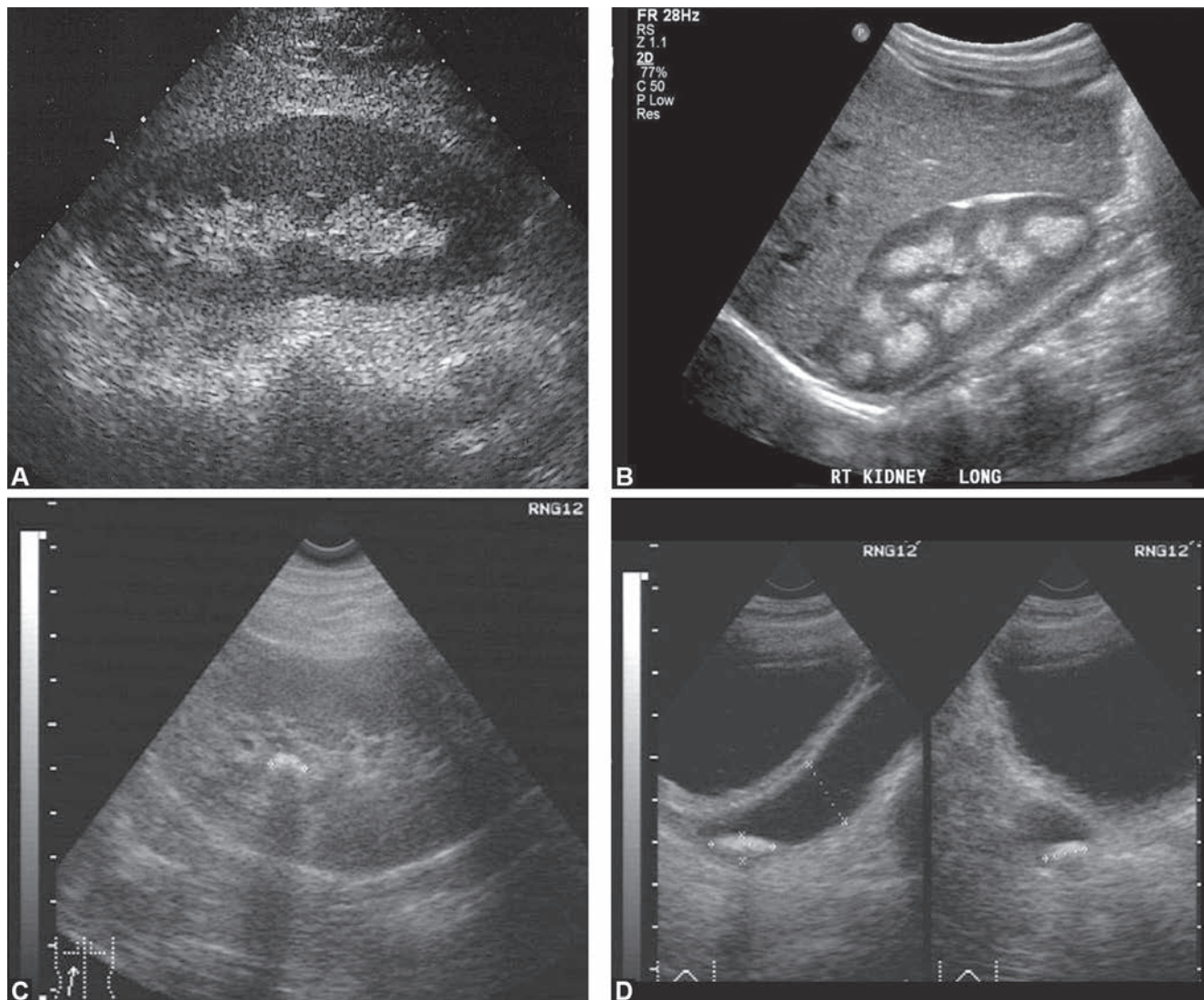
The US is the most commonly used tool for the diagnosis and further monitoring of renal stone disease. Nephrocalcinosis appears as echogenic foci in the renal parenchyma. It most commonly affects the medulla, but may be cortical or diffuse in distribution. Isolated renal cortical calcinosis may be seen after renal cortical necrosis. Medullary nephrocalcinosis is further classified radiographically by the distribution and the density of deposits as Grade I—with mild increase in echogenicity around the border of the medullary pyramids; Grade II—with mild diffuse increase in echogenicity of the entire medullary pyramid; Grade III—with a greater, more homogeneous increase in the echogenicity of the entire medullary pyramid.⁸

Stones are detected on ultrasound as echogenic areas with a distal “acoustic shadow”, i.e. a line of hypoechogenicity where the sound waves are not transmitted as they are blocked by the solid stone material. The USS is good at detecting renal and bladder stones but poor at detecting ureteric stones particularly small ones.

The USS also provides important information regarding whether there is any obstruction of the renal system, or any structural anomaly. Being nonradiating it can be used easily for serial studies to monitor progress. However a limiting factor is its subjectiveness particularly where monitoring for changes in stone size is concerned.

Plain X-ray

A plain abdominal X-ray of a properly prepared child (after adequate bowel clearance) can reveal stones in the renal tract if the stones are radiopaque. Most stones containing calcium and dense nephrocalcinosis will be radiopaque, and include calcium oxalate and calcium phosphate stones. Struvite and cystine stones are of intermediate density. Uric acid stones are radiolucent and cannot be detected without administration of contrast. Small stones of any variety may be missed on X-ray.



Figs 1A to D: Ultrasound scans; (A) Normal kidney; (B) Nephrocalcinosis; (C) Renal stone; (D) Ureteral stone with proximal dilatation

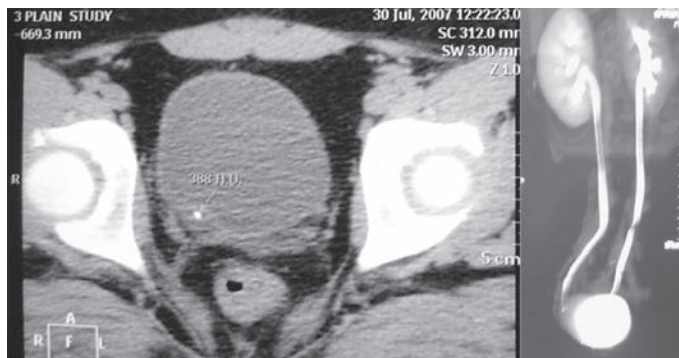


Fig. 2: Non-enhanced CT scan showing uric acid stone in left lower ureter near ureterovesical junction, which was not identified on US

Intravenous Urogram (IVU)

IVU was very popular for detecting stones prior to the widespread availability of ultrasound scans. They show even radiolucent stones as filling defects and are particularly good for determining the exact site of the stone related to the urinary tract and the presence or absence of proximal dilatation. However, the large radiation dose involved due to the repeated films and the risk of contrast nephropathy have greatly limited the use of this modality particularly when sufficient information is obtained by US.

CT Abdomen

The noncontrast CT scan is a sensitive modality for the detection of small ureteric stones. The limiting factor is the associated radiation and it is reserved for special situations where the index of suspicion is high but US is not helpful.

DTPA/MAG3 Scans

These isotope scans cannot detect stone, but are used to monitor degree of obstruction and individual renal function.

Blood and Urine Examination

Since a large proportion of children have underlying metabolic causes of stone formation, a blood and urinary stone profile should be sent. This is most important if there is family history or if the involvement is bilateral, multiple and recurrent. As screening tests, spot urinary values using solute—creatinine ratios are useful. However, since values may differ with time, diet and age, suspicious findings should be confirmed with 24 hour urinary collections, or when that is difficult using timed urinary collections. Normal values are given in Table 2.

The metabolic stone profile includes:

Blood for—urea, creatinine, electrolytes, bicarbonate, calcium, phosphate, magnesium and uric acid.

Urine is tested for—pH, osmolarity, creatinine, calcium, magnesium, phosphate, oxalate, cystine, urate, citrate. Urine should be checked microscopically for RBC's, pus cells and any typical crystals and a culture should be included to exclude infection. If stones are passed, these should be collected and analyzed. Infrared spectroscopy or X-ray diffusion methods are superior to chemical analysis.

MANAGEMENT

General Management

There are certain measures that in general reduce stone formation,^{2,7} and these are: (1) maintain good hydration and good urine flow with adequate fluid intake and early treatment of any obstructive urological lesion (2) early detection and control of urinary tract infection (3) low salt diet—sodium and calcium share common sites for reabsorption in the renal tubules and restricting sodium intake encourages calcium reabsorption, thus reducing hypercalciuria. Excesses of dietary calcium, oxalate and protein beyond RDA should be avoided. (4) Inhibitors of stone formation include citrate, potassium and magnesium, supplements. (5) the use of alpha adrenergic antagonists and calcium channel blockers by relaxing urethral smooth muscle have recently been tried for urethral stones in adults⁹ (6) avoid immobilization.

Stones that are less than 5 mm in diameter and not associated with obstructive changes usually do not require removal as they may pass through the urinary tracts and can be excreted. Larger stones need removal particularly if they are associated with symptoms such as pain or swelling or obstruction detected on USS or IVU. The options for stone removal are:

- **ESWL:** Extracorporeal shock wave lithotripsy can be used for fragmentation of stones that are less than 1 to 2 cm, with normal renal function, no infection and favorable anatomy. Reduction in stone size enables excretion through the urinary tract. Although there are concerns regarding the consequence of this therapy on the developing kidneys, with proper case selection the process is reported to be safe and effective.¹⁰

Table 2: Normal values of urinary excretion of different solutes^{2,8}

Solute	Age group	Solute/creatinine ratio	Timed excretion
Calcium	<6 months	<0.8 mg/mg	<4 mg/kg/24 hours
	7–12 months	<0.6 mg/mg	
	>2 years	<0.21 mg/mg	
Oxalate	<1 year	0.15–0.26 mg/mg	>2 years: <45 mg/1.73 m ² /24 hours
	1–5 years	0.11–0.12 mg/mg	
	5–12 years	0.006–0.15 mg/mg	
	>12 years	0.002–0.083 mg/mg	
Cystine		<75mg/g	<60 mg/1.73 m ² /24 hours
Uric acid	0–1 year	<2.2	<815 mg/1.73 m ² /24 hours
	1–3 years	<1.9	
	3–5 years	<1.5	
	5–10 years	<0.9	
	>10 years	<0.6	
Citrate		>180–400 mg/g	
Magnesium	>2 years	≥0.12 mg/mg	≥88 mg/1.73 m ² /24 hours

- *Surgical removal:* Lower ureteric, bladder and urethral stones may be removed by a variety of urethro-cysto-uretero-scopic maneuvers. Stones in the upper urinary tracts require nephrostomies for clearance by open or per-cutaneous methods. Particularly in metabolic conditions where recurrence is common, repeated surgical procedures can cause renal parenchymal or ureteral muscle damage.^{10,11}

Specific Management

Specific metabolic conditions require specific therapies which need to be urgently instituted to prevent progress,

Table 3: Specific management of metabolic urinary stone disease

Hypercalciuria	<ul style="list-style-type: none"> • Avoid immobilization • Low sodium diet • Avoid excess calcium or vitamin D intake • Correct deficiencies of potassium and phosphate • Stop causative drugs (frusemide/steroids) if possible • Correct hypercalcemia if present • Correct acidosis if present • Thiazide diuretics
Hyperoxaluria	<ul style="list-style-type: none"> • Avoid foods rich in oxalate • Treatment of fat malabsorption (low fat diet, bile acid sequestrants) • Treatment with oxalate degrading bacteria under trial • In genetic hyperoxalurias: <ul style="list-style-type: none"> – Pyridoxine – Early intensive hemodialysis if renal insufficiency – Liver transplant replenishes enzyme defects – Combined liver and kidney transplant if ESRD.
Hyperuricosuria	<ul style="list-style-type: none"> • Avoid excess protein intake • Maintain urinary pH above 7.0 • Allopurinol
Cystinuria	<ul style="list-style-type: none"> • Very high fluid intake • Maintain urinary pH above 7.5 • α-Mercaptopropionylglycine or penicillamine
Struvite	<ul style="list-style-type: none"> • Treat UTI • Remove stasis producing factors

new stone formation and ensuing renal damage.^{4,9} These are summarized in Table 3.

CONCLUSION

Although urolithiasis and nephrocalcinosis are rare in childhood, they can be recurrent and progressive, and are often due to underlying metabolic or structural defects. All affected children therefore, need a detailed diagnostic evaluation to look for causative factors. Several non-invasive and minimally invasive methods are now available for the removal of stones that cause symptoms, UTI or obstruction. Medical management includes general measures of mobilization, hydration, analgesia, treatment of UTI and supplementation with various crystal inhibitors. Specific therapy is aimed at the management of any specific etiological factor that is diagnosed followed by close monitoring with aim to prevent recurrence or progression.

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Hereditary Nephropathies

PK Pruthi, Kanav Anand

INTRODUCTION

Hereditary renal disorders are an important cause of chronic kidney disease in children. This group includes a variety of disorders like:

- Alport syndrome
- Thin basement membrane disease
- Polycystic kidney disease
- Nephronophthisis—medullary cystic disease complex
- Cystinosis
- Nail patella syndrome
- Lowe syndrome.

ALPORT SYNDROME

Alport syndrome (hereditary nephritis) is an inherited progressive form of glomerular disease that is often associated with sensorineural hearing loss and ocular abnormalities¹. This syndrome is a primary basement membrane disorder arising from mutations in genes encoding several members of the type IV collagen protein family. These alpha IV collagen chains are normally located in various basement membranes of the kidney, cochlea and eye.

Genetics

Transmission of Alport syndrome can be X-linked, autosomal recessive or autosomal dominant. X-linked transmission accounts for approximately 80 percent of affected patients and arises from mutations in the *COL4A5* gene on the X chromosome. Autosomal recessive variant is responsible for about 15 percent of patients with Alport syndrome and arises from genetic defects in either the *COL4A3* and *COL4A4* genes while, autosomal dominant disease occurs in about 5 percent of patients with Alport syndrome and arises from heterozygous mutations in the *COL4A3* or *COL4A4* genes.

Clinical Manifestations

The course of Alport syndrome is gender and genetic transmission dependent. Males with X-linked or recessive forms of the disease are at high-risk for progression to end stage renal disease. Females and those with the autosomal dominant form do better and show less rapid progression.

The clinical manifestations vary according to the system involved:

- *Renal manifestations:*¹
 - Asymptomatic persistent microscopic hematuria (onset is usually below 10 years of age).
 - Recurrent episodes of gross hematuria, which usually follows upper respiratory tract infections.
 - Proteinuria, hypertension and progressive renal insufficiency can develop over a period of time.
 - End stage renal disease (ESRD) usually occurs between the ages of 16 and 35 years in patients with X-linked or autosomal recessive disease.

The Alport nephropathy progresses through a series of clinical phases. Phase I typically lasts from birth until late childhood or early adolescence and is characterized by isolated hematuria, with normal protein excretion and renal function. In Phase II, proteinuria is superimposed on hematuria but renal function remains normal. Patients in Phase III exhibit declining renal function in addition to hematuria and proteinuria, and those in phase IV have ESRD.

- *Hearing loss:*²
 - Bilateral sensorineural hearing loss is usually in the range of high frequency to begin with and later it progresses over time to frequencies in the range of conversational speech. In general, the rate of hearing loss is similar to the progression of renal insufficiency.

- *Ocular manifestations:*^{3,4}
 - Lens — Anterior lenticonus occurs in 20 to 30 percent of males with X-linked Alport syndrome and is pathognomonic of the disease.
 - Retina — Bilateral white or yellow granulations that are superficially located in the retina surrounding the foveal area (known as Dot-fleck retinopathy) are specific for Alport syndrome.
 - Cornea — Posterior polymorphous dystrophy and recurrent corneal erosions are observed sometimes.
- *Leiomyomatosis:* Leiomyomas may be found within the respiratory, gastrointestinal and female reproductive tracts.⁵
- *Arterial disease:* Aneurysms of the thoracic and abdominal aorta are occasionally associated features.
- *Others:* Alport syndrome may be associated with abnormal platelet numbers and size, hyperprolinuria, hypoparathyroidism, midface hypoplasia and cerebral dysfunction.⁶

DIAGNOSIS

Although the possibility of Alport syndrome is generally suspected from the family history of renal failure and deafness,⁷ the diagnosis is usually confirmed by a skin or renal biopsy. In a renal biopsy specimen, the characteristic finding of longitudinal splitting of the lamina densa of the glomerular basement membrane (GBM) detected by electron microscopy is diagnostic for Alport syndrome. Light microscopy findings include mesangial matrix expansion

with segmental proliferation, presence of lipid laden foam cells and irregular thickening of capillary walls. Immunostaining of type IV collagen demonstrates absence or an abnormal distribution of the alpha-3, alpha-4 and/or alpha-5(IV) chains of the GBM.

In recent times, molecular genetic testing is being used to diagnose Alport syndrome and it may eventually become the diagnostic procedure of choice because it is noninvasive and can be extremely accurate.⁸

DIFFERENTIAL DIAGNOSIS

Other glomerular disorders that present in children with microscopic hematuria include IgA nephropathy and thin basement membrane nephropathy. Megathrombocytopenia (thrombocytopenia with large or giant platelets) has been described in some families with autosomal dominant hereditary nephritis and sensorineural deafness. This complex has been referred to as Epstein syndrome or Fechtner syndrome when associated with leukocyte cytoplasmic inclusions (Table 1).

MANAGEMENT

Currently there is no specific treatment available for Alport syndrome. Angiotensin antagonists (ACE inhibitors and/or Angiotensin receptor blockers) and cyclosporine are being used currently for delaying the progression of disease.^{9,10} In patients who develop end-stage renal disease, transplantation is the preferred modality for renal replacement therapy. Recurrent disease does not occur

Table 1: Familial glomerular hematurias

	<i>Genetic locus</i>	<i>Protein product</i>	<i>Renal symptoms</i>	<i>ESRD</i>	<i>GBM Ultrastructure</i>	<i>Extrarenal manifestations</i>
<i>Type IV collagen disorders</i>						
<i>Alport syndrome</i>						
X-linked	<i>COL4A5</i>	$\alpha 5(\text{IV})$	Hematuria, proteinuria, hypertension	All males, some females	Thinning (early) lamellation (late)	Deafness, lenticonus, perimacular flecks
Autosomal recessive	<i>COL4A3</i> <i>COL4A4</i> (biallelic)	$\alpha 3(\text{IV})$ $\alpha 4(\text{IV})$	Hematuria, proteinuria, hypertension	All males and females	Thinning (early), lamellation (late)	Deafness, lenticonus, perimacular
Autosomal dominant	<i>COL4A3</i> <i>COL4A4</i> (heterozygous)	$\alpha 3(\text{IV})$ $\alpha 4(\text{IV})$	Hematuria, proteinuria, hypertension	Males and females (late)	Thinning (early), lamellation (late)	Deafness
Thin basement membrane nephropathy	<i>COL4A3</i> <i>COL4A4</i> (heterozygous)	$\alpha 3(\text{IV})$ $\alpha 4(\text{IV})$	Hematuria	Rare	Thinning	Rare
<i>MYH9 disorders</i>						
Epstein syndrome	<i>MYH9</i> (hyterozygous)	NMMHC-11AA ³	Hematuria, proteinuria	Yes	Lamellation	Deafness, large platelets
Fechtner syndrome	<i>MYH9</i> (hyterozygous)	NMMHC-11AA ³	Hematuria, proteinuria	Yes	Lamellation	Deafness, large platelets, May-Hegglin anomaly

in the transplanted graft because the donor kidney has a normal glomerular basement membrane (GBM). However, anti-glomerular basement membrane antibody disease occurs in approximately 3 percent of affected males who receive transplants.

THIN BASEMENT MEMBRANE DISEASE

It is an autosomal dominant condition resulting in familial persistent microscopic hematuria¹¹. There may be episodes of gross hematuria which may be syn infectious. It is usually not associated with proteinuria, hypertension or progression to end stage renal disease but still patients diagnosed to have this condition should be kept under close follow-up. Proteinuria has been found to occur in up to 30 percent of adult patients as compared to a negligible number in pediatric patients.¹² This diagnosis is mostly pathological rather than clinical. Renal biopsy findings are suggestive of diffuse thinning of glomerular basement membrane, with normal staining for type IV collagen. Light microscopy typically shows no abnormalities. Treatment is usually not required as the course of the disease is very benign.

POLYCYSTIC KIDNEY DISEASE

Polycystic kidney disease can present in 2 genetically distinct forms, autosomal dominant polycystic kidney disease (ADPKD) and autosomal recessive polycystic kidney disease (ARPKD).

Autosomal Dominant Polycystic Kidney Disease

Autosomal dominant polycystic kidney (ADPKD) is the most common inherited kidney disease, having an incidence of 1 in 1000 livebirths. It is associated with mutations in PKD1 (85 percent) and PKD 2 gene encoding polycystin 1 and 2.¹¹ ADPKD has a variable presentation and it varies even within families. A positive family history may be obtained in approximately 60 percent of the patients. The presentation can be:

- Antenatal ultrasound showing large kidneys with or without cysts, occasionally associated with oligohydramnios.
- In children, ADPKD may be detected incidentally or on screening at any age including neonatal age group. Symptoms are rare during childhood. Occasionally they may present with abdominal pain, palpable abdominal mass, gross/microscopic hematuria, urinary tract infection, hypertension or nephrolithiasis.
- Adults may be asymptomatic with cysts being incidentally detected on ultrasound.
- Chronic kidney disease may be seen in 60 to 70 percent patients usually by sixth decade of life.

Table 2: Diagnostic criteria for ADPKD

Positive family history with autosomal dominant pattern

- Ultrasound screening of parents may be positive

Enlarged kidneys with multiple bilateral renal cysts (on ultrasound or CT scan)

- Age 15-39 years: >2 renal cysts (unilateral/bilateral)
- Age 40-59 years: >1 renal cyst in each kidney
- Age >60 years: >3 renal cysts

- *Extra renal manifestations:* Cysts in the liver, pancreas, spleen, ovaries, testis; cerebral aneurysms, mitral valve prolapse and coarctation of aorta.

The condition can be diagnosed with ultrasound showing one or more cysts, although a negative ultrasound does not exclude ADPKD till fourth decade of life. The diagnostic criteria for ADPKD as described by Pei et al¹³ are shown in Table 2.

Family screening can be undertaken for parents of index case, or grandparents if parents are younger than 30 years.¹⁴ If the child is asymptomatic, USG screening should be done every 5 years. The child also needs to be screened for hypertension and proteinuria on an annual basis. There is no specific treatment for ADPKD, but if the child is having hypertension or proteinuria then ACE inhibitors may be used. Reduction of cyst volume by surgical decompression or percutaneous aspiration may be done for painful cysts. Sirolimus or *everolimus* may be tried to retard the cyst growth and delay the onset of renal failure.

Autosomal Recessive Polycystic Kidney Disease

The incidence of autosomal recessive polycystic kidney disease (ARPKD) is 1 in 10,000 to 40,000 livebirths. The underlying genetic defect is in PKHD 1 gene which codes for fibrocystin. The clinical presentation is variable:

- Antenatal ultrasound may show enlarged kidneys with loss of *corticomedullary* differentiation and *oligohydramnios*. Majority of patients with ARPKD present in infancy. They may have Potter's phenotype with large palpable flank masses and pulmonary hypoplasia. They may also have renal insufficiency at birth.¹⁵
- In older children, the presentation may be with hypertension, polyuria, renal dysfunction or recurrent urinary tract infections.
- Chronic kidney disease may also be a presenting feature as it occurs very early during the natural course of the disease.
- The extra renal manifestations of the disease include:
 - Liver involvement is overt in 50 to 60 percent and microscopic abnormality is seen in 100 percent of the patients. Congenital hepatic fibrosis may present with hepatomegaly and portal hypertension. Histopathology shows ductal plate abnormalities.¹⁶

Table 3: Diagnostic criteria for diagnosis of ARPKD

Ultrasound features – enlarged, echogenic kidneys with poor corticomedullary differentiation
One or more of the following:

- Absence of renal cysts in both parents when aged more than 30 years
- Clinical, laboratory or radiographic evidence of hepatic fibrosis
- Hepatic pathology demonstrating characteristic ductal plate abnormality
- Previous affected sibling with pathologically confirmed disease
- Parental consanguinity suggestive of autosomal recessive inheritance

- Choledochal cysts, Caroli's disease.
- Hypersplenism, esophageal varices and cholangitis may complicate liver disease.

The diagnostic criteria for ARPKD as suggested by Zerres et al¹⁷ are shown in Table 3.

Renal histopathology may reveal medullary duct ectasia, tubular atrophy and interstitial fibrosis. There is no specific treatment but vasopressin receptor antagonists, tyrosine kinase inhibitors, rapamycin and *octreotide* hold some promise. Hypertension needs to be controlled if present¹⁸. Yearly ultrasound for hepatic and splenic size is recommended. Endoscopic evaluation of oesophageal varices can be done along with monitoring of the hematological parameters. Chronic kidney disease should be managed conservatively initially and renal replacement therapy is to be considered if required. If antenatal ultrasonography is suggestive of severely affected fetus with early onset oligohydramnios, termination of pregnancy may be considered.

NEPHRONOPHTHISIS—MEDULLARY CYSTIC DISEASE COMPLEX

It consists of a group of inherited disorders with chronic sclerosing tubulointerstitial nephropathy which results in chronic kidney disease.

Nephronophthisis (NPH)

NPH has an autosomal recessive inheritance and it is the most common genetic cause of chronic kidney disease in the first two decades of life. NPH is classified as infantile NPH, juvenile NPH and adolescent NPH depending on the mutation in NPHP 2, 1 and 3 respectively. NPHP gene encodes nephrocystins. Juvenile onset NPH is the most common type.^{19,20}

Clinical Features

- Insidious onset of chronic kidney disease leading to ESRD by 2nd decade of life

- Polyuria, polydipsia, secondary enuresis
- Anemia, rickets
- Renal salt wasting and salt craving
- Hypertension and hematuria are rare presentations
- Extra renal manifestations:
 - Retinitis pigmentosa in Senior Loken syndrome
 - Oculomotor apraxia
 - Visual loss
 - Hepatic fibrosis
 - Hypoplasia of cerebellar vermis in Joubert's syndrome
 - Situs inversus

Ultrasonography reveals small to normal sized kidneys which are echogenic with small cysts in medulla or cortico medullary junction.

Medullary Cystic Kidney Disease

Medullary cystic kidney disease (MCKD) is an autosomal dominant condition resulting from mutations in MCKD 1 and 2 gene and presents in early adulthood (third decade).²¹ It is associated with hyperuricemia and gout, and not associated with any extra renal features or syndromes. Treatment is symptomatic and involves management of chronic kidney disease. Post-transplant—there is no recurrence of the disease in the renal allograft.

CYSTINOSIS

Cystinosis is an autosomal recessive condition characterized by defective lysosomal transport of cystine, leading to increased intralysosomal cysteine accumulation.²² The defective gene is CTNS, which encodes cystinosisin, a lysosomal membrane protein that promotes cystine exit from lysosomes.

Clinical Presentation

- Symptoms usually become prominent in the second half of infancy, with a median age at onset of symptoms being 10 months.²³
- Poor weight gain or weight loss, inadequate feeding, vomiting, constipation, lethargy, weakness, excessive thirst, and polyuria.
- Growth retardation and vitamin D resistant rickets.
- Blond hair which are sparse and thin.
- Hypothyroidism, impaired glucose tolerance, delayed puberty.
- *Eye:* Fundoscopy may reveal a patchy depigmentation of the retina with peripheral clumps of pigment. Cornea, iris and conjunctiva may show deposition of crystals.
- In the absence of cystine-depleting therapy, progressive glomerular damage leads to end-stage renal disease by the end of the first decade, but this can occur as early as 2 to 3 years.²⁴
- *CNS symptoms:* Bradykinesia, tremors, memory loss, dementia, rigidity, weakness, paresthesia, dysarthria, and dysphagia.

Management includes supportive treatment, conservative treatment for chronic kidney disease along with initiation of oral cysteamine therapy. Cysteamine eye drops have also been tried to prevent deposition of cystine crystals in the eyes. Renal transplantation is successful but it doesn't correct the systemic disorder and cystine continues to accumulate in the nonrenal tissues.

NAIL PATELLA SYNDROME

Nail patella syndrome is an autosomal dominant condition resulting from the mutation of LMNX1B gene. The clinical features of this condition include absent or hypoplastic patella with dystrophic nails.²⁵ Pelvis X-ray may reveal iliac horns. Renal involvement may be in the form of proteinuria, hypertension, hematuria, urinary acidification and concentration defect. In this condition, chronic kidney disease may occur in 10 to 20 percent of the cases. Treatment with ACE inhibitors may be initiated to reduce the proteinuria and manage hypertension.

LOWE SYNDROME

Lowe syndrome is better known as oculocerebrorenal syndrome and it has a X-linked recessive inheritance. The gene mutated in this disorder is OCRL1 gene. In this syndrome, there is involvement of eyes, brain and kidneys.²⁶ Renal manifestations include Fanconi syndrome, hypercalciuria, nephrocalcinosis, urolithiasis and end stage renal disease (ESRD). Extrarenal manifestations include glaucoma, cataract, psychomotor retardation and hypotonia.¹¹

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Section 11

Pediatric Surgery

Editor
Rajeev Kulshreshtha

Inguinoscrotal Swelling

Kapil Vidyarthi

Inguinoscrotal swelling is one of the most common surgical problems encountered in children. Common nonacute surgical problems in the region are:

- Abnormalities of processus vaginalis
- Abnormalities of descent of testis
- Varicocele
- Lymphadenitis
- Saphena varix
- Lymphangiectasia
- Diffuse lipoma of cord
- Benign neoplasms
- Malignant tumors.

ABNORMALITIES OF PROCESSUS VAGINALIS

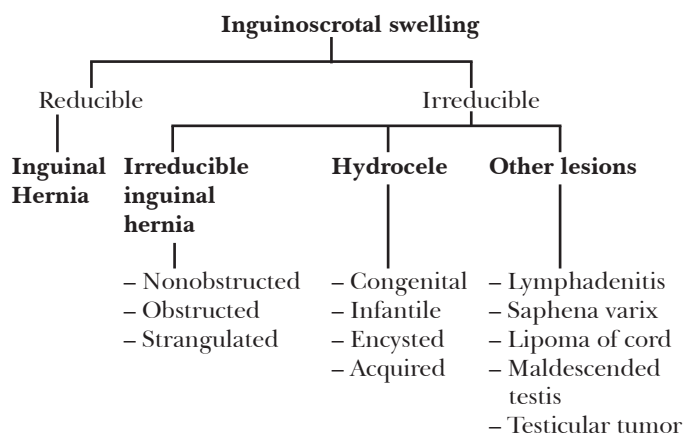
Processus vaginalis is the covering of testis. It normally closes before birth. If it fails to close it gives rise to various abnormalities detailed below (Figs 1A and B). If the communication with the peritoneum is big it gives rise to hernia (Fig. 2) and if the communication is small, it gives rise to *hydrocele* (Figs 3 and 4).

Processus vaginalis is integral part of the process of descent of testis by providing necessary hydraulic force for the descent. It tends to close around birth of the child. However in approximately 20 percent individuals it tends to remain patent throughout life without causing hernia.

A patent processus vaginalis is a potential hernia.¹ However all processus vaginalis are not troublemakers. There are some *factors responsible for herniation* in patent processus vaginalis. These are undescended testis, exstrophy bladder, ascites, ventriculoperitoneal shunt, connective tissue disorders and chronic respiratory diseases. Inguinal hernias and hydrocele are the most common problems associated with patent processus vaginalis.

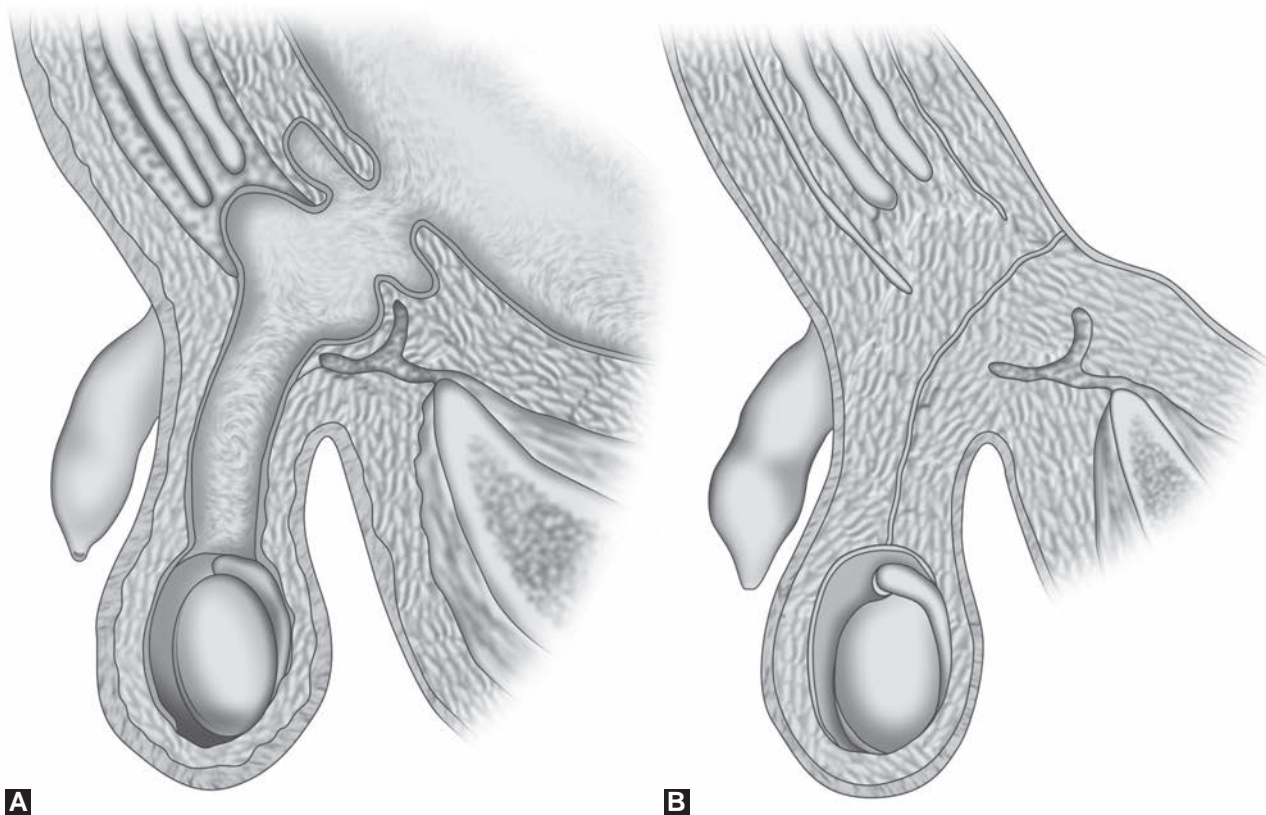
Approach to an inguinoscrotal swelling can be summarized in Flow chart 1.

Flow chart 1: Inguinoscrotal swelling



INGUINAL HERNIA

About three to five percent of healthy,² full-term babies may be born with an inguinal hernia and one-third of hernias of infancy and childhood appear in the first 6 months of life. In premature infants, the incidence of inguinal hernia is substantially increased, up to 30 percent. In just over 10 percent of cases, there can be a family history of similar problem. Inguinal hernia is associated with a multitude of genetic syndromes.³ Disorders of the microfibril, elastin, collagen, and the glycosaminoglycan component of the extracellular matrix can result in an increase in the likelihood of inguinal hernia. In addition, inguinal hernia may be the presenting feature of disorders of sexual differentiation. Inguinal hernia of unknown etiology also occurs more commonly in several other groups of genetic diseases including chromosomal disorders, microdeletion disorders such as 2q11.2 microdeletion, and in single gene disorders.⁴ However, overall chances of inguinal hernia being a part of genetic disorder is low and does not merit



Figs 1A and B: Processus vaginalis: (A) Open; (B) Closed

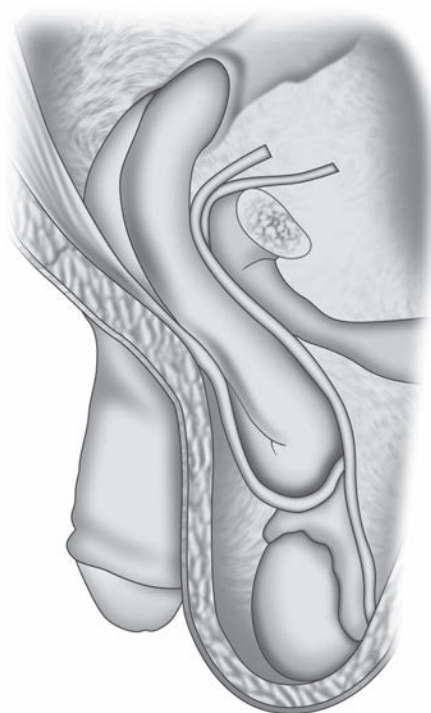


Fig. 2: Left inguinal hernia

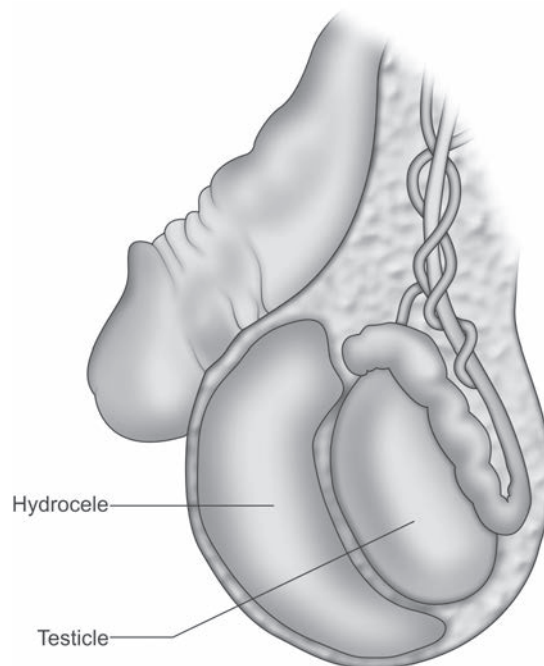


Fig. 3: Infantile hydrocele

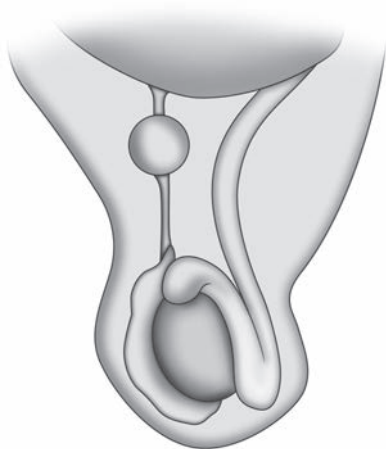


Fig. 4: Encysted hydrocele of cord

genetic work-up. However, connective tissue abnormalities, a part of many genetic disorders, are predisposing factors for PPV culminating into inguinal hernia. Right side hernias are commoner than left. Inguinal hernia is less common in girls.

Clinical Presentation

A reducible swelling in one or both inguinoscrotal regions, is an inguinal hernia unless and until proved otherwise. Diagnosis is obvious and does not require any further investigations. However more often the child is brought with history of such swelling with no apparent abnormality on examination. It may not be possible to make the child strain to elicit impulse, as the child may be too small to comply with the request. Even a bigger child may not understand the importance of the request and may not fall in line. *Ultrasonography* and *computerized tomography (CT) scan* have been ordered with absolutely no additional help. The defect will be revealed only if contents are present at time of examination by whatever means. Moreover, in event of a negative imaging, it becomes difficult for the lay relatives to understand that the problem actually exists.

In such situation, *definite history* by a responsible and intelligent parent can be considered sufficient. A *digital photograph* taken at the time of swelling can be still more helpful.⁵ Gentle rolling of spermatic cord over a bony prominence, like pubic tubercle, usually reveals a feeling of rubbing rubber – *silky glove sign*. The finding is due to thickened spermatic cord as well as hypertrophied cremasteric muscle.⁶ The finding is an irrefutable evidence of a patent processus, most likely a hernia.

Treatment

There is no dispute that the treatment of reducible inguinal hernia is an elective *herniotomy* under general anesthesia. There is plenty of discussion in recent past

about *open versus laparoscopic* herniotomy. At present, there is no definite proved advantage of one over the other. It also depends on surgical acumen of the surgeon. An accomplished laparoscopist will be able to do as good a job as an expert nonlaparoscopic surgeon.

In past, surgeons used to resort to *contralateral exploration* to avoid second surgery. At present, pediatric anesthesia is reasonably safe even in preterms and medically compromised children.⁷ Thus contralateral exploration is not warranted. Contralateral exploration exposes the delicate cord structures to unnecessary handling especially when the sac does not exist. However, it will be prudent on the part of surgeon, to explain to the parents the possibility of contralateral hernia developing at a later date.

The *timing of surgery* is, at presentation. There is no wisdom in waiting and getting the hernia obstructed with its associated complications. There has been discussion on timing of herniotomy in a neonate, specially prematures, in view of reports of postanesthesia apnea in these children.⁸ However, obstruction is more troublesome in these patients and it is advisable to operate them before they are discharged from NICU. By that time comorbid conditions will have been taken care of anyway.

Herniotomy might not be adequate in the presence of connective tissue disorders and some form of posterior wall repair may have to be added to reduce the possibility of a recurrence. There are reports of spontaneous closure of processus vaginalis and cure of inguinal hernia⁹ especially in neonates and prematures. However, one has to be extremely vigilant about obstruction. The author would not like to advocate it especially in our context where availability of surgical expertise is not absolutely guaranteed.

Irreducible hernia: In the absence of signs of obstruction or strangulation, an attempt may be made to reduce the hernia by gentle manipulation, aided by sedation and elevation of foot end of the bed. It will be worthwhile postponing surgery for 48 to 72 hours if satisfactory reduction has been achieved. This reduces the edema and makes surgery safer from patient's point of view. If not reduced, it should be treated as an obstructed hernia.

Obstructed inguinal hernia: In the presence of clinical evidence of intestinal obstruction, emergency surgical intervention is needed. It is still possible to open the sac, reduce the contents and proceed with herniotomy.

Strangulated inguinal hernia: When there are signs of vascular compromise and systemic evidence of toxemia, it is better to undertake a laparotomy and handle the gut from the peritoneal aspect. It may still be possible to do a herniotomy, approaching the internal ring from within.

HYDROCELE

We have a patent processus vaginalis communicating with peritoneum as in an inguinal hernia. However, the

communication is small and intestines do not come out. It is only peritoneal fluid which forms the contents. It is *not possible to reduce* the contents manually because of 'inverted ink bottle effect'. The contents will be *transilluminant*. There is no tenderness or any other sign of inflammation. In a communicating hydrocele, there may not be a swelling when the child wakes from sleep. During sleep, the fluid quietly slips back into the peritoneal cavity. It reappears, when the activity resumes in the form of kicking and playing.

In a noncommunicating and encysted hydrocele, this finding will not be there.

Treatment is herniotomy under general anesthesia. There is no controversy about approach to this. The approach has to be inguinal rather than scrotal. We have to close the internal ring. Eversion of sac is bound to lead to recurrence as the basic problem has not been tackled. However in these cases one can safely wait for spontaneous closure of communication. It is advisable to wait for at least 18 months. At least 75 percent will automatically get cured. Alternative medicine takes credit for these type of cases. It is not uncommon to find a child cured of inguinoscrotal swelling by touching a brinjal, blessed by a babaji, to the swelling and keeping at an unapproachable place. The swelling shrinks with the brinjal. The fact is that it would have shrunk any way with or without treatment. Placebos have also been tried for this. The treatment is sometimes used in an inguinal hernia rather than hydrocele with its own peril.

INGUINAL LYMPHADENITIS

The region richly abounds in lymph nodes and all abnormalities of lymphatic system are bound to reflect in the area. These are nonreducible, lobulated, nontransilluminant and much more firm than other abnormalities in the area. An inflammatory mass will be tender on palpation. An abscess may be fluctuant. The nodes are more often nonspecific and reactive in this area. However, tuberculosis, lymphoma, etc. form important differential diagnosis as lymphadenopathy anywhere else in body. The problem is dealt with in detail in other sections.

TESTICULAR NEOPLASM

Any firm to hard, nontender testicular swelling is highly suspicious and is to be treated as neoplastic unless proved otherwise.

Clinical Presentation

About 85 percent of children with testicular tumors present with *painless scrotal swelling*. There may be a *secondary hydrocele* in 10 to 25 percent cases. At times *scrotal pain* may be a presenting complaint. A *history of trauma* may be present. But more often the incident alerts the child to the

presence of a painless and enlarged testicle rather than causing it.

Physical examination usually reveals a painless scrotal swelling with a firm to hard consistency or associated hydrocele. Some hormonally active tumors may appear in association with *precocious puberty* or *gynecomastia*. The lesion is *nontransilluminant* and is mainly *limited to scrotum*. However, at times, there is growth of tumor along spermatic cord giving rise to an *inguinoscrotal swelling*.

Testicular tumors are reported to be benign in approximately 70 percent cases. Benign teratoma is the most common testicular tumor, followed by Leydig-cell tumor, epidermoid cyst and Sertoli cell tumor. Other benign tumors are cystic dysplasia, and intratesticular focal fibrosis. Malignancy has been reported in approximately 30 percent of cases. Common malignant tumors are yolk-sac tumor, and embryonal carcinoma. Malignant tumors are more often reported in adolescents (77%).¹⁰

Treatment

Orchiectomy has traditionally been the gold standard for testicular tumors in children. Any suspicion of the testicular tumor warrants an inguinal approach to prevent scrotal violation by the tumor. Current trends emphasize that testis-sparing surgery should be performed for benign lesions such as teratoma, Leydig cell tumor, and epidermoid cyst based on frozen biopsy findings. Literature findings and our experience suggest that radical inguinal orchidectomy is the accurate treatment for Stage I malignant germ cell tumors and Group I and IIa paratesticular rhabdomyosarcoma. Retroperitoneal lymph node excision is not of benefit either as a staging or therapeutic procedure in Stage I and Group I and IIa diseases of these tumors.¹¹ Retroperitoneal lymph node excision should be reserved for malignant germ cell tumors patients who have persistent elevation of alpha-fetoprotein after orchiectomy in the presence of normal total body CT scan, and for patients presenting with Stage II and III disease with definitive abnormality on CT scans, and group IIb, Ic, and III paratesticular rhabdomyosarcoma patients with radiologic evidence of retroperitoneal involvement on CT scans. High ligation should be done as a complementary procedure after scrotal orchiectomy to increase the survival rates.

VARICOCELE

A varicocele is mass of enlarged and swollen veins in the testicle that essentially feels like a bag of worms. A varicocele is generally neither harmful nor painful. However, it can cause a discomfort and a dragging sensation in groin. Approximately 15 percent of boys have this condition, which almost always occurs on the left side since left testicular vein drains into renal vein and has no valves. Therefore, the pressure of larger veins is transmitted to

it. A varicocele usually develops at puberty, but can occur earlier. A varicocele developing in a younger child should alert to the possibility of a lesion in its drainage area, e.g. renal tumor. Only occasionally does an adolescent with a varicocele experience any pain or discomfort. Therefore, the condition is usually discovered during a routine physical examinations or incidentally while bathing, when the large veins can be easily seen and felt. Physical examination in standing posture reveals the lesion more often. There may be an impulse on coughing. The swelling may reduce completely on lying down. Horizontal lie of the testis has recently been observed in association with varicoceles in a pediatric population. The condition may revert to normal after surgery for varicocele has been performed. Horizontal lie of the testis in children is a new clinical sign that should alert the examiner to the possibility of an underlying varicocele.¹²

Treatment, if required can be an open or laparoscopic ligation of testicular vein.

Saphena varix is a varicosity of saphenous vein at its drainage into femoral vein. It is not common in children. If present, a cause has to be found out and managed.

UNDESCENDED TESTIS

At times, the testis can be palpated in inguinal region usually in superficial inguinal pouch. If it can be manipulated into the scrotum, it is labeled as retractile testis and needs no further treatment. A true undescended testis cannot be brought to scrotum by manipulation and has to be surgically corrected. A word of caution about imaging studies in this regard. A retractile testis present in canal at time of imaging – ultrasound/ CT/ MRI – will be labeled as undescended testis unless manipulated at time of procedure. Clinical examination is more informative in this regard.

Other benign tumors: Lipoma of cord, lymphangioma of cord and lymphangie, etc. can present as inguinoscrotal swelling. The attachment to cord can be ascertained by fixing the cord, by pulling the testis down and making it

taut. A tumor attached to cord will move along with the cord and vice versa.

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Abdominal Trauma

Alpana Prasad

INTRODUCTION

Abdominal trauma is one of the major causes of severe injury in children. It is the most common initially missed fatal injury in childhood.¹ It accounts for approximately 10 percent of deaths from injury in childhood. To minimize the morbidity and mortality associated with these injuries, a high degree of suspicion and an early diagnosis is essential.

Abdominal injury in children is mainly due to blunt trauma, with road-traffic accidents being the reason in majority of cases.² Pedestrian injuries are the second most common cause of abdominal injury in children. The mechanism of injury depends on the chronologic and developmental age of the child and it determines the pattern of other associated injuries. Injury due to fall is more common in toddlers and causes significant associated head and extremity injuries.³ Pedestrian and bicycle injuries are more often seen in school age children and may cause multiple injuries to head, neck, trunk and extremities. Bicycle handlebar injuries in children include traumatic pancreatitis, renal and splenic injury, duodenal hematoma and bowel perforation.⁴ Abdominal injury may be caused by seatbelt which has been incorrectly used or is not suitable for a small child. Penetrating injuries such as gun-shots and stab-wounds are less common and seen in older children and adolescents and account for a disproportionate number of trauma related deaths. Abdominal trauma secondary to abuse is not uncommon particularly in younger children with delayed presentation and relatively more severe injuries.

There is a higher risk of multiple organ injury in a child as the kinetic energy from an external force is absorbed by a body mass that is considerably smaller. Also the relatively large, superficial liver, spleen and the kidneys are not well protected from blunt trauma by the pliable ribs and thin abdominal wall muscles, and organ

injury may occur without fracture of the overlying ribs.³ In children the kidneys retain fetal lobulations which may lead to easier separation and fracture and also the urinary bladder is an intra-abdominal organ and at risk during abdominal trauma.

ASSESSMENT OF A CHILD WITH ABDOMINAL INJURY

Clinical assessment begins with primary survey ABCDE sequence (airway, breathing, circulation, disability, exposure) and resuscitation. Oxygenation and ventilation must be the priority as the main cause of cardiac arrest in children is respiratory arrest. Early signs of bleeding in an injured child are tachycardia and cold peripheries. Blood pressure is not a reliable indicator of circulatory status. An intra-abdominal or pelvic injury must be suspected when the primary survey reveals evidence of bleeding without an obvious injury to account for this. The child is methodically examined for injuries in the secondary survey. A child's stage of development and inability to communicate verbally may delay the examination. Any external evidence of injury on the abdomen is noted. Abdominal distension, tenderness and guarding indicate an intra-abdominal pathology and worsening of these abdominal signs suggest progressive peritonitis from bleeding or intestinal or bladder injury. Physical examination of a child's abdomen in trauma has been generally considered an unreliable and inaccurate indicator of injury and may lead to missed injuries.¹ Hence, these children need to undergo further investigations to identify their injuries.

Laboratory investigations may be relatively normal on admission and to detect an evolving pathology, serial measurements are necessary. Progressive fall in hemoglobin and hematocrit may be an evidence of continuing hemorrhage. Persistent metabolic acidosis may indicate hypovolemia or tissue ischemia as seen in intestinal

injury, while progressively rising serum amylase levels suggest pancreatic duct injury. Other than a urine analysis, routine “trauma panels” are not sensitive or specific for identifying intra-abdominal injury in children.^{5,6} Elevation of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are predictive of internal abdominal injury.⁷

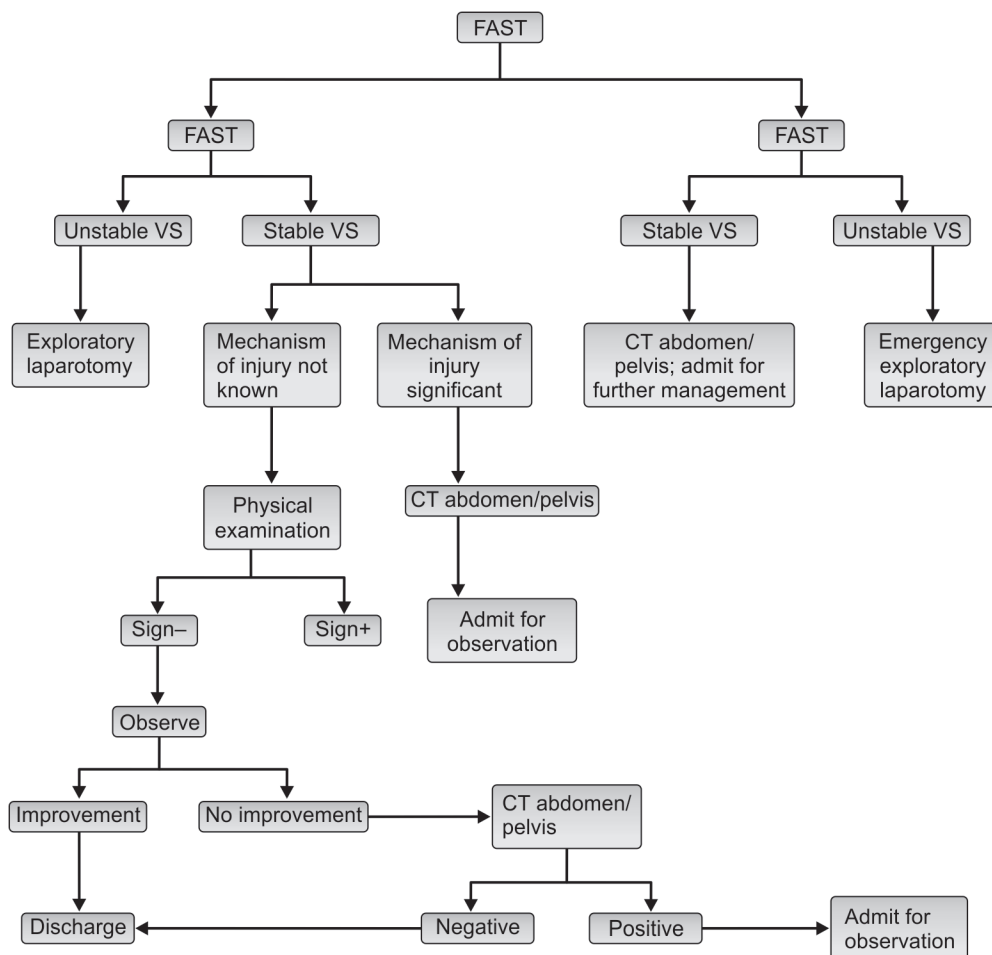
There is an increasing reliance on imaging modalities to identify intra-abdominal injuries since the increasing prevalence of nonoperative management. The modern imaging techniques like ultrasound and CT scan have become sensitive but they have their limitations. The initial emergency X-rays must include an AP view of the abdomen and pelvis to identify pneumoperitoneum, or acute gastric dilatation or any pelvic fracture besides those of the cervical spine and chest.

Focused abdominal sonography for trauma (FAST) is portable, easy, quick and noninvasive modality for initial screening of children with abdominal trauma for

identification of solid organ injury and free intraperitoneal fluid.⁸ The FAST examination in children has a high specificity (95%) but low sensitivity (33%) in identifying intestinal injury, and it does not provide the same information as a CT scan.^{9,10} A positive FAST exam in a hemodynamically unstable child would indicate an urgent laparotomy whereas the same in a stable child should be followed by abdominal CT scan to better define the injury.¹¹ A negative FAST in an unstable patient warrants examination for an extra-abdominal source of bleeding, while in a stable patient it should be followed with observation for any evolving symptoms and follow-up FAST or CT scan according to the clinical condition. Ultrasound should be used in conjunction with physical examination and laboratory investigations to determine the need for further imaging studies (Flow chart 1).

The preferred method for identifying abdominal and retroperitoneal injuries is CT scan with intravenous contrast enhancement. The greatest limitation of abdominal

Flow chart 1: Algorithm for imaging in pediatric abdominal trauma



FAST – Focused abdominal sonography for trauma
VS – Vital sign

CT in trauma is the inability to reliably diagnose bowel injury. The presence of free intraperitoneal fluid in the absence of an injury to solid organs must raise suspicion of intestinal perforation. CT is contraindicated when there is respiratory or hemodynamic instability or if there is an extra-abdominal injury like a head injury requiring immediate intervention.^{12,13}

Diagnostic peritoneal lavage (DPL) may be useful in evaluating the abdomen of an unconscious child who is too unstable to be shifted for CECT abdomen or when imaging facility is not available. Routine use of DPL in children is not recommended because it is painful and hence, will make subsequent clinical assessment difficult and presence of residual lavage fluid will cause confusion in interpretation of follow-up US or CT scan. Intravenous pyelography and angiography are useful in selected situations. Tc-99 radioisotope scanning may be rarely used.

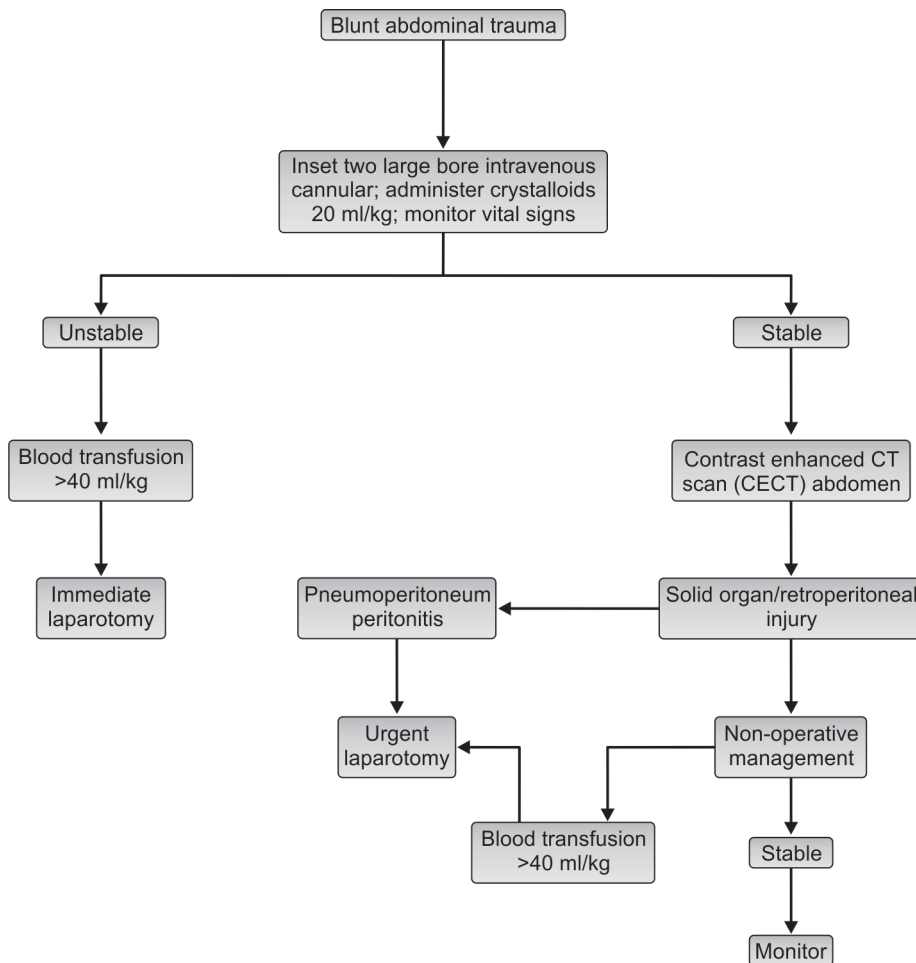
It must be remembered that there are some injuries that can be missed even on a CECT scan and hence, observation at a tertiary trauma center is the only proven modality to decrease the risk of missed abdominal trauma.¹⁴

MANAGEMENT

The general principles of emergency management of a child with abdominal trauma should follow advanced trauma life support (ATLS) and advanced pediatric life support (APLS) guidelines. Vital signs are monitored. For rapid infusion of fluids, two large bore intravenous lines are inserted. A nasogastric tube is inserted to empty the stomach and a urethral catheter is placed to measure urine output accurately. A suprapubic catheter may be required if there is blood at the urethral meatus. Hypovolemic shock is managed by administering initial fluid bolus of crystalloids, normal saline or ringer lactate, and later whole blood or packed cells depending on the rate of hemorrhage and the degree of shock. A child in severe shock would require intubation and mechanical ventilation (Flow chart 2).

Management of abdominal injuries in children has evolved significantly over the last four decades. The observation that most solid organ injuries would “heal themselves” and that operative intervention could interfere with this healing process, provided the basis for the development of

Flow chart 2: Algorithm for management blunt trauma abdomen



the current concept of nonoperative management for most blunt solid organ injuries.^{15,16} In patients with solid organ injury, the risk of hollow viscus injury is three to four percent and increases with the number of injured solid organs. Hence, the child needs to be admitted for repeated clinical assessments, continuous monitoring of vital signs and urine output, serial estimations of hemoglobin, hematocrit and serum amylase levels as indicated. This is the most sensitive method to detect a hollow visceral or mesenteric injury that may require laparotomy.¹⁷

INDICATIONS FOR SURGERY

Continuing hemorrhage requiring transfusion in excess of 40 ml/kg of packed red blood cells remains to be the most common indication for surgical exploration. Laparotomy is also indicated for penetrating injuries and when there is evidence of intestinal, mesenteric or a major pancreatic injury. Bleeding and hollow visceral injury aside, a percentage of conservatively managed patients may ultimately come to some type of intervention for ongoing complications, particularly biliary and urine leaks as well as delayed vascular complications. The majority of these can be managed outside of the acute period and in addition, many interventions will be performed percutaneously and endoscopically, avoiding open exploration.^{18,19} Despite their delayed intervention, the long-term outcome of this group of patients is not compromised, with the benefit that they spared the insults of early surgery.

Role of laparoscopy in pediatric abdominal trauma is yet to be defined. It has been recommended as an alternative to laparotomy in blunt abdominal trauma and also in stable children with penetrating wound of the abdominal wall.²⁰

MANAGEMENT OF SPECIFIC ORGAN INJURIES

Splenic Injury

Spleen is the most commonly injured organ in blunt abdominal trauma in children as it is not well protected by overlying ribs. More than 50 percent of these children have

multiple solid organ injuries mainly to the liver and left kidney and up to 85 percent have extraabdominal injuries. Splenic injury presents clinically with left upper quadrant pain and tenderness and referred pain to the left shoulder. Chest X-ray may show contusion in the lower lobe of left lung, often without overlying rib fracture. In a hemodynamically stable child, an abdominal CECT scan helps in diagnosing and grading the splenic injury (Table 1).²

The immediate consequence of splenic trauma is hemorrhage and in >90 percent cases the bleeding stops spontaneously within hours of injury. Following initial resuscitation, children who remain hemodynamically unstable, requiring blood transfusion >40 ml/kg or are suspected to have another intra-abdominal injury requiring exploration, are an absolute indication for surgery.^{21,22} Spleen should be preserved whenever possible and techniques like partial splenectomy, splenorrhaphy, splenic artery ligation and selective splenic artery embolization have become the mainstay of splenic injury management. Splenic preservation prevents overwhelming postsplenectomy infection (OPSI), which has an incidence of 2 to 11 percent following post-traumatic splenectomy and a mortality rate of up to 50 percent.²³

Nonoperative management involves hospitalisation for bed rest and monitoring until the abdominal signs have resolved. Majority of the hemodynamically stable children with isolated blunt splenic injuries can be treated safely with less than a week hospital stay, followed by three weeks of quiet activity at home and then three months of light activity with avoidance of contact sports, followed by resumption of complete, normal lifestyle. Less than 10 percent of children with isolated splenic injury require a blood transfusion. Delayed complications in these patients are rare. Secondary acute hemorrhage or rupture of a subcapsular hematoma may necessitate blood transfusion and splenectomy. Fatal delayed hemorrhage is very rare but a devastating complication and hence, residual hematoma needs to be followed up closely. Splenic abscess, if detected, can be drained percutaneously. Non-operative management of pediatric splenic injuries leads to complete recovery in 90 to 98 percent of patients.

Table 1: Grading of splenic injuries

Grade 1	Subcapsular hematoma <10% of surface area or capsular tear <1 cm in depth
Grade 2	Subcapsular hematoma of 10-50% of surface area, intraparenchymal hematoma of <5 cm in diameter or laceration of 1-3 cm in depth and not involving trabecular vessels
Grade 3	Subcapsular hematoma >50% of surface area or expanding and ruptured subcapsular or parenchymal hematoma, intraparenchymal hematoma of >5 cm or expanding, or laceration >3 cm in depth or involving trabecular vessels
Grade 4	Laceration involving segmental or hilar vessels with devascularization of >25% of the spleen
Grade 5	Shattered spleen or hilar vascular injury

Hepatic Injury

Liver is the second most common intra-abdominal organ to be injured following blunt trauma in children as it is relatively large and unprotected. It should be suspected in any child with significant mechanism of injury, with right upper abdominal pain or tenderness or contusion or right rib fractures. Injury to the porta hepatis may be associated with damage to the duodenum and pancreas. Gallbladder and extrahepatic bile duct injuries are rare and may present with a biloma or biliary fistula.

In hemodynamically stable patients, CECT abdomen is done for grading the extent and pattern of liver injury.²⁴ In unstable patients, diagnosis should be made at laparotomy. Laboratory finding predictive of hepatic injury is AST >400 IU/L or ALT >250 IU/L. It has been shown that increased ALT levels of more than 131 IU/L and the presence of abdominal trauma were indicative of intra-abdominal injury with 100 percent sensitivity.²⁵

Management depends on the hemodynamic stability of the child and not on anatomical grade of the injury. Stable patients are managed nonoperatively by serial abdominal examination and serial hematocrit and liver enzyme estimation. If despite fluid resuscitation and blood transfusion, a child is unstable, then an exploratory laparotomy is indicated (Table 2).

Majority of children (85-90%) with blunt hepatic trauma have relatively low-grade (grade 1-3) injuries that can be managed nonoperatively and of these only 2 to 10 percent required a blood transfusion. Angiographic embolization is gaining acceptance in the management of higher grade hepatic injuries.^{25,26}

The risk of complications following nonoperative management is approximately 10 percent, which includes delayed hemorrhage, abscess formation and bilioma. In symptomatic patients, follow-up imaging with USG or CT scan is recommended to identify residual hematoma or other fluid collections. Intra-abdominal bleeding is the

major cause of death from liver injury. Hepatic injuries have a higher mortality risk (2.5%) than splenic injuries (0.7%), and hepatosplenic injuries have the highest risk of mortality (8.6%).²⁴

Pancreatic Injury

As compared to other solid organ injuries, pancreatic injury is relatively uncommon, occurring in 3 to 12 percent of children with abdominal trauma. It is almost always due to blunt trauma causing compression of the pancreas against the lumbar vertebral column. Fall on to the handlebar of a bicycle or a deliberate blow or kick are a common mechanism of pancreatic injury. Injury to head of pancreas may be associated with duodenal and bile duct injury, while injury to tail of pancreas may be associated with splenic injury. Due to the retroperitoneal location of the pancreas, its injury is difficult to diagnose initially as the clinical signs and laboratory markers may be subtle and require time to evolve. A progressive rise in serum amylase levels during the first 24 to 48 hours strongly suggests major pancreatic duct injury, however, measurement of serum or urinary lipase level is more specific for pancreatic injury. Abdominal CECT scan is the preferred imaging modality but it tends to underestimate the severity of pancreatic injury and has a widely variable sensitivity ranging from 28 to 85 percent. Pancreatic duct injury is best visualized by endoscopic retrograde cholangiopancreatography (ERCP) or magnetic resonance cholangiopancreatography (MRCP).²⁷ With ERCP there is a risk of pancreatitis or perforation, whereas MRCP is safer, sensitive and noninvasive (Table 3).

Pancreatic injuries without ductal disruption can be safely managed nonoperatively with bowel rest and intravenous feeding and result in low morbidity.²⁷ However, compared to other solid organ injuries, pancreatic injury is most likely to fail nonoperative management.²⁸ Urgent surgery is preferred when the main pancreatic duct has

Table 2: Grading of liver injuries

Grade 1	Subcapsular hematoma <10% surface area, capsular tear, parenchymal laceration <1 cm deep, isolated periportal blood tracking
Grade 2	Subcapsular hematoma 10-50% surface area, intraparenchymal hematoma 1-3 cm thick, parenchymal laceration 1-3 cm deep and <10 cm in length
Grade 3	Subcapsular hematoma >50% surface area or expanding, ruptured, intraparenchymal hematoma >3 cm thick or expanding, parenchymal laceration >3 cm deep
Grade 4	Subcapsular/parenchymal hematoma >10 cm thick, Parenchymal disruption involving 25-75% of hepatic lobe (lobar destruction or devascularization)
Grade 5	Parenchymal disruption involving >75% of hepatic lobe (global destruction or devascularization of liver), juxtahepatic venous injury
Grade 6	Hepatic avulsion

Table 3: Grading of pancreatic injuries

Grade 1	Contusion or hematoma
Grade 2	Capsular or parenchymal disruption without major ductal injury
Grade 3a	Capsular or parenchymal disruption with ductal involvement distal to the superior mesenteric vessels; intact duodenum
Grade 3b	Capsular or parenchymal disruption with ductal involvement to the right of the superior mesenteric vessels; intact duodenum
Grade 4	Combined extensive pancreatic and duodenal crush injury

Table 4: Grading of renal injuries

Grade 1	Contusion, subcapsular hematoma nonexpanding, no laceration
Grade 2	Non-expanding perirenal hematoma, parenchymal laceration <1 cm deep, no urinary extravasation
Grade 3	1 cm deep parenchymal laceration without urinary extravasation
Grade 4	Parenchymal laceration extending through renal cortex, medulla and collecting system, main renal artery or vein injury with contained hemorrhage
Grade 5	Complete shattered kidney, avulsion of renal hilum

been transected with or without associated duodenal injury. Complications of pancreatic injury are pseudocyst formation, pancreatic abscess, fistula, duct stricture and chronic pancreatitis. To monitor the resolution of pancreatic injury and to detect pseudocyst formation, these patients need to be followed with serial serum amylase/lipase estimation and USG or CT scan. More than 50 percent of pseudocysts will resolve with nonoperative management and the remaining may be treated by ultrasound guided percutaneous drainage or endoscopic or open cystogastrostomy. A persistent pancreatic fistula may require excision and a duct stricture is usually treated by endoscopic dilatation and stenting.

Gastrointestinal Tract Injuries

Gastrointestinal tract injuries occur less frequently in children (1-5%) than solid organ injuries, and their clinical presentation is more subtle. Localized blunt force such as a seat belt, cycle handlebar, road traffic accident, or deliberate blow or kick is a common mechanism of intestinal injury. It should be suspected in a child with trauma presenting with abdominal pain and tenderness and on the initial examination there is peritonitis or hemodynamic instability due to mesenteric bleeding. The most important and sensitive method for diagnosing intestinal or mesenteric injury is by serial abdominal examination. Imaging modalities like FAST scans are less sensitive for intestinal injuries and abdominal CT scan with intravenous contrast is preferred.¹⁰ Specific CT scan findings suggestive of intestinal injury are the presence of extraluminal air, extraluminal contrast material, or a moderate-to- large amount

of free fluid without evidence of solid organ injury, and these are indications for surgical exploration.

Intestinal contusion or intramural hematoma may cause temporary intestinal obstruction but usually heal without complication. A hemodynamically stable child with no clear clinical or radiographic evidence of intestinal injury serial monitoring is required. Any child with initial or evolving peritonitis or intestinal injury on imaging should undergo an exploratory laparotomy.

Renal Injuries

Kidney is susceptible to injury in children because of the compliance of the overlying ribs and the paucity of perinephric fat to absorb the energy of an impact. Renal injury should be suspected in any child with significant trauma presenting with abdominal or flank pain, tenderness, ecchymosis or posterior rib fractures.²⁹ Injury to kidneys range from contusion to parenchymal laceration with fragmentation (Table 4). Hematuria is strongly suggestive of renal injury but the degree of hematuria does not correlate with the severity of renal injury (Table 4).

Hemodynamically stable children with gross hematuria should undergo abdominal CT scan with IV contrast to diagnose and grade renal injury. In unstable patients, diagnosis is usually made at laparotomy. The standard practice is renal preservation.³⁰ Nonoperative management is successful in most contusions or parenchymal lacerations with or without urinary extravasation. Perinephric hematoma or urinoma should be monitored by an USG scan. In the presence of a major hemorrhage, ongoing significant hematuria or an expanding flank mass,

angiography with selective embolization is the preferred treatment modality. Complications that may develop following nonoperative management are abscess formation, renal cyst, dystrophic calcification or urethral obstruction. Hypotension is a possible late complication after renal injury and long-term follow-up is advised.

CONCLUSION

Pediatric abdominal trauma management has evolved significantly in the last two decades.^{15,16} Recent advances in the diagnosis and treatment of abdominal injury in children has been contributed by radiologists (improved imaging) and pediatric surgeons (minimal access surgery), which has made pediatric trauma care increasingly non-operative.^{17,18} Nonetheless, in the multidisciplinary care of a critically injured child, the pediatric surgeon should remain in charge as the decision not to operate is always a surgical decision.

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Common Pediatric Surgical Emergencies

Kapil Vidyarthi

Mainly consists of Acute abdomen, Acute Scrotum, Respiratory Distress and Trauma. Each one of these problems will be dealt with in details, concentrating mainly on current perspective and controversies.

ACUTE ABDOMEN

It generally refers to acute pain in abdomen. However, vomiting bilious or nonbilious is also usually associated. Systemic manifestations in the form of fever, dehydration or toxemia may also be associated.

The clinical presentation of patients with an acute abdomen is often nonspecific. Both surgical and nonsurgical diseases may present with a similar clinical history and symptoms. Findings may be normal in patients who need emergency surgery (such as appendicitis) and may be abnormal in patients without a surgical disease (like salpingitis).

Laboratory findings (leucocyte count, erythrocyte sedimentation rate, CRP) are equally nonconclusive.

RADIOLOGY

A plain abdominal film has a limited value in the evaluation of abdominal pain. A normal film does not exclude an ileus or other pathology and may falsely reassure the clinician. An ileus (Fig. 1) may not be appreciated on a plain abdominal film if bowel loops are filled with fluid only without intraluminal air. Alternatively if a plain abdominal film does indicate an ileus than sonography or CT are usually needed to identify its cause. Thus, a plain abdominal film is seldom useful, with the exception of detection of kidney stones or a pneumoperitoneum (Fig. 2).

Common causes of acute abdomen are:¹

- | | |
|------------------------------------|------------------------------|
| • Trauma | Appendicitis |
| • Intussusception | Meckel's Diverticulitis |
| • Malrotation with midgut volvulus | Incarcerated inguinal hernia |

- | | |
|---|---------------------------|
| • Peritonitis with or without perforation | Necrotizing enterocolitis |
| • Adhesions with intestinal obstruction | Ruptured ovarian cyst |

Other less common causes are:

- | | |
|-------------------------------|----------------------------|
| • Constipation | Gastrointestinal infection |
| • Other infections | Viral illnesses |
| • Pelvic inflammatory disease | Mesenteric lymphadenitis |
| • Foreign body ingestion | Intestinal colic |



Fig. 1: Small Bowel Obstruction



Fig. 2: Massive Pneumoperitoneum

ACUTE APPENDICITIS

The condition may not be as sinister as it used to be in past, because of availability of modern antibiotics. However, considering morbidity (if not mortality) associated with it, the condition needs a due consideration.

Clinical Presentation

The classic triad of symptomatology consists of pain in periumbilical region shifting to RIF (Kocher's Sign), vomiting – initially ingested food and later bilious, and rebound tenderness in right iliac fossa (Blumberg sign). Low grade fever and leucocytosis are additional features.

Other clinical signs are²—*Rovsing's sign*—pain in right iliac fossa while palpating on Left side of abdomen.

Psoas sign or “*Obraztsova's sign*”: Right lower quadrant pain produced with either the passive extension of the patient's right hip (patient lying on left side, with knee in flexion) or by the patient's active flexion of the right hip while supine.

Obturator sign: Flexing and internal rotation of the hip causes pain in the hypogastrium.

Dunphy's sign: Increased pain in the right lower quadrant with coughing.

Sitkovskiy (Rosenstein)'s sign: Increased pain in the right iliac region as patient lies on his/her left side.

Bartomier-Michelson's sign: Increased pain on palpation at the right iliac region as patient lies on his/her left side compared to when patient was on supine position.

Aure-Rozanova's sign: Increased pain on palpation with finger in right Petit triangle (can be a positive Shchetkin-Bloomberg's sign) - typical in retrocecal position of the appendix.

Investigations

Sonography has the advantage of close patient contact, enabling assessment of the spot of maximum tenderness and the severity of illness without exposing the child to radiation. However, In general the diagnostic accuracy of CT is higher than sonography. In patients with inconclusive US results, CT can serve as an adjunct to sonography, and *vice versa*.

A number of clinical and laboratory based scoring systems have been devised to assist diagnosis -

Alvarado score:³ It is most widely used.

Migratory right iliac fossa pain	1Pt.
RIF Tenderness	2Pts.
Anorexia	1 Pt.
Rebound Tenderness	2 Pts.
Nausea and vomiting	1Pt.
Fever	1 Pt.
Leucocytosis	2 Pts.
Segmented Neutrophils	1 Pt.

A score below 5 is strongly against a diagnosis of appendicitis, while a score of 7 or more is strongly predictive of acute appendicitis. In patients with an equivocal score of 5 to 6, CT scan is used to further reduce the rate of negative appendectomy.

Tzanakis Scoring:⁴

Right lower abdominal tenderness	4 Points
Rebound tenderness	3 Points
Leucocytosis >12,000	2 Points
Positive ultrasound scan	6 Points

A score 8 or more points - >96 percent chance of appendicitis.

At *sonography* and *CT* the appendix is seen as a blind-ending nonperistaltic tubular structure arising from the base of the cecum. *The outer-to-outer diameter of the appendix is the most important imaging criterion*. Although an overlap of appendiceal diameters in normal and inflamed appendices can incidentally be found, a threshold value of 6 to 7 mm is generally used. *A normal appendix has a maximum diameter of 6 mm, is surrounded by homogeneous noninflamed fat, is compressible and often contains intraluminal gas.*

An inflamed appendix has a diameter larger than 6 mm, and is usually surrounded by inflamed fat. The presence of a fecolith or hypervascularity on Doppler, strongly supports inflammation.

CT depicts an inflamed appendix as a fluid-filled blind-ending tubular structure surrounded by fat-stranding. In patients who lack intra-abdominal fat the use of IV contrast can be helpful in depicting the inflamed appendix.

Matrix metalloproteinase (MMP) levels can be used as biomarkers of increased risk of appendiceal rupture among patients with *acute appendicitis* according to a cohort study. MMP-1 was higher in gangrenous ($p<0.05$) and perforated appendicitis ($p<0.01$) compared with controls. MMP-9 was most abundantly expressed in inflamed appendix and reached a tenfold higher expression in all groups with appendicitis compared with controls ($p<0.001$).

Treatment of appendicitis remains surgical excision of inflamed appendix – open or laparoscopic (Figs 3 and 4). The debate is on which of the procedure to resort to. If necessary expertise and equipment are available, *laparoscopy* does have some advantages. The morbidity is much less and we have the advantage of scanning rest of the peritoneal cavity for complications as well as other defects.

Nonoperative outcome: If surgical excision is not resorted to, an attempt is made by the peritoneum to localize the infection with the help of omentum, adjoining bowel loops and exudates. The inflamed organ is encased with the structures and a lump is formed. The lump can be taken care of at a later date – about 6 wks., either laparoscopically or by open surgery.

However, the favorable outcome may not be there in all cases. This is especially, seen in smaller children where omentum is not developed properly. Possible *complications* are—Perforation, gangrene, generalized peritonitis, or septicemia. The intestinal adhesions may lead to intestinal obstruction. Complications can also be handled laparoscopically or by open surgery depending on the expertise of the surgeon.

MECKEL'S DIVERTICULUM

It is a vitellointestinal duct remnant, present in approx. 2 percent of the population and may become symptomatic

at any age. It may remain asymptomatic throughout life. Of the symptomatic patients,⁵ 42 percent present with bowel obstruction, 38 percent have rectal bleeding, 14 percent diverticulitis, and 6 percent umbilical pathology. It is most common differential diagnosis for acute appendicitis. Classical teaching is that if abdomen is opened with a diagnosis of appendicitis and appendix is found normal, look for Meckel's diverticulitis (Fig. 5).

It may also present as

Intestinal Obstruction (42%): Volvulus and intussusception (Fig. 6) are the most common causes of obstruction.



Fig. 4: Open appendectomy (For color version see plate 14)

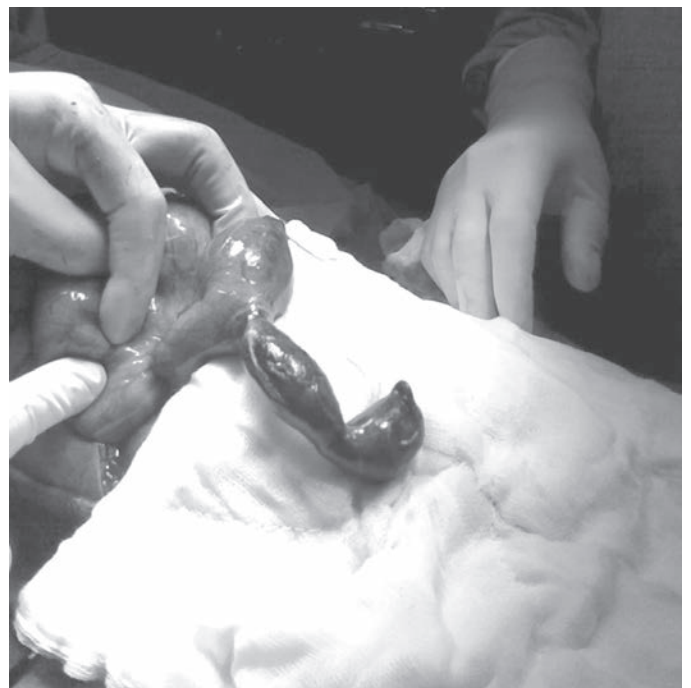


Fig. 5: Meckel's diverticulum (For color version see plate 15)

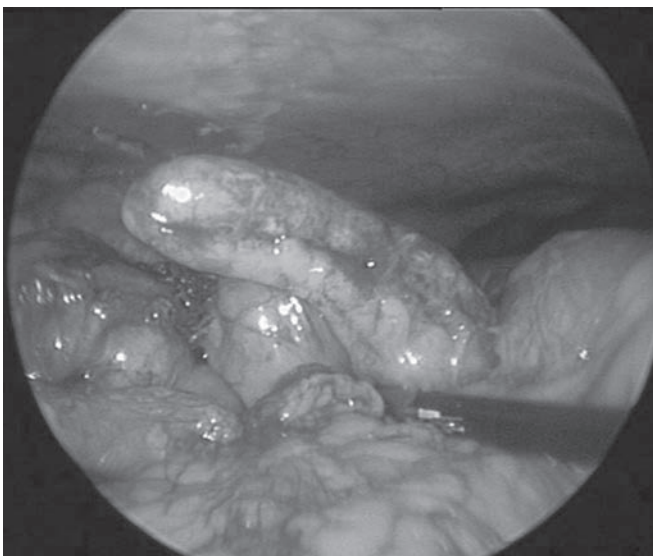


Fig. 3: Laparoscopic appendectomy (For color version see plate 14)



Fig. 6: Lead point for intussusception
(For color version see plate 15)

Predisposing factors for bowel obstruction are fibrous bands to umbilicus or mesentery. There are no specific signs and symptoms except small bowel obstruction and diagnosis is made at surgery. Release of band may relieve obstruction. However, if there is vascular compromise resection of devitalized bowel and anastomosis of healthy gut may have to be resorted to. Similarly, if the organ forms the lead point to an intussusception, the aberration has to be corrected and the devitalized bowel is resected. Meckle's diverticulum is excised along with a margin of healthy bowel either by wedge resection or end to end anastomosis.

Hematochezia (38%): Severe painless rectal bleeding may occur. The blood is often altered (maroon colored). However, when bleeding is massive, fresh blood may appear at rectum. A nuclear medicine Meckel scan is positive in 85 percent,⁶ depending on presence or absence of ectopic gastric mucosa. Colonoscopy and gastroscopy rule out other causes of bleeding. In the symptomatic group, ectopic mucosa is present in 61 percent of the resected specimens. Gastric 88 percent, pancreatic 7 percent, and gastric with pancreatic 3 percent were the most common ectopic tissue. The surgical dilemma is whether to remove an asymptomatic diverticulum found incidentally at surgery.⁷

INTUSSUSCEPTION

Intussusception is defined as the telescoping or invagination of a proximal portion of intestine (intussusceptum)

into a more distal portion (intussusciens) is one of the most common causes of bowel obstruction in infants and toddlers. The incidence of intussusception is 1.5 to 4 cases per 1000 live births, with a male-to-female ratio of 3:2. The greatest incidence of idiopathic intussusception is in infants aged 9 to 24 months. A seasonal incidence has been described, with peaks in the spring, summer, and the middle of winter. These periods correspond to peaks in the occurrence of seasonal gastroenteritis and upper respiratory tract infections.

Etiology: Intussusception is ileocolic (see the first image below) in 80 percent of cases but may also be ileoileal, colocolic, or ileoileocolic. Most infants and toddlers (95%) with the condition do not have an identifiable specific lead point. In these idiopathic cases, careful examination may reveal hypertrophied mural lymphoid tissues (Peyer patches), which are due to adenovirus or rotavirus infection. A specific lead point that draws the proximal intestine and its mesentery inward and propagates it distally through peristalsis is identified in only 5 percent of cases and is most commonly found in cases of ileoileal intussusception. Specific lead points are more commonly found in children older than 3 years. Meckel diverticulum is the most common lead point,⁸ followed by polyps, such as with Peutz-Jeghers syndrome, and intestinal duplications. Other lead points described include lymphomas, lymphangiectasias, submucosal hemorrhage with Henoch-Schönlein purpura, trichobezoars with Rapunzel syndrome, caseating granulomas due to abdominal tuberculosis, hemangiomas, and lymphosarcomas.

Children with cystic fibrosis (CF) may present with intussusception due to inspissated meconium in the terminal ileum.

Postoperative jejunoileal or ileoileal intussusception, which has no specific lead point in most cases, accounts for approximately 1 percent of intussusceptions in children of all ages. When a lead point is present with postoperative intussusceptions,⁹ several cases have been reported after appendectomy with stump inversion.⁸ Other rare reported types of intussusception include retrograde jejunojejunal intussusception following duodenal atresia repair and an ileoileal type resulting from blunt abdominal trauma. Although the vast majority of intussusception cases are idiopathic, a familial anatomical tendency that may predispose to the condition in the face of viral infection has also been reported.

Clinical Presentation: Most infants with intussusception have a history of intermittent severe cramping or colicky abdominal pain, occurring every 5 to 30 minutes. During these attacks, the infant screams and flexes at the waist, draws the legs up to the abdomen, and may appear pale. These episodes may last for only a few seconds and are separated by periods of calm normal appearance and activity. However, some infants become quite lethargic

and somnolent between attacks. Early on, the infant may vomit undigested food. As attacks continue, emesis may turn bilious. Stools that appear normal in character early in the course of the illness eventually become dark red and mucoid (resembling currant jelly) - a sign of intestinal ischemia and mucosal sloughing.

Initial inspection may reveal a robust infant who appears healthy. Between attacks, the infant may appear somnolent or quite normal, and findings on examination of the abdomen may be unremarkable. During an attack or spasm, the infant suddenly appears startled or anxious and begins to scream. Upon initial inspection, the abdomen may appear scaphoid; during paroxysms, it may be rigid; and later in the course of the illness, it may become distended with signs of peritonitis. Careful palpation after an attack has subsided may reveal an ill-defined or sausage-shaped mass.

With early ileocolic intussusception, the mass is typically found in the right upper quadrant or abdomen. The right lower quadrant may seem empty upon examination - *Dance sign*. This mass may be difficult to locate in inconsolable infants because of abdominal rigidity from muscle straining. If episodes of cramping are witnessed, the careful examiner may auscultate peristaltic rushes in the area of the intussusception.

The rectal examination should commence with inspection of fecal material in the diaper. Normal-appearing stool should be tested for occult blood. The presence of mucoid or frankly bloody stool supports the diagnosis. Rarely, inspection of the anus reveals the prolapsed tip of the intussusception. A digital rectal examination should be performed routinely, looking for blood or a mass higher in the anal canal.

The 3 strongest clinical predictors for high-risk are: male older than age 5 months and a report of lethargy. If a patient is older than 5 months, then he or she may be considered low-risk if the abdominal radiograph is negative and there is diarrhea with no bilious emesis.

MANAGEMENT

Stable patients in whom the index of suspicion for intussusception is high but who do not have evidence of ischemic bowel, perforation, or sepsis may undergo immediate contrast enema for diagnosis and treatment of suspected intussusception.

Immediate surgery is indicated in unstable patients, in patients who have peritonitis, and in patients with bowel perforation during attempted enema reduction. Elevated temperature and WBC counts have also served as relative indicators for surgery. Patients requiring surgery must be aggressively resuscitated with fluids, and care must be taken to preserve body temperature preoperatively, intraoperatively, and postoperatively.

Plain Radiography

Early in the course of the illness, findings on plain radiographic examination of the abdomen (supine and upright) may be unremarkable. Findings suggestive of intussusception include dilated loops of small bowel with or without air-fluid levels, an airless or opacified right lower quadrant (see the image below), or both. Occasionally, the intussusceptum is apparent on plain abdominal radiography. In order to increase the diagnostic accuracy, a left-side down decubitus radiographic view of the abdomen can be helpful.

Ultrasonography

The utility of ultrasonography in the diagnosis of intussusception has been verified by a number of authors, with a sensitivity and specificity of 100 percent. Characteristic ultrasonographic findings include a *target sign* visible on transverse section and a *pseudo-kidney* sign viewed on longitudinal section. Ultrasonography has also been studied as a tool to help differentiate the types of intussusception. A transient small bowel intussusception is most likely located in the right lower quadrant or periumbilical region, has a smaller anteroposterior diameter (1.38 cm vs 2.53 cm), has a thinner outer rim (0.26 cm vs 0.53 cm), and is absent of lymph nodes, in contrast to ileocolic intussusception. With small bowel intussusception, the length may be helpful in determining the necessity of surgery. An intussusception length of more than 3.5 cm independently predicts the likelihood of surgery being performed, with a sensitivity of 93 percent and specificity of 100 percent.

*Diagnostic and therapeutic enema:*¹⁰ Once the diagnosis of intussusception is entertained, surgical personnel should be notified and an intravenous line and nasogastric tube placed. The surgeon is preferably present in the radiology suite at the time of contrast enema examination. The diagnostic enema is therapeutic in 80 to 90 percent of patients. Thus, treatment is usually concluded in the radiology suite, and these patients are observed until they can tolerate an oral diet. A successful therapeutic reduction must demonstrate free flow of contrast (air or barium series) proximal to the ileocecal valve. Historically, patients in whom enema reduction was unsuccessful were taken immediately to the operating room for laparotomy and manual reduction. However, in patients who are clinically stable, second and third attempts at pneumatic or hydrostatic reduction have proven effective.

Either Barium or Air can be used for contrast enema. Perforation is a risk with either barium or air but poses less of a problem with air; as the combination of barium and feces may result in severe peritonitis with wide peritoneal soilage.

In preparation for contrast study, patients should have intravenous access. A lubricated straight catheter is placed into the rectum and secured by taping the buttocks

together tightly. While many radiologists prefer a balloon-tipped catheter, laceration or perforation of the rectum is a risk with balloon inflation.

A manometer and blood pressure cuff are connected to the catheter, and air is insufflated slowly to a pressure of 70 to 80 mm Hg (maximum 120 mm Hg) and followed fluoroscopically as it percolates proximally through the colon. The column of air stops at the intussusception, and a plain radiograph is taken. If no intussusception exists or if the reduction is successful, air is observed to rapidly pass into the small bowel. Another radiograph is taken at this point, and the air is allowed to escape prior to removal of the catheter. At the completion of the procedure, post-reduction radiography (in supine and decubitus/ upright views) should be used to confirm the absence of free air. Difficult reductions may require several attempts. The use of glucagon (0.5 mg/kg) for facilitating relaxation of the bowel has yielded mixed results and is not routinely used. Success rates of 80 to 90 percent for pneumatic reduction have been reported. In the stable patient, suggestion of a recurrence following enema reduction necessitates a repeat enema examination. Ultrasonographically guided hydrostatic reduction for childhood ileocolic intussusception is preferred because it is safe, accurate, has a higher success rate, and can avoid radiation exposure risk.

Preoperative Management: Expedient diagnosis and management is essential to successful outcomes in infants with intussusception. Once the diagnosis of intussusception is entertained, surgical personnel should be notified, an intravenous line inserted, and intravenous hydration started. A nasogastric tube should be inserted and placed to suction. If the patient is markedly distended or has a dilated loop of bowel, an abdominal radiograph should be obtained. Antibiotics should be administered based on clinical suspicion of peritonitis or infection (sepsis) or in patients with a markedly elevated WBC count.

If the intussusception can be reduced with an enema (Fig. 7), the hospital stay typically lasts 3 days.

Preoperative Details: Preoperatively, intravenous crystalloid resuscitation is begun. Broad-spectrum intravenous antibiotics are administered.

Intraoperative Details (Fig. 8)

The abdomen and bowel are typically explored through a right upper quadrant transverse incision. After inspection for signs of perforation, the intussusception is identified and delivered into the wound. First, an attempt is made at manual reduction by retrograde milking of the intussusceptum. Although gentle pulling may aid in reduction, avoid vigorous pulling apart of the intussuscepted segment of bowel.

If manual reduction is unsuccessful, if a mass or pathologic lead point is present, or if perforation has occurred, segmental bowel resection is necessary. After resection, a



Fig. 7: Barium enema reduction



Fig. 8: Intussusception (For color version see plate 15)

primary anastomosis may be performed. Often, after successful manual reduction, the involved segment of bowel appears edematous, hyperemic, or ischemic. These findings do not necessarily mandate resection. Laparoscopy in the management of intussusception was initially limited to a diagnostic role. It was used to confirm unreduced bowel following an enema with prompt conversion to an open procedure. The laparoscope allowed the surgeons to avoid unnecessary open procedures in cases of spontaneous reduction following enema and enhanced the efficacy of hydrostatic or pneumatic reductions, reducing the need for an open procedure in approximately 30

percent of cases. Continued experience with laparoscopy and improved technology has led some centers to successfully utilize the technique for therapeutic reduction in confirmed cases of pediatric intussusception.

Several small series have been published demonstrating the laparoscopic approach as safe, effective, and cost efficient when compared to the open technique. Postoperative complications between the open and laparoscopic groups are not significantly different. A major concern regarding the laparoscopic approach is the inability to reduce the intussusception using the standard retrograde fashion of the open technique. Some authors voice concern that a surgeon reducing an intussusception laparoscopically must apply pull and tension on an often friable segment of bowel, increasing the risk of bowel perforation. Additionally, because most cases of intussusception in older children are secondary to a pathologic lead point, the laparoscopic technique may not be appropriate in these patients. In order to minimize the rate of conversion to the open approach, the patient should be seen within 36 hours of the onset of symptoms and have no peritoneal signs. The role of laparoscopy in intussusception is evolving and will be better defined as technology progresses and experience with the minimally invasive approach to this disease grows.

Postoperative follow-up: Intravenous fluid resuscitation is continued and calculated, taking into consideration maintenance requirements and third-space losses. Upon resolution of ileus, diet is advanced at the discretion of the surgeon.

In older children and in cases of recurrent intussusception (after 3-4 episodes) successfully reduced with an enema, consider evaluating the patient for a lead point (e.g. upper GI series, Meckel scan).

Complications

Intussusception results in bowel obstruction; thus, complications such as dehydration and aspiration from emesis can occur. Ischemia and bowel necrosis can cause bowel perforation and sepsis. Necrosis of a significant length of intestine can lead to complications associated with short bowel syndrome. Whether treated by operative or radiographic reduction, late stricture (4-8 wk) may occur within the length of intestine involved.

Prognosis

The overall mortality rate of intussusception is less than 1 percent. Recurrence rates following nonoperative reduction and surgical reduction are approximately 5 percent and 1 to 4 percent, respectively. The following criteria are associated with a higher failure rate of nonoperative reduction:

- Raised neutrophil percentage
- Rectal bleeding
- Failed reduction with barium at another institution
- Age older than 2 years or younger than 3 months
- Duration of symptoms longer than 24 hours
- Small-bowel obstruction on radiograph
- Dehydration of greater than 5 percent
- Inexperienced radiologist.

Factors significantly predictive of bowel perforation are younger age and a longer duration of symptoms. The risk of postoperative adhesive small-bowel obstruction following nonoperative reduction is 0 percent; for operative reduction, it has been reported in as many as 5 percent of patients.

Transient intussusception diagnosed on Ultrasonography for pain abdomen, in the absence of clinical signs of intestinal obstruction, can safely be observed. One must look for lead points if intussusception occurs repeatedly, especially in bigger children. In doubtful cases contrast enema can be used.

CHOLECYSTITIS

Cholecystitis occurs when a calculus obstructs the cystic duct. The trapped bile causes inflammation of the gallbladder wall. As gallstones are often occult on CT, sonography is the preferred imaging method for the evaluation of cholecystitis, also allowing assessment of the compressibility of the gallbladder. The diagnosis of a hydropic gall bladder is solely made on the noncompressibility of the gall bladder. Do not rely on measurements. Some gallbladders happen to be small and others are large.

The imaging appearance of cholecystitis consists of an enlarged hydropic (meaning noncompressible) gallbladder with a thickened wall in the region of maximum tenderness (*Murphy sign*). The inflamed gallbladder usually contains stones or sludge, whereas the obstructing calculus itself may or may not be identified because it is located deep within the gallbladder neck or cystic duct. The gallbladder may be surrounded by inflamed fat, but on sonography this frequently is not seen, while CT sometimes does show fat-stranding. Potential pitfalls are pancreatitis, hepatitis or right-sided heart failure, which all may lead to thickening of the gallbladder wall without cholecystitis. Therefore, be certain that hydropic obstruction of the gallbladder is present before assigning the diagnosis of cholecystitis.

An acute abdomen with LUQ pain is rare. Its most common cause is gastric pathology in which radiological imaging plays a minor role. Inflamed fat is shown as fat-stranding at CT. Inflamed fat usefully points out where and what the problem is. As a rule, the organ or structure in the centre or nearest to the inflamed fat is the cause of the inflammation. Thickening of bowel wall indicates inflammation or tumor, and has an extensive differential diagnosis. Thickening

of small bowel loops usually indicates regional inflammation, as small bowel tumors (carcinoid, lymphoma, GIST) are relatively infrequent. In patients with local colonic wall thickening a carcinoma is a prime concern.

Small-bowel obstruction (SBO) accounts for approximately 4 percent of all patients presenting with an acute abdomen. The diagnosis of SBO is made when you see dilated small bowel and collapsed small bowel loops. If obstruction is present, try to identify its cause and location (adhesion, tumor, volvulus, intussusception, inguinal hernia). Adhesions account for 60 to 80 percent of all cases and are the likely cause when a smooth transition from dilated to collapsed small-bowel loops is noted. Bands or internal herniation associated with Meckle's diverticulum are an important cause of small bowel obstruction. Mal rotation with or without volvulus is an unusual cause of pain abdomen in children beyond infancy. If investigated during pain signs of obstruction may be present. However, during remission, clinical findings may not be present.

The 'Small Bowel Feces Sign' (SBFS)¹¹ is a very useful sign as it is seen at the zone of transition thus facilitating identification of the cause of the obstruction. The SBFS has been defined as gas and particulate material within a dilated small-bowel loop that simulates the appearance of feces.

ACUTE SCROTUM

The acute pain in scrotum should never be ignored, as the child is in real danger of losing his testis. The patient's history and physical examination are the key to the diagnosis and often guide decision making regarding whether or not surgical intervention is appropriate. Imaging studies should complement, but not replace, sound clinical judgment. When making a decision for conservative, nonsurgical care, the provider must balance the potential morbidity of surgical exploration against the potential cost of missing a surgical diagnosis. A small but real, negative exploration rate is acceptable to minimize the risk of missing a critical surgical diagnosis.

*Causes of Acute Scrotal Pain and Swelling.*¹²

Ischemic conditions

- *Torsion of the testis:* Intravaginal; extravaginal (prenatal or neonatal)
- Appendiceal torsion, testis or epididymis
- Testicular infarction due to other vascular insult (cord injury, thrombosis).

Trauma

- Testicular rupture
- Intratesticular hematoma, testicular contusion
- Hematocele.

Infectious conditions

- Acute epididymitis
- Acute epididymo-orchitis

- Acute orchitis
- Abscess (intratesticular, intravaginal, scrotal cutaneous cysts)
- Gangrenous infections (Fournier's gangrene).

Inflammatory conditions

- Henoch-Schönlein purpura (HSP) - vasculitis of scrotal wall
- Fat necrosis of scrotal wall.

Hernia

Incarcerated, strangulated inguinal hernia, with or without associated testicular ischemia.

Acute on chronic events

- Spermatocoele—rupture or hemorrhage
- Hydrocoele—rupture, hemorrhage or infection
- Testicular tumor with rupture, hemorrhage, infarction or infection
- Varicocele.

TESTICULAR TORSION (FIG. 9)

The testicle is typically covered by the tunica vaginalis, creating a potential space around the testis. Normally, the tunica vaginalis attaches to the posterior surface of the testicle and allows for very little mobility of the testicle within the scrotum. Some patients have an inappropriately high attachment of the tunica vaginalis, such that the testicle can rotate freely on the spermatic cord within the tunica vaginalis (intravaginal testicular torsion). This congenital anomaly, called the "bell clapper deformity," results in a transverse as opposed to longitudinal lie of the affected testes. This congenital abnormality is present in approximately 12 percent of human males (Fig. 10).

During testis torsion, the testicle twists spontaneously on the spermatic cord, causing venous occlusion and engorgement, with subsequent arterial ischemia and infarction. Experimental evidence indicates that 720° twist is required to compromise flow through the testicular



Fig. 9: Torsion left testis with retraction
(For color version see plate 15)



Fig. 10: Gangrene of testis (For color version see plate 15)

artery and result in ischemia. In neonates, the testicle frequently has not yet descended into the scrotum, after which it becomes attached within the tunica vaginalis. This increased mobility of the testicle predisposes it to torsion (extravaginal testicular torsion).

Testis torsion is the most common cause of testis loss. The incidence is approximately 1:4000. Torsion more often involves the left testicle. Among neonatal testicular torsion cases, 70 percent occur prenatally and 30 percent occur postnatally. The testis salvage rate approaches 100 percent in patients who undergo detorsion within 6 hours of the start of pain. However, there is only a 20 percent viability rate if detorsion occurs >12 hours; and virtually no viability if detorsion is delayed >24 hours.

CLINICAL PRESENTATION

Testicular torsion presents with the rapid onset of severe testicular pain and swelling. The onset of pain may be preceded by trauma, physical activity, or by no activity (e.g., during sleep). It most often occurs in children of adolescents. Torsion should be in the differential for any sudden acute scrotal pain or swelling.

The classic *physical examination* findings with testis torsion are an *exquisitely tender testicle* with a high, horizontal lie. Normally the testicle has a vertical lie within the tunica vaginalis of the scrotum – that is, the longitudinal axis of the testis is oriented vertically. With torsion and twisting of the spermatic cord, the testis may assume an altered lie based on the degree of twisting. After venous outflow is occluded, there is swelling and occlusion of arterial flow. Early on, one may be able to palpate the torted cord and

the testis below it; later in the course, however, progressive edema and inflammation ensues, such that after 12 to 24 hours, the entire hemiscrotum appears as a confluent mass without identifiable landmarks. At this stage, the physical examination may be indistinguishable from that seen with epididymo-orchitis. Importantly, with torsion, signs of infection are usually absent: patients are usually afebrile, free of irritative voiding symptoms such as dysuria, and harbor a normal urinalysis and normal white blood cell count. (In later torsion, however, an elevated WBC may be seen in response to the inflammation).

Diagnosis is mainly clinical – acute onset of symptoms, excruciating pain and classical examination findings as described above. However, confirmation may be made either a nuclear scan or a color Doppler study to look for the vascular flow of testicle. Inflammatory pathology will reveal normal or increased vascularity while torsion will show reduced or absent blood supply to the affected organ.

Treatment

Surgical intervention is urgent, without wasting time for investigations. Investigations should be carried out only during the time operation theater is being prepared. An attempt should always be made to derotate and give the organ a chance to regain its vascularity. However, if, after a suitable time lag, there is no change in color of the testicle, an orchidectomy should be done (Fig. 9). Doubtful testicle should be left alone and reviewed later if required.

STRANGULATED INGUINAL HERNIA

An inguinal hernia is a common surgical entity and is an emergency only if *irreducible*. The risk of irreducibility is always associated with an inguinal hernia, more so in neonates and infants. An irreducible hernia progresses to *intestinal obstruction* when the lumen of entrapped bowel gets occluded due to ensuing edema or the bulk of the contents. However, the most sinister is the *strangulation*, when the entrapped organs lose their blood supply and are in imminent danger of gangrene. By the time the stage of strangulation is reached, the child may already be dehydrated due to intestinal obstruction and vomiting. He may be toxic due to devitalized bowel, and have tachycardia and fever. The affected hemiscrotum may be exquisitely tender and angry looking. The surgical exploration is urgent and a laparotomy may be more appropriate. The gangrenous bowel/ the bowel which fails to regain its blood supply needs to be resected.

Reducible inguinal hernia → Irreducible inguinal hernia → Obstructed inguinal hernia → Strangulated hernia
Surgical options – Reducible inguinal hernia - Elective herniotomy

Irreducible inguinal hernia - Reduce and elective herniotomy

Obstructed inguinal hernia - Emergency surgery
 Strangulated hernia - Urgent laparotomy.

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Common Surgical Problems for the Pediatrician in Office Practice

Sushmita N Bhatnagar

INTRODUCTION

Keep me away from the wisdom which does not cry, the philosophy which does not laugh and the greatness which does not bow before children.

—Khalil Gibran

To deal with children is a challenging task and to deal with those with illnesses is in itself a herculean effort. But with compassion, love and understanding of the several conditions which affect them, we could manage them appropriately and give the young lives and young minds a safe and comfortable future, which is what this famous quote says.

A child who has to undergo surgery is dealing with not only physical illness, but also the psychological impact of undergoing surgery and its effects apart from the physiological stress of a surgical procedure. Hence, dealing with children with surgical conditions has to take into account all of these factors so as to decrease his/her anxiety, minimize the psychological trauma and promote healing of the surgical wound. Studies have indicated that postoperative recovery has been delayed if the preoperative preparation is not adequate.¹ Whether the child is first seen by a general practitioner, a pediatrician, a physician, or even an adult surgeon before being referred to Pediatric Surgeon, it is important to allay the anxiety of the parents as well as the child as anxiety in children undergoing surgery is expressed in various forms.² Also important is the timing of surgical intervention, which affects the outcome of the condition.

Several other essential considerations in children include a proper understanding of pathophysiology of the underlying condition, an accurate calculation of the losses of fluids, of blood and adequate replacement of these in the surgical conditions. Imperative to a good outcome is adequate preoperative preparation as surgery is a major

event in the life of the child. This includes preparation of the child and parents for surgery; in terms of acceptance of the surgical procedure, the time required for recovery, adequate nutrition before and after surgery, and prevention of infections during this period.

The common conditions which the pediatricians come across in their office practice are classified as follows:

- Genitourinary conditions
 - Hernia (inguinal, umbilical)
 - Hydrocele
 - Undescended testis
 - Hypospadias
 - Labial synechiae
 - Phimosis
- Injuries and burns
- Gastrointestinal conditions
 - Abdominal pain
 - Constipation
 - Vomiting
- Surgical infections
 - Abscesses (with or without lymphadenopathy)
 - Necrotizing fasciitis

GENITOURINARY CONDITIONS

Inguinal Hernia

The word hernia comes from Hippocrates who used the Greek *hernias* for bud or bulge to describe abdominal protrusions. Androise Pare about 400 years ago described treatment of incarcerated hernia with trusses. In spite of the advances in technology and science, inguinal hernia still remains a surgical disease and all hernias need to be surgically corrected (Fig. 1).

Hernia present as inguinal or sometimes inguinoscrotal swelling which increases (while coughing, crying, running) and decreases/disappears (while sleeping) in size. Herniae



Fig. 1: Large left sided inguinal hernia
(For color version see plate 16)



Fig. 2: Bilateral small hydroceles
(For color version see plate 16)

need surgery at the earliest, the younger the child, the earlier the need to operate due to high chances of incarceration, obstruction and testicular infarction and necrosis.

Another entity which needs special mention is fluid hernia, wherein the sac contains only fluid and not bowel loops. This is often termed as communicating hydrocele. The treatment for this condition remains surgical.

Hernia in a girl child is a similar entity and requires similar treatment, except with a slight difference in that a preoperative assessment to rule out disorder of sexual development is necessary in all. It was thought of in the past that girls have a higher incidence of femoral herniae, but even in females the incidence of inguinal herniae are more common than the femoral counterpart.³

Umbilical Hernia

The incidence of umbilical hernia is highest in the newborn period and gradually decreases with increasing age. Umbilical hernia is either congenital or acquired. Majority of these are congenital, the acquired ones are associated with gross ascites or any condition with increased intra-abdominal pressure such as children with hydrocephalus in whom a Ventriculo-peritoneal shunt has been performed. This indicates the defect in the umbilical ring. The differential diagnosis includes paraumbilical hernia, minor omphalocele.

Most of the umbilical herniae are isolated conditions, but infrequently large umbilical herniae are associated with mucopolysaccharide storage disease (such as Hunter-Hurler syndrome, osteogenesis imperfecta, and Ehlers-Danlos syndrome), Beckwith-Wiedemann syndrome, Down's syndrome, congenital hypothyroidism, fetal hydantoin syndrome, Freeman-Sheldon syndrome.⁴ The size of the umbilical defect varies from 1 cm to 5 cm usually but more than 5 cm occasionally. Clinically these herniae increase on crying, coughing, sitting, walking, straining and reduce on sleeping often completely. Most

of the umbilical hernia present as painless bulge, but some present as pain in abdomen which occurs due to drag on the mesentery along with bowel loops into the hernial sac.

When the size is small <1 to 2 cm, the chances of strangulation of bowel loops increases and so is the incidence of spontaneous closure. Closure or repair of the hernia is unnecessary in children less than 3 years of age as spontaneous closure occurs in up to 85 percent of children with small defects.⁵ Larger defects even though the risk of complications is very low, often require surgical intervention earlier as spontaneous closure is very unlikely.

Hydrocele

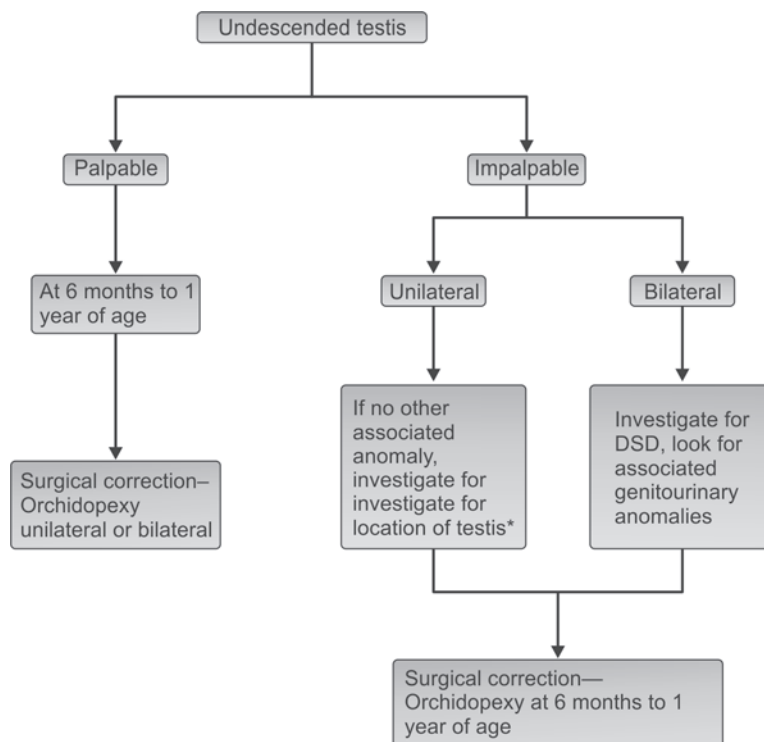
Hydroceles present as scrotal swelling or sometimes inguinoscrotal swelling which does not show much change in size. These are collections of fluids around the testicles which gradually get reabsorbed (Fig. 2). In children less than 2 years of age, no surgical intervention is required as the hydrocele may completely disappear, unless the hydrocele is very large in size, is growing rapidly or is causing pain.

Distinguishing hernia from hydrocele is important as the treatment plan for both the conditions varies. Reducing the swelling and getting above the swelling are two important clinical landmarks to differentiate both these conditions. In hernia, surgery is to be done at the earliest, whereas in hydrocele surgical intervention is deferred till about 2 years of age.

Undescended Testis

Undescended testis (UDT) is the most common birth defect concerning the male genitalia. A child could have unilateral or bilateral undescended testis (cryptorchidism) (Fig. 3). Also important to note is whether the undescended testis is palpable or impalpable. The management of child with UDT is dependant on the above parameters. A management algorithm is hereby described in Flow Chart 1.

Flow chart 1: Undescended testis



*Laparoscopy has been a decisive modality of investigation for nonpalpable undescended testis.^{6,7} It also helps in differentiating true undescended testis from atrophic testis and vanishing testis

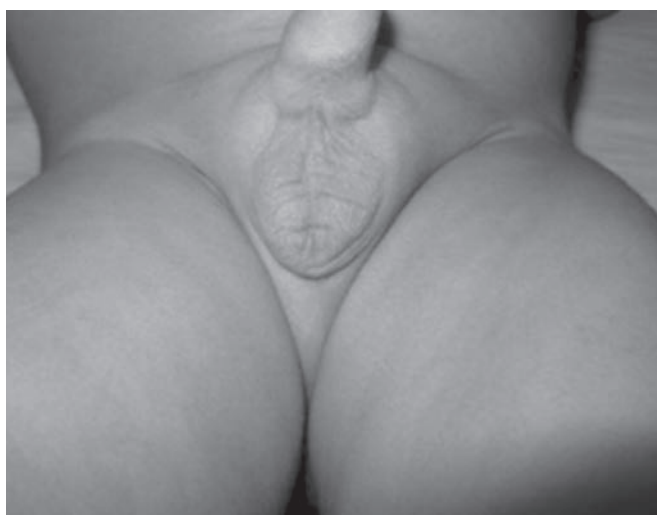


Fig. 3: Bilateral undescended testis
(For color version see plate 16)



Fig. 4: Penoscrotal hypospadias with chordee
(For color version see plate 16)

Hypospadias

Hypospadias is a purely surgical condition in which the opening of the urethral meatus which is ectopically located on the ventrum from the scrotal to the glans (Figs 4 and 5). There are about 300 different types of operative procedures described in literature, and it is up to the surgeon to select the type of repair that he/she is

most comfortable with. In recent times with improved instrumentation, improved pre- and postoperative care and antibiotics and with newer techniques, the focus is on single stage repair for most hypospadias except the severe penoscrotal and scrotal types with severe chordee. Three crucial considerations in any child with hypospadias are:



Fig. 5: Distal penile hypospadias with left congenital hydrocele
(For color version see plate 16)



Fig. 6: Phimosis (pathological)
(For color version see plate 16)

- Any severe hypospadias needs to be investigated for disorder of sexual differentiation (DSD).
- Circumcision should never be done in child with any type of hypospadias as the foreskin is required for reconstruction.
- The timing of repair on an average is between 1 to 2 years of age and all stages of surgical correction must complete before the child is of school going age.

Labial Synechiae

Adhesions between the labia minora result in labial synechiae which are a common general pediatric presentation in office practice. Since there are many misconceptions, girls with this condition often undergo unnecessary investigations for ambiguous genitalia and surgical procedures for correction. Depending on the severity of the adhesions, the child could be asymptomatic and brought for abnormal appearance of genitalia or present with severe urinary complaints like burning micturition, dribbling, thin stream and urinary tract infection.

The treatment is division of the adhesions in the outpatient department with a probe or an artery forceps after application of local anesthetic cream such as lidocaine and application of estrogen/steroid creams three times in a day for about 4 to 6 weeks.^{8,9}

Phimosis

Phimosis is the most commonly encountered condition in office practice (Fig. 6). Almost every male child presents to the OPD either with symptoms (less commonly), but mainly without symptoms but with inability to retract the prepuce. This subject has been widely discussed in

multiple forums, but one needs to remember the following significant features which are essential for unnecessary surgical interventions. These are as follows:

- All boys have phimosis at birth, known as physiological phimosis. This condition does not need any intervention. As the child grows, the prepuce gradually opens up and starts retracting, the process completing by about 6 to 7 years of age. Differentiation between physiological and pathological phimosis is crucial for further management.
- Some boys present with symptoms such as ballooning of prepuce, thin stream, recurrent balanoposthitis and urinary tract infection. All except ballooning of prepuce need some form of intervention. Ballooning of prepuce is not an indication for circumcision.
- Circumcision is not the only treatment option for pathological phimosis. Lesser surgical options include preputial retraction under local or general anesthesia followed by steroid cream applications over a period of 4 to 6 weeks to prevent rephimosis and prepuceoplasty in which the prepuce is not excised thus maintaining the normal anatomy and function of the prepuce.¹⁰ Several different techniques for prepuceoplasty are described in literature, but the technique designed by the author is a ventral vertical incision and transverse suturing thus dividing the preputial ring and enlarging the prepuceal orifice for easy retraction of prepuce.

INJURIES AND BURNS

Children of all ages are injured very frequently. The degree of injury ranges from minor to major and the differentiation or identification of each category and appropriate triage of each child is of primary significance.

The main reasons for injuries in children are:

- **Falls:** All falls do not lead to internal organ injury, but all children who have had a fall must be assessed for injury to the three main parts; the head, the chest and the abdomen. Injuries to these parts even though may seem minor must be monitored closely, either in a hospital setting or at home by an experienced and qualified person.
- **Cuts and bruises:** Most of these are trivial injuries. Those on the face, tongue and genital area need a detailed assessment and many a times surgical intervention to prevent excessive bleeding or disfigurement.
- **Burns:** The most common burns in children are the scald injuries which are superficial. These burns can be managed at primary care level and even at home. Prevention of infection should be a primary focus. Whatever the cause of the burns, if the surface of burns is larger or if the severity and the degree of burn is greater, a tertiary care center and an experienced medical professional is necessary.

Tips for burns in children include:

- Remove the cause for causing burns immediately.
- Reduce the temperature of the burnt area, but ice application is not to be done as it increases the skin damage.
- Assess the surface of the burnt area. If more than 10 percent body surface is burnt, immediate hospitalization is essential as there is rapid fluid shift leading to severe dehydration in children.
- Burns on the head, face, neck, hands, joints and genitals need immediate attention. In facial burns due to fire, edema of the respiratory tract occurs very rapidly and causes complete obstruction which could lead to rapid death.
- Chemical and electrical burns are misleading as to the area involved and severity, hence must not be treated at home or primary care unit.

GASTROINTESTINAL CONDITIONS

Abdominal Pain

Abdominal pain can be really worrying at times and children do tend to suffer from abdominal pain at some point or the other. It is important to differentiate between an acute abdominal pain and a chronic one. The acute abdomen can be due inflammatory or obstructive causes, both of which need to be attended to immediately. The child could be having appendicitis, typhilitis, typhoid, intussusception, or calculus in the kidney or ureter causing acute

pain. The treatment depends on the cause of pain, but generally almost all of these children need intravenous antibiotics and sometimes surgical intervention on an emergency basis.

The chronic pains could be either recurrent abdominal pain (RAP) or non-specific abdominal pain (NSAP). The cause for both could be either organic or psychogenic. Evaluating the cause and a detailed study is mandatory before surgical intervention is contemplated.

Without serial observations, abdominal pain in the child should not be neglected. Surgical opinion should be sought in the following circumstances:

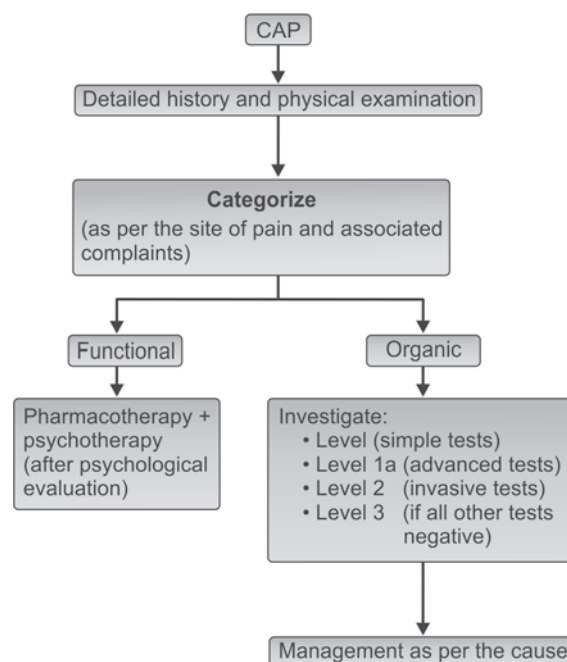
- Continuous/Colicky severe abdominal pain for more than 6 hours
- Pain with nausea and vomiting
- Fever with abdominal pain
- Tenderness of the abdomen
- Bilious vomiting associated with pain
- Pain associated with urinary complaints.

Chronic abdominal pain (CAP) is a challenging problem both for the pediatrician and the pediatric surgeon. While it is difficult to pinpoint the exact cause of CAP, it is important to workup these children in a systematic manner.¹¹ A simple algorithm is described in Flow chart 2.

Constipation

In the present era wherein children regularly consume junk food and low fiber diet, the presenting complaint of constipation with or without pain in abdomen occurs in about 30 to 40 percent of children coming to the outpatients department.

Flow chart 2: Chronic abdominal pain



Though there are many existing definitions of constipation, the Paris consensus on childhood constipation terminology (PACCT) defines constipation as “a period of 8 weeks with at least 2 of the following symptoms: defecation frequency less than 3 times per week, fecal incontinence frequency greater than once per week, passage of large stools that clog the toilet, palpable abdominal or rectal fecal mass, stool withholding behavior, or painful defecation.”¹²

A thorough dietary history is absolutely mandatory before labeling a child as habitual constipation or Hirschsprung's disease. Clinically the pointers for Hirschsprung's disease are:

- History of delayed passage of meconium
- No passage of flatus
- No soiling (which is common with habitual constipation)
- Abdominal distension
- *On per rectal examination:* Stools not felt at the anal verge and expulsive passage of feces on withdrawing finger
- Plain X-ray abdomen showing large gas filled dilated loops with or without air-fluid levels (large dilated loops absent in children with habitual constipation).

Treatment depends on the causative factor. Whilst habitual constipation has to be corrected with diet, laxatives, suppositories and occasionally enemas, Hirschsprung's disease needs surgical intervention for all types.

Vomiting

The causes of vomiting in children vary as per the age of the child. Also, it is more common in infants than in older children, often with conditions affecting systems other than gastrointestinal tract. Important considerations in a child with vomiting are:

- Associated weight loss (Gastroesophageal reflux)
- Lump in abdomen (Pyloric stenosis/solid abdominal tumor)
- Bilious vomiting (Intestinal obstruction/Peritonitis/Septic ileus)
- Coffee ground vomit or fresh blood in vomit (Portal hypertension/Mallory-Weiss disease)
- Associated high grade fever (any infective condition, abdominal or extra-abdominal).

A child with vomiting needs urgent attention if the vomiting is recurrent and if there is accompanied refusal of feeds. Investigations for diagnosis can wait till dehydration is corrected. Hemoglobin levels and serum electrolytes are mandatory in such children. Blood grouping and cross matching should be done in all such children as surgical intervention may be needed in a majority of these children.

SURGICAL INFECTIONS

Abscess

Soft tissue infections in children lead to formation of abscesses. For superficial small abscesses on the skin,

systemic antibiotics are not necessary, but deep lesions in children require hospitalization, intravenous antibiotics and surgical drainage irrespective of the site of occurrence. Abscess in the pleural cavity (empyema) is the most common site of internal abscess. Abscesses in the brain, kidney, liver, pericardium could be fatal, hence need rapid diagnosis and multimodality treatment.

Necrotizing Fasciitis

This is a severe life-threatening condition resulting in a rapid necrosis of the soft tissues including fascia and subcutaneous tissues. It could be primary infection from the skin or could be secondary as part of systemic septicemia. Either way, surgical debridement and appropriate broad spectrum antibiotics must be instituted early to prevent mortality.¹³

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Section 12

Emergency Pediatrics

Editor
Suresh Gupta

Pediatric Poisonings: Emergency Room Assessment and Management

Suresh Gupta

BACKGROUND

Optimal management of the poisoned patient requires recognition and integration of available key resources. The management and investigation of the poisoned patient, like other clinical situations, is enhanced by the ability to access expert resources like poison control center or clinical toxicologist. The goals of this chapter are:

- To provide an approach for the assessment and diagnosis of poisonings
- To provide a generic approach to managing common poisonings and their complications
- To provide a framework for consideration of a poisoning etiology in the clinician's differential diagnosis.

This chapter is not all inclusive or comprehensive but is intended to provide a framework for the clinical approach and management of the poisoned patient. The general approach to the poisoned patient can be summarized as:

- Stabilization
- History
- Examination
- Diagnosis
- Decontamination
- Enhanced elimination
- Poison-specific treatment
- Disposition (Flow chart 1).

Clinicians should have a high index of suspicion and be quick to consider an alternate toxin or medical condition in cases where the history is inconsistent with the patient's clinical presentation. In difficult cases, if it is felt appropriate, the physician should consult with the poison control center or a clinical toxicologist.

STABILIZATION

Stabilization is the first priority in managing toxic ingestion. The patient should be rapidly assessed to determine

adequacy of airway and ventilation, mental status, and cardiovascular function. At this point, the clinician should also search for and correct hypoxia and hypoglycemia. Initial management priorities are maintenance and protection of the airway, support of ventilation, and support of circulation. Unstable patients should be placed on a cardiac monitor with measurement of vital signs every 5 to 15 minutes until the patient is stabilized to the point where monitoring is no longer necessary. The potential for rapid changes in the patient's condition should be considered in making decisions about airway and ventilatory support.

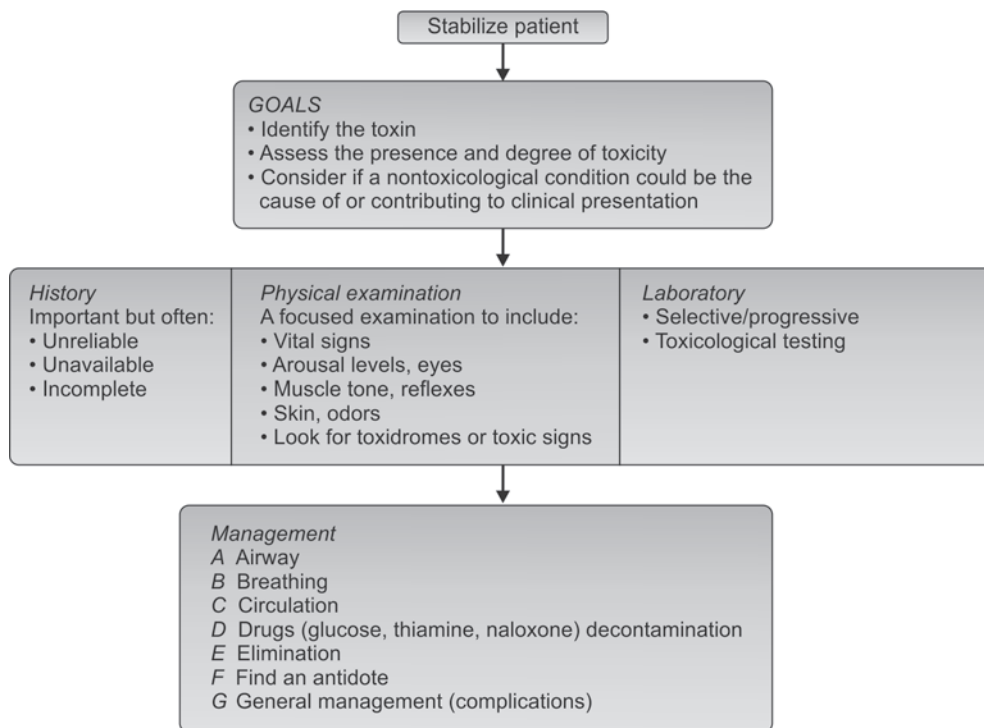
Managing Common Complications

Common complications of poisoning include depressed mental status, seizures, agitation, hypotension, bradycardia, and vomiting. Most of these can be treated empirically without knowledge of the toxin involved and without specific antidotes (Table 1). Management of these complications occurs concurrently with history, physical examination and specific laboratory tests.

Coma and Altered Mental Status

- Concurrently with the "ABC's", (airway, breathing, and circulation) the clinician must search for and treat hypoglycemia, hypoxia, head injury, CNS infection, and sepsis.
- Oxygen saturation should be measured in all comatose patients or patients with altered mental status. All of these patients should be given supplemental oxygen.
- Bedside this, glucose testing should be performed in all patients with altered mental status. Administer intravenous dextrose (adults: D50W; children D25W in dose of 2-4 cc/ kg). Glucose should be given immediately to all persons with suspected hypoglycemia even if the glucometer reading is normal (since false

Flow chart 1: Assessment and management of a poisoned patient



negatives can occur). It is dangerous to wait for the formal laboratory measurement of glucose before giving D50W.

- Naloxone may be given to all obtunded patients or reserved for those with hypoventilation, small pupils, or history of opioid use. In apneic patients, the initial dose of naloxone is 2 mg in adults and 0.1 mg/kg in children. Most patients will respond to small doses of naloxone but up to 10 mg may rarely be required.
- Flumazenil, a benzodiazepine antagonist, should not be routinely administered in the patient presenting with coma or altered mental status. Reversal of benzodiazepine effect in mixed drug ingestion involving cyclic antidepressants and chloral hydrate may result in seizures or arrhythmia with fatal outcomes.

Seizures

- Toxic seizures are often transient, in which case no specific treatment is required.
- When treatment is required, benzodiazepines (e.g. diazepam or lorazepam) are usually effective.
- If benzodiazepines fail, barbiturates (e.g. phenobarbital) almost always suffice.
- Phenytoin probably has no role in toxin-induced seizures and is theoretically harmful in tricyclic poisoning.

- Phenytoin also has no role and is harmful in theophylline overdoses.
- Isoniazid may cause severe seizures that respond poorly to the usual treatment. Pyridoxine (Vitamin B₆) is required in these unusual poisonings.

Agitation

- Severe agitation presents a risk to both the patient and health care providers and should be considered as a medical emergency.
- Police or paramedics who bring a severely agitated patient to the hospital should be asked to remain until the patient has been safely restrained and adequately sedated.
- Immediately life-threatening causes such as hypoxia, hypoglycemia, head injury, and CNS infection should be considered and treated as indicated.
- Management consists of pharmacological sedation, judicious use of physical restraint and a diligent search for a life-threatening cause of agitation.
- Venous access can usually be achieved with sufficient manpower and it is preferable to use intravenous rather than intramuscular sedation.
- Benzodiazepines such as diazepam or lorazepam (titrate to effect in aliquots of 5 to 10 mg every 5 minutes in adults or 0.1 mg/kg in children) are the drugs

Table 1: Treatment options for managing common complications**Agitation**

<i>Situation</i>	<i>Pharmacological management</i>
<ul style="list-style-type: none"> • Most agitated patients • Belligerent drunk 	<ul style="list-style-type: none"> • Diazepam or lorazepam • Haloperidol

Adjunct management

- Ask police, paramedics, or hospital security to assist with restraining patient if required
- Look for and treat other causes of agitation:
 - Hypoglycemia
 - Hypoxia
 - Brain injury
 - Infectious causes
 - Measure temperature and cool if indicated

Altered mental status*

<i>Clinical condition</i>	<i>Treatment</i>
<ul style="list-style-type: none"> • Hypoxia • Hypoglycemia • Opiate overdose 	<ul style="list-style-type: none"> • Oxygen • Glucose, thiamine (in adults) • Consider naloxone hydrochloride

* Treatment of the most common causes of altered mental status that can be recognized and treated in the first five minutes of care

Drug-induced bradycardia

<i>Situation</i>	<i>Treatment</i>
<ul style="list-style-type: none"> • Bradycardia in general 	<ul style="list-style-type: none"> • Treat underlying cause like hypoxia, electrolyte disturbances, etc. • Atropine • External or internal pacemaker
<ul style="list-style-type: none"> • Digoxin poisoning • Opiate overdose 	<ul style="list-style-type: none"> • Digibind® • Naloxone hydrochloride

Hypotension

<i>Toxin</i>	<i>1st line therapy</i>	<i>2nd line therapy</i>	<i>3rd line therapy</i>
General drug-induced hypotension	Normal saline fluid bolus	Dopamine infusion*	
Hypotension secondary to β -blockers	Normal saline fluid bolus	Glucagon bolus followed by infusion if necessary	Epinephrine infusion*
Hypotension secondary to calcium channel blockers	Normal saline fluid bolus	Calcium infusion glucagon bolus followed by infusion if necessary	Epinephrine or Dopamine infusion*
Hypotension secondary to cyclic antidepressants or membrane depressant drugs	Normal saline fluid bolus	Sodium bicarbonate bolus	Norepinephrine infusion*

*Titrate to maintain systolic BP above 3rd centile (in children above 10 year >90 mm Hg)

Seizures

<i>Toxin</i>	<i>Initial therapy</i>	<i>Refractory seizures</i>
General drug-induced seizure	Benzodiazepine - diazepam or lorazepam	Phenobarbital
Isoniazid (INH)	Benzodiazepine Diazepam or lorazepam	Pyridoxine Thiopental (must intubate patient)

of choice for rapid sedation in most cases of toxin-induced agitation. However, it carries the risk of respiratory depression in patients poisoned with alcohol or another sedative.

- Agitated patients often develop life-threatening hyperthermia, so an accurate measurement of temperature is imperative in all of these patients. Patients who feel hot to touch should be cooled empirically if there is any delay in obtaining an accurate temperature.

Hypotension

- Drug-induced hypotension is most often caused by vasodilation or volume loss and usually responds to fluids or catecholamine pressors.
- Bicarbonate may be required for hypotension caused by tricyclic antidepressants or other drugs that inhibit sodium channels.
- Hypotension caused by cardiotoxic drugs such as β -blockers, calcium channel blockers, or sodium channel blockers may require glucagon, calcium, or catecholamine pressors. A clinical toxicologist should be involved early in the management of such cases.

Drug-Induced Bradycardia

- Agents causing bradycardia are listed in Table 2.
- Opiates cause moderate bradycardia that responds to naloxone.
- Standard doses of atropine (0.5 to 3 mg in adults and 0.01 mg/kg in children) may be effective in mild cases of drug-induced bradycardia.

- Large doses of atropine may be required to treat bradycardia and other toxicity caused by cholinergic agents such as organophosphate insecticides.
- Pacemakers should be considered when bradycardia fails to respond to atropine. Pacemakers should be avoided in digoxin overdose because of the risk of inducing ventricular dysrhythmias.
- Digoxin induced bradycardia may require Digibind® (digitalis antibodies).
- Bradycardia caused by calcium channel blockers or β -blockers is often difficult to treat and may require glucagon, catecholamine infusions, or more specialized therapy.
- Clinical toxicologist should be consulted for these patients with significant drug-induced bradycardia, especially if it does not respond to atropine.

Intractable Vomiting

- Toxin-induced intractable vomiting usually responds to metoclopramide. The initial dose is 10 mg in adults or 0.1-0.2 mg/kg in children intravenously and a total dose of up to 1 mg/kg may be required.
- When metoclopramide fails, a more potent agent such as ondansetron (8 mg IV over 15 minutes) may be required.
- Vomiting associated with activated charcoal administration may be treated by having the patient take charcoal through a straw or through a nasogastric tube. Administering activated charcoal through the nasogastric tube by slow drip rather than by push may be successful in these circumstances.

Table 2: Toxic conditions and causative agents (limited list)

Agitated delirium	<ul style="list-style-type: none"> • Alcohol toxicity/withdrawal • Anticholinergics • Hallucinogens 	<ul style="list-style-type: none"> • Phencyclidine • Sympathomimetics (e.g. cocaine)
Anion-gap acidosis (MUD-PILE CATS)	<ul style="list-style-type: none"> • Methanol • Uremia • Ketoacidosis—diabetic, starvation, alcoholic <p><i>Note:</i> Common are ketoacidosis, lactic acidosis, salicylates. If these excluded toxic then alcohol poisoning like ethanol/ethylene glycol should be considered</p>	<ul style="list-style-type: none"> • Paraldehyde, phenformin, metformin • Iron, isoniazid • Lactic acidosis • Ethylene glycol • Cyanide • Acetyl salicylic acid • Toluene • Solvents
Bradycardia	<ul style="list-style-type: none"> • β-blockers • Ca-channel blockers • Digoxin <p><i>Note:</i> The “big three” causes are β-blockers, calcium channel blockers, and digoxin</p>	<ul style="list-style-type: none"> • Alpha agonists (e.g. phenylpropanolamine) • Beta 2-antagonists • Clonidine • Cholinergic agents • Opiates • Cyclic antidepressants

Contd...

Coma/obtundation	<ul style="list-style-type: none"> • Alcohols • Anticholinergics • Anticonvulsants: Barbiturates, phenytoin, carbamazepine, valproate, etc.) • Cholinergics <p><i>Note:</i> Any toxin that causes seizures or hypotension will also cause obtundation or coma</p>	<ul style="list-style-type: none"> • Neuroleptics (phenothiazines, butyrophenones, etc.) • Sedative hypnotics (e.g. benzodiazepines, chloral hydrate, meprobamate, etc.) • Opiates • Oral hypoglycemics • Tricyclic antidepressants
Elevated osmolal gap	<ul style="list-style-type: none"> • Ethylene glycol <p><i>Note:</i> Most important causes are methanol and ethylene glycol. Also consider shock, trauma, organ failure, or nonalcoholic ketoacidosis as causes of an elevated osmolal gap</p>	<ul style="list-style-type: none"> • Propylene glycol • Isopropyl alcohol • Mannitol • Methanol • Ethanol
Hypotension	<ul style="list-style-type: none"> • Angiotensin-converting enzyme inhibitors • β-blockers • Ca-channel blockers • Iron 	<ul style="list-style-type: none"> • Phenothiazines • Sedative hypnotics • Theophylline • Tricyclic antidepressants • Vasodilators
Radio-opaque compounds	<ul style="list-style-type: none"> • Chloral hydrate • Heavy metals • Iron • Phenothiazines 	<ul style="list-style-type: none"> • Sustained-release (enteric coated) compounds • Toxins in containers (e.g. body packers)
Seizures	<ul style="list-style-type: none"> • Alcohol withdrawal • Sedative hypnotic withdrawal • Amphetamines • Anticholinergics • Caffeine <p><i>Note:</i> Any toxin that causes hypotension or hypoglycemia can also cause seizures. Intractable seizures not responsive to usual management may be caused by isoniazid</p>	<ul style="list-style-type: none"> • Camphor • Carbamazepine • Cocaine • Isoniazid • Oral hypoglycemics • Propranolol • Propoxyphene • Sodium channel blockers • Theophylline • Tricyclic antidepressants
Sodium channel blockade	<ul style="list-style-type: none"> • Antihistamines (large overdoses) <p><i>Note:</i> Drugs with membrane stabilizing effect, or the ability to inhibit fast sodium channels, cause a significant number of fatalities. Toxicity is characterized by coma, seizures, hypotension, arrhythmias and a widened QRS on ECG</p>	<ul style="list-style-type: none"> • Carbamazepine • Class Ia and Ic antiarrhythmics • Cocaine • Mesoridazine • Propranolol • Propoxyphene • Thioridazine • Tricyclic antidepressants
Tachycardia	<ul style="list-style-type: none"> • Amphetamines • Angiotensin converting enzyme (ACE) inhibitors • Anticholinergics • Cocaine • Iron 	<ul style="list-style-type: none"> • Phenothiazines • Sedative hypnotics • Theophylline • Vasodilators (e.g. nitroglycerin) • Tricyclic antidepressants

- When vomiting complicates whole bowel irrigation, the procedure should be stopped until vomiting is controlled, then restarted at a lower rate.
- Numerous toxins may cause vomiting in overdose. Common causes of severe vomiting include digoxin, lithium, iron, theophylline, heavy metals, acetaminophen and ASA.

HISTORY

- History and physical examination are performed concurrently with stabilization.
- The history should include the five “W”s:
 - Who:* The patient’s age, weight, relationship to others present, and gender
 - What:* The name and dosage of medication(s) or substance(s) of abuse or other coingestants and amount ingested
 - When:* The time and date of ingestion
 - Where:* The route of poisoning
 - Why:* Whether intentional or accidental, and associated details.
- Other important historical points include a review of systems, specifically the presence of seizures, agitation, coma, vomiting, headache, and shortness of breath.
- Clinicians should be aware that in some cases the history is unreliable. Patients may not know what they ingested, the patient’s altered mental status or psychosis may impede communication, or the patient may intentionally mislead the clinician.
- Clinicians should have a high index of suspicion and be quick to consider an alternate toxin or medical condition in cases where the history is inconsistent with the patient’s clinical presentation. In such difficult cases, consultation with clinical toxicologist or poison control center may prove helpful.

PHYSICAL EXAMINATION

- A complete physical examination should be performed to detect complications and to help with the diagnosis.
- Specific attention should be paid to vital signs, mental status (depressed or agitated), respiration (depressed, evidence of pulmonary edema or aspiration), pupils (size, reactivity, presence of nystagmus), skin (diaphoresis or abnormally dry, blisters) and bowel sounds (increased or decreased).
- Based on findings from physical examination, the clinician should specifically consider the presence of a toxidrome. Common toxidromes are given in Table 3.

DIAGNOSIS

- Identification of the toxin involved is based on history, physical examination and clinical course as well as selected diagnostic tests (see below).

- Review of Table 2 (toxic conditions and causative agents) and Table 3 (common toxidromes and causes) may help suggest a causative agent. Specific drug levels (as discussed below) may be helpful in confirming the diagnosis and in making management decisions.
- Additional tests for an intentional overdose include the following:
 - An electrocardiogram as a screen for poisoning with tricyclic antidepressants or other cardiotoxic agents (tricyclics cause widened QRS intervals and tachycardia)
 - Chest radiographs are useful to detect pulmonary damage in patients with suspected aspiration, non-cardiogenic pulmonary edema, or other lung injury
 - Abdominal radiographs are useful screening tools in patients who may have ingested radiopaque material such as lithium, iron, lead, and other heavy metals. Drug packet and enteric-coated compounds may also be detectable on plain films.

DECONTAMINATION

After the patient is stabilized, consideration should be given to removing the toxin. The choice of decontamination should be made based on the clinical status and the suspected toxin.

Inhalation Exposure

Patients with an inhalation exposure should be removed from the source, with care taken to avoid exposure of the rescuers.

Cutaneous Exposure

When toxic compounds have been splashed into the eyes or onto the skin, copious irrigation with water is usually enough to remove the poison.*

Note: An important exception is hydrofluoric acid, which can cause chemical burns. Skin exposed to hydrofluoric acid should be covered with calcium containing gels. If this fails to relieve pain, calcium salts must be infiltrated locally or delivered through an arterial line.

Ingested Toxins

It is reasonable to withhold decontamination in patients who have taken a nontoxic or minimally toxic ingestion.

- Single dose *activated charcoal* is the preferred method of gastrointestinal (GI) decontamination for the vast majority of toxic ingestion
- Induced emesis with Ipecac has little role in adult or pediatric poisonings in either the hospital or prehospital phase
- Current thinking places a decreasing emphasis on the role of *gastric lavage*. Lavage should not be used routinely as its use may be associated with significant

Table 3: Common toxidromes and causes

<i>Toxidromes and causes</i>	<i>Characteristics</i>
Alcohol withdrawal	<ul style="list-style-type: none"> • Delirium • Tachycardia • Hypertension • Hyperthermia • Tremors beginning in first 5 to 10 hours • Seizures are generalized and are typically isolated or occur in a brief flurry beginning at 6 to 48 hours after reduced intake. Focal or protracted seizures are atypical and warrant investigation. • Delerium tremens in some patients after several days
Anticholinergic toxidrome Antihistamines, antipruritics anti-cholinergic (datura), cyclic antidepressants, antiparkinsonian agents, antiemetics, antispasmodics	<ul style="list-style-type: none"> • Altered mental status (hallucinations, agitation, coma) • Tachycardia • Large pupils • Dry skin • Decreased bowel sounds • Urinary retention
Cholinergic toxidrome Organophosphate, Carbamate insecticides	<ul style="list-style-type: none"> • Lacrimation, salivation • Bradycardia • Respiratory secretions • Hypoxia • Diaphoresis • Increased bowel sounds • Vomiting • Diarrhea and urinary incontinence • Fasciculations may occur and muscle weakness can result in respiratory failure
Sympathomimetic toxidrome Overdose of cocaine, amphetamines, alcohol and sedative hypnotic withdrawal results in similar findings	<ul style="list-style-type: none"> • Elevated vital signs • Tachycardia • Hypertension • Hyperthermia • Agitated delirium is common • Large pupils • Diaphoresis (unless severely dehydrated) • Bowel sounds present <p><i>Note:</i> This toxidrome is usually differentiated from the anticholinergic toxidrome by the presence of marked diaphoresis.</p>
Opiate toxidrome Overdose of heroin and other opiates	<ul style="list-style-type: none"> • Respiratory depression • Depressed mental status • Small pupils • Slight bradycardia (unless hypoxic or hypovolemic) • Prompt response to naloxone hydrochloride
Benzodiazepine/sedative hypnotic toxidrome Overdose of benzodiazepines Some sedative hypnotics	<ul style="list-style-type: none"> • Depressed mental status • Relatively small pupils • Vital signs usually normal • Significant respiratory depression is rare with pure benzodiazepine overdose • Hypotension in large ingestion
Phenothiazine toxidrome Overdose of phenothiazines	<ul style="list-style-type: none"> • Depressed mental status • Small pupils • Do not respond to naloxone hydrochloride
Sedative hypnotic withdrawal	<ul style="list-style-type: none"> • Similar manifestations to alcohol withdrawal, but with a different time course that varies with the half-life of the agent involved

complications. If lavage is considered, assessment of the need to protect the airway and attention to patient position, tube placement, and lavage technique is essential to minimize complications. Lavage may be beneficial in a limited number of situations:

- In the first hour after ingestion
- In life-threatening ingestion (e.g. β -blockers, calcium channel blockers, cyclic antidepressants, theophylline)
- With toxins which cause concretions or pylorospasm.
- Whole bowel irrigation is best used for toxins that are poorly bound to activated charcoal such as iron, lithium or lead, as well as for sustained-release medications (e.g. certain formulations of lithium, theophylline, or calcium channel blockers). Whole bowel irrigation is also useful for removal of ingested drug packets in “body packers” or “stuffers”. This procedure is quite safe in patients who are not vomiting and who have normal gut function.
- Achieved by instilling polyethylene glycol bowel preparation at a rate of 1 to 2 L/ h in adults (500 cc/ h in children) through a nasogastric tube to induce osmotic diarrhea
- Continue until rectal effluent is clear (usually about 6 hours)
- With radiopaque compounds, continue until repeat radiographs are clear.
- Cathartics (e.g. magnesium citrate) are of questionable benefit and probably play a limited role. There may be an argument for adding one dose of cathartic to the initial dose of activated charcoal. However, this is of questionable benefit.

ENHANCED ELIMINATION

- The simplest methods of enhanced elimination are multiple dose activated charcoal (MDAC) and urinary alkalization.
- Due to possible complications, MDAC should be reserved for significant poisonings with agents that form concretions, desorb from activated charcoal in the intestines, or have significant enterohepatic circulation. The MDAC may also be beneficial in very large ingestion where it is impossible to deliver sufficient charcoal in a single dose. In general, it is desirable to administer at least 10 times as much charcoal as toxin on a per weight basis. Examples of toxins that may be suitable for MDAC include large ingestion of theophylline or some anticonvulsants (phenytoin, carbamazepine, valproate, and phenobarbital).
 - Since many preparations of activated charcoal come premixed with sorbitol, the clinician must be aware that repeated doses of MDAC with cathartics with every dose of charcoal may induce severe diarrhea and result in significant dehydration, particularly

in pediatric and geriatric populations. It is recommended that activated charcoal premixed with sorbitol be given every 2nd or 3rd dose. The most efficient and effective way is to monitor cathartic response and administer an activated charcoal/cathartic mixture accordingly.

- Urinary alkalization enhances renal elimination of weak acids such as salicylates, phenobarbital, and chlorpropamide.
 - Urinary alkalization is achieved by infusing bicarbonate-containing fluids: 3 ampules (150 mEq) of sodium bicarbonate to 1 L of D5W and run at 250 cc/ hour (run the IV at 1.5 times of maintenance fluids in children)
 - Achieving urinary alkalization is virtually impossible if there is total body potassium depletion even in the presence of normokalemia on the electrolyte panel. Potassium supplementation is virtually uniformly required
 - Follow urinary pH hourly. Blood pH and electrolytes should be monitored regularly. The frequency of monitoring is dependent upon the severity of the clinical situation
 - The goal is to achieve a urine pH of 8.
- Extracorporeal removal of toxins by hemodialysis or hemoperfusion requires specialized equipment and expertise. Consult clinical toxicologist or poison control center where extracorporeal removal may be necessary.
 - The most common agents requiring extracorporeal removal are the toxic alcohols (ethylene glycol and methanol), lithium, salicylates, and theophylline. Consultation with a nephrologist is recommended when managing a patient with significant toxicity or very high levels following ingestion of one of these agents.
- Other methods of enhanced elimination such as acidification of urine, forced diuresis and continuous gastric suction are not recommended.

ANTIDOTES

Commonly used antidotes, which are useful, are given in Table 4. As there are very few poisonings for which antidotes are available, most of the poisonings are managed with supportive treatment.

- Antidotes are typically given after the patient has been stabilized and the diagnosis has been made.
- In certain cases, prompt administration of antidote is imperative.
- Glucose must be given immediately in hypoglycemia.
- Prompt administration of naloxone may avoid the need for endotracheal intubation in opiate overdose.
- Pyridoxine should be given as soon as possible for seizures associated with isoniazid overdose.

Table 4: Antidote therapy for poisonings

<i>Toxin</i>	<i>Antidote/Pediatric dose</i>
Acetaminophen	N-acetylcysteine, Loading dose: 140 mg orally; Maintenance doses: 70 mg/kg every 4 hours for 17 doses orally
Anticholinergics	Physostigmine salicylate 0.02 mg/kg slow IV infusion over 3-5 minutes titrate to effect
Arsenic	Succimer (DMSA) 10 mg/kg orally 3 times a day British Anti-Lewisite (BAL) (dimercaprol) 3-5 mg/ kg IM every 4-6 hrs only if unable to tolerate succimer
Benzodiazepines	Flumazenil 0.01 mg/ kg IV bolus titrate to effect or total dose of 1-3 mg * It should not be routinely administered in the patient presenting with coma or altered mental status. Reversal of benzodiazepine effect in mixed drug ingestion involving cyclic antidepressants and chloral hydrate may result in seizures or arrhythmias with fatal outcomes
β -blockers	Glucagon 0.15 mg/kg IV bolus, then 0.1 mg/kg/h IV infusion titrate to effect
Calcium channel blockers	Calcium chloride (10%): 0.1-0.2 ml/kg IV bolus, repeat doses and IV infusions commonly required Glucagon: 0.15 mg/kg IV bolus followed by 0.1 mg/kg/h IV infusions (titrate to effect)
Carbamates	Atropine: 0.1 mg/kg IV bolus, repeat doses titrate to effect
Cyanide	Cyanide antidote kit: Sodium nitrite (3%): 0.15-0.33 ml/kg to maximum of 300 mg slow IV infusion followed by sodium thiosulfate: 400 mg/kg up to 12.5 g IV infusion
Digoxin	Digoxin immune antibody fragment: Empiric dosing: 10-20 vials IV bolus for life-threatening toxicity (See package insert for other dosing regimens)
Ethylene glycol, Methanol	Ethanol (10%): Loading dose 10 ml/kg IV or orally followed by maintenance dose 1-2 ml/ kg/ h IV infusion or orally Fomepizole: 15 mg/ kg IV bolus, repeat doses may be necessary
Iron	Desferoxamine: 5-15 mg/ kg/ h IV infusion
Isoniazid	Pyridoxine: 1 g per gram ingested or empiric dosing 75 mg/kg IV bolus up to 5 g
Lead	Succimer (DMSA) (if patient is able to tolerate oral medication orally) 10 mg/kg \times 3 times a day, repeat doses are common BAL (dimercaprol): (only for lead encephalopathy) 3-5 mg/kg IM or 50-75 mg/m ² Calcium disodium EDTA: (Start 4 hrs after BAL ministration) 20-30 mg/ kg diluted in 250 ml IV infusion over 12-24 hours
Methemoglobinemia	Methylene blue: 1-2 mg/ kg slow IV infusion, repeat as needed
Opioids	Naloxone hydrochloride: 0.4-2 mg IV titrated to effect
Organophosphate	Atropine: 0.1 mg/ kg IV bolus, repeat dose titrated to effect Pralidoxime: 20-40 mg/ kg slow IV infusion followed by 5-10 mg/ kg/ h continuous infusion or 20 mg/ kg every 4 hours
Salicylates	Sodium bicarbonate: 150 mEq + 40 mEq KCl in 1L of D5 infused to maintain urine output at 1-2 mL/ kg/ h urine pH 7.5
Tricyclic antidepressants	Sodium bicarbonate: 1-2 mEq/ kg IV bolus, repeat boluses titrate to QRS duration (do not exceed arterial pH 7.55)
Warfarin, Superwarfarins	Fresh frozen plasma: Fresh frozen plasma for life-threatening hemorrhage. Vitamin K1 0.6 mg/kg slow IV infusion, SC or orally

LABORATORY INVESTIGATIONS FOR POISONED PATIENTS

Timely and effective use of the laboratory is important factors in enhancing the value of the tests it provides and for avoiding the expense of inappropriate laboratory testing and treatment. In general, toxicological testing can serve a number of purposes including:

- Confirming a toxic etiology and obviate the need for further diagnostic studies

- Identifying a specific agent
- Assessing the severity of the intoxication
- Predicting the outcome
- Guiding management decisions
- Assessing efficacy of treatment
- Guiding transfer decisions.

It is a good idea to incorporate the principle of “progressive” laboratory investigation in the context of the care of a poisoned patient. In this context, “progressive”

refers to a systematic progression from general laboratory tests to increasingly specific and more sophisticated tests as the clinical situation warrants. For example, the presence of an anion gap on the electrolyte panel together with a documented metabolic acidosis on arterial blood gases would prompt an investigation of ASA, methanol or ethylene glycol as potential etiologic agents. Recognition of each of these toxins requires specific management and ongoing laboratory assessment or therapy that may include transfer to another facility depending upon local resources.

The full spectrum of laboratory tests required for the assessment and management of the poisoned patient is not currently available in most of the hospitals in India. Additionally, prolonged turnaround time may limit the value of the test results in clinical management. In recognition of this reality, a systematic approach to the laboratory investigation of the poisoned patient is essential. The following key concepts are used in laboratory investigations for poisoned patients.

Progressive testing: Progressive testing is a systematic, sequential testing protocol that initially involves the performance of general laboratory tests (e.g. electrolytes, urea, glucose, osmolality), the results from which may then direct the physician to order or the laboratory to perform more sophisticated, specific tests to aid diagnosis (e.g. salicylate, methanol).

Selective testing: Selective testing is specific laboratory testing, either qualitative (e.g. tricyclic antidepressant screen) or quantitative (e.g. acetaminophen), which involves analysis for a particular compound or group of compounds. Selective testing is in contrast to comprehensive testing (e.g. "Tox" or "Drug" screens) which involve simultaneous testing or screening for a larger group of unrelated compounds. Comprehensive testing is usually more sophisticated, labor intensive, and expensive than selective testing. However, not all known compounds can be detected.

DISPOSITION

If adequate health care facilities are not available then one should consider transfer in the following circumstances:

- Inability to stabilize patient
- Deteriorating patient
- Resource limitations including staff, timely diagnostic testing and monitoring equipment
- Clinical judgment suggests a need for transfer
- Inability to provide patient with ongoing maintenance
- Lack of availability of toxin-specific therapy

- Management and disposition of patients following decontamination is toxin and patient specific, occasionally requiring interventions such as dialysis, hemodialysis and hemoperfusion
- Most patients require only minor supportive care and recover without sequel. Patients with uncomplicated acetaminophen ingestion requiring N-acetylcysteine antidote administration can be managed locally
- All patients who have taken a suicidal ingestion require assessment of suicidal risk prior to discharge.

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Common Emergency Procedures in Pediatric Office Practice

Suresh Gupta

Pediatricians see lots of emergencies in their office practice which need to be attended immediately. Most of the pediatric training during medical college focuses on medical emergencies only. This article focuses on those common pediatric emergency procedures which they can perform in their office practice.

REMOVAL OF A FOREIGN BODY FROM THE EAR

Core Facts

Common foreign bodies include toy parts, earring parts, hair beads, eraser tips, food items; or stones. It is most common under 8 years of age with peak incidence in the toddler age group 2 to 3 years. Event is usually witnessed by an adult, or alluded to by the child. If witnessed, further trauma to the ear may have occurred as a result of parental attempts to remove it. Indications of ear irrigation or manual removal include foreign body and obstruction of the external canal by cerumen. Minor complications include laceration of the ear canal, perforated tympanic membrane, or a secondary infection. These may occur with the foreign body itself or as a result of removing it. More serious complications include disruption of ossicles, canal hematoma, or facial nerve palsy.

Procedure

Three methods are available for removal of a foreign body, all requiring cooperation or restraint of the child. Because a minor laceration of the ear canal is often unavoidable, the parents should be aware of this complication before the physician undertakes the use of curette or forceps. After removal by any method, it is important to visualize the eardrum and document its condition.

Irrigation

Straighten the ear canal and visualize the foreign body directly with speculum, making sure the tympanic membrane is intact. If the foreign body is sponge or expansible when wet, this method should be avoided. Remove the speculum and irrigate the ear canal by injecting a constant stream of water at body temperature. Use a 20 to 50 ml syringe attached to a flexible intravenous catheter tip. Repeated irrigation may be necessary to provide complete emptying.

Curette

Visualize the foreign body with a speculum, preferably using an operation head otoscope, then very slowly advance the curette just beyond the foreign body as shown, while applying pressure to the foreign body, slowly withdraw the curette until the foreign body is removed.

Forceps

Visualize the foreign body with a speculum and look for a protruding edge of the foreign material. Carefully guide the forceps in the closed position under direct visualization through the speculum. Just a few millimeters from the edge of the foreign body open the forceps and grasp the edge gently. Withdraw the forceps, visualizing the foreign body simultaneously to minimize the chance of a complication.

EVERSION OF THE EYELIDS

Core Facts

Opening the eyelids of an infant or child can be tedious task if not done properly. Eversion of eyelids is required

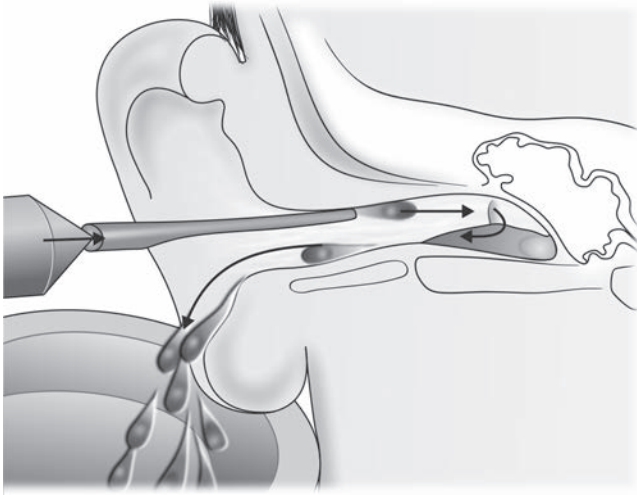


Fig. 1: Irrigation of ear for removal of foreign body or cerumen

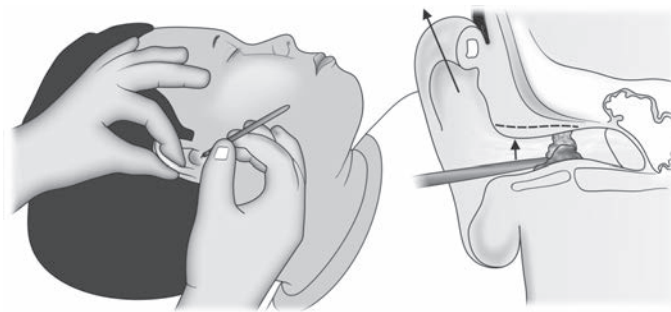


Fig. 2: Use of curette for removal of foreign body or cerumen

for identification of a foreign body or infection; instillation of medications to the conjunctiva; or removal of a foreign body. The minor complications may include mild contusion or ecchymoses (rarely).

Procedure

Have an assistant restrain the infant on the examining table in the supine position with the examining table in the supine position with the arms wrapped around the head. Alternatively, small infants can sit on the lap of a parent who then holds the infant's head still.

Eversion Upper Lid

Upper lid eversion is the more difficult, normally requiring cooperation or restraint, because the examiner needs to use both hands. After restraining the child, grasp the eyelash with distal upper lid between the index finger and thumb. Ask the child to look down at the floor if he or she will cooperate. Draw the eyelid downward and place

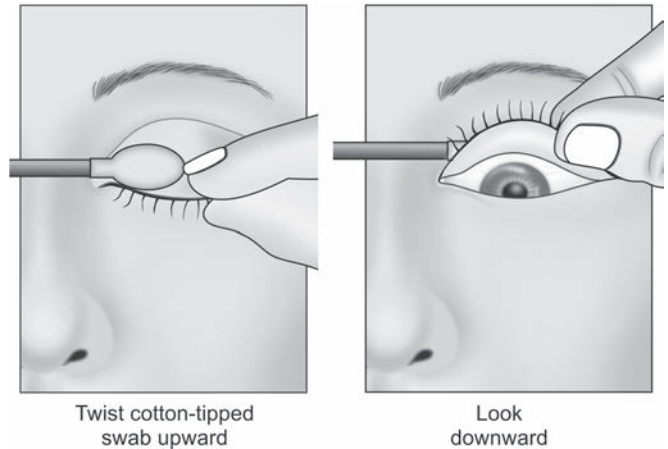


Fig. 3: Eversion of upper eyelids

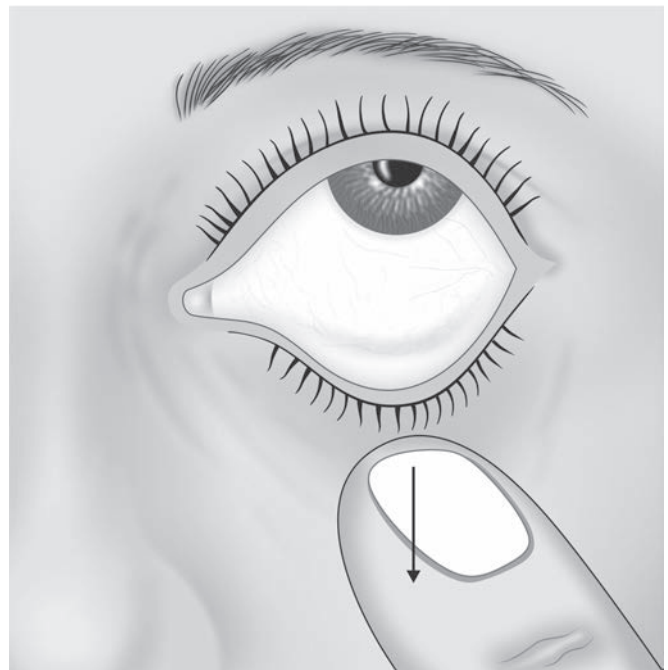


Fig. 4: Eversion of lower eyelid

a clean cotton swab across the superior tarsal margin. In one motion, move the swab slightly downward and pull the eyelid slightly upward. This maneuver should bend the eyelid slightly upward and backward and expose the palpebral surface. To restore the lid to its usual position, lift the swab slightly while maintaining pressure along the upper lid margin and turn the thumb and index finger downward.

Eversion Lower Lid

Place a thumb or finger at the base of the lower lid and gently retract it in a caudal and posterior direction while the child looks upward, while the eyelid is everted, removal of a foreign body can be accomplished. Use a clean cotton

swab and apply it to foreign body to flick it from the conjunctival surface.

IRRIGATION OF THE CONJUNCTIVA

Core Facts

The indication or irrigation of eye includes presence of a foreign body or caustic substance on the corneal or conjunctiva. Concentrated alkalis are found in sparklers and oven/drain cleaners. Damage to the cornea, sclera, or conjunctiva is due to liquefaction necrosis as a result of hydroxyl ions that combine with tissue fatty acids and proteins. Extensive, deep burns, corneal opacification, and conjunctival pallor may develop, and have potentially devastating outcomes. Acids are found in bleach and household cleaners. Damage is due to fatty acid and protein precipitates, causing coagulation necrosis. Burns are more superficial than alkali injuries; however, serious damage is possible if not irrigated immediately. The minor complications of irrigation of the conjunctiva include subconjunctival hemorrhage or corneal abrasion (rare) in a child who is not adequately restrained and conjunctival erythema.

Procedure

Place the child supine over a large sink or pail. Instill 1 to 2 drops of topical ophthalmic anesthetic solution. To restrain an uncooperative child, two assistants are necessary. The person holding the head should wear a gown and may use gauze under each thumb to help keep the eyelids open. Allow bacteriostatic normal saline solution (between room and body temperature) to flow through a set of intravenous tubing. Drip the fluid rapidly into the conjunctival sac. Irrigate for a minimum of 5 minutes for acid using at least 1 liter. Irrigate for 20 minutes for alkali or unknown substance using at least 2 liters. Tap water at

room temperature is an acceptable alternative for irrigation fluid, especially if it can be done immediately. After irrigation, the eye should be carefully examined for corneal and conjunctival integrity, including staining with fluorescein dye.

REMOVAL OF A NASAL FOREIGN BODY

Core Facts

Nasal foreign bodies are most common in 2 to 3-year-old and common foreign bodies include toy parts, beads, insects, paper, and food items. Symptoms depend on how long the object has been lodged in the nasal passages. Usually the child is seen placing an object up the nose that cannot be recovered, or there is a report of pain. Without this, it may remain buried for an unknown amount of time, and is suspected when a purulent, unilateral discharge develops, suggesting a secondary infection. The complications of the procedure may include rhinosinusitis; mucosal laceration; epistaxis; aspiration; and incomplete removal of the foreign body. These are the complications seen with the instrumental removal rather than the positive pressure techniques.

Procedure

Positive Pressure Techniques

Positive pressure techniques are not widely used. When attempted, they may be quite successful, less painful and frightening, and do not require restraints and instrumentation. It is more likely to be successful with an acute foreign body. After vasoconstriction, with use of either mouth-to-mouth by parent, or with AMBU bag and mask applied to mouth of child, occlude the opposite nostril and give a gentle, positive-pressure breath to expel the object. I have personally found these techniques to be



Fig. 5: Irrigation of conjunctiva



Fig. 6: Parent's kiss—a positive pressure technique to remove nasal foreign body

useful and very effective. The pediatricians must try these methods in their clinics before referring the child to otolaryngologists and mostly it will be realized that it can be done without the help of otolaryngologist.

Instrumental Removal

The child should be lying down and restrained. The patient must be kept still during instrumentation of the nose in order to prevent injury to the internal nasal structures. After applying a topical vasoconstrictor-anesthetic agent to shrink the nasal membranes, visualize the interior of the nose with a nasal speculum and a headlight or directed light as shown in figure. Purulent secretions should be gently removed by use of Frazier suction tip until the foreign body is clearly seen. Attempt to extract the object with suction, a hook, or alligator forceps as determined by the size, nature, and position of the object. Figure shows a hook being placed around a round foreign body. Do not push the foreign body into the posterior nasopharynx as the struggling child may aspirate it. The use of irrigation is not recommended because the foreign body may slip posteriorly and be aspirated or hygroscopic foreign bodies may swell and becomes lodged in the nose. After the foreign body has been removed, oral antimicrobial agents may be used in an effort to prevent an infection in the traumatized area.

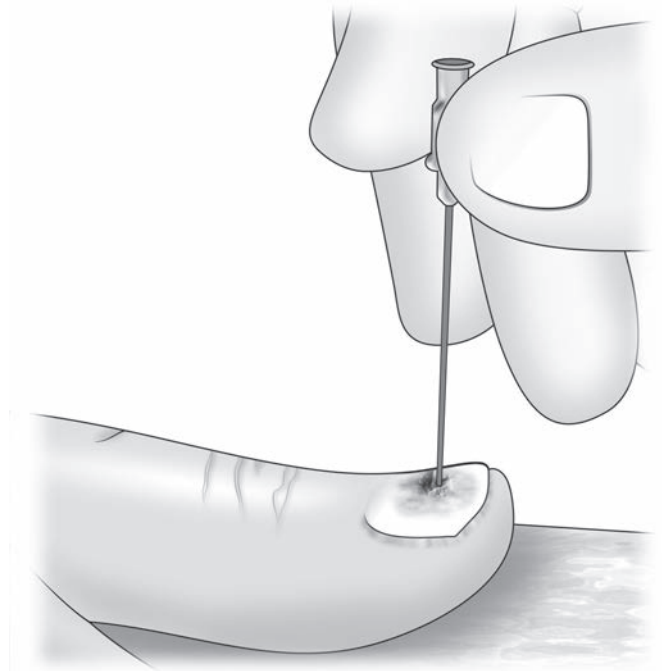


Fig. 7: Drainage of subungual hematomas

DRAINAGE OF A SUBUNGUAL HEMATOMA

Core Facts

Hematoma formation into the potential space above the nail bed and beneath the nail may result from simple closed minor blunt trauma, nail bed laceration with or without phalanx fracture, or laceration of nail margins. Black, blue, or red discoloration is visible through the nail. The nail is tender to palpation. Distal phalanx fracture may also be present, depending on the force of the trauma. If present, splinting the finger for 5 to 7 days post-trephination will alleviate pain. If a nail bed laceration is present and extends beyond the margins of the nail, removal and repair of the nail bed may be required. The indication for drainage of subungual hematoma is blood under pressure beneath a nail bed, either proximally or distally. The complications due to drainage are uncommon and may include bleeding and infection.

Procedure

Subungual hematomas occur from trauma in the proximal or distal nail bed. Generally the hematoma causes pain that is immediately relieved with drainage. A digital nerve block may be used for anesthesia but is usually not necessary. Making a hole in the nail relieves a hematoma of the proximal nail bed. Restrain the child and digit on a table. Soak the fingertip in povidone-iodine solutions for several

minutes. Hold a scalpel with blade perpendicular to the nail in the center of the hematoma. Puncture the nail by simultaneously applying downward and rotary pressure. Apply pressure sterile gauze to drain the blood for several minutes, and then cover with a sterile dressing.

Alternatively use a microcautery unit or 18-gauge needle or fire-sterilized and heated paper clip and apply gentle persistent controlled pressure to the center of the hematoma perpendicular to the nail until the nail is melted/ punctured. This permits drainage of the hematoma. Guard against puncture or burn of the underlying nail bed. A heated metal wire of paper clip is more rapid and less painful than making a hole with a scalpel. If the hematoma extends to (or close to) the margin of the nail bed, lift the end of the nail with the flat part of a small scissor until the hematoma drains spontaneously.

INCISION AND DRAINAGE OF A PARONYCHIA

Core Facts

A paronychia is a partially circumferential cellulitis or abscess around the base of a nail of the lateral finger or toe tip. A locally contained cellulitis is termed an eponychia, which may resolve spontaneously or progress to invade surrounding tissues. The most common bacteria are *Staphylococcus aureus*. Chronic paronychia may be caused by atypical mycobacteria and fungal infections. Paronychia results from minor trauma, such as nail biting or occasionally a sliver of foreign material, puncturing

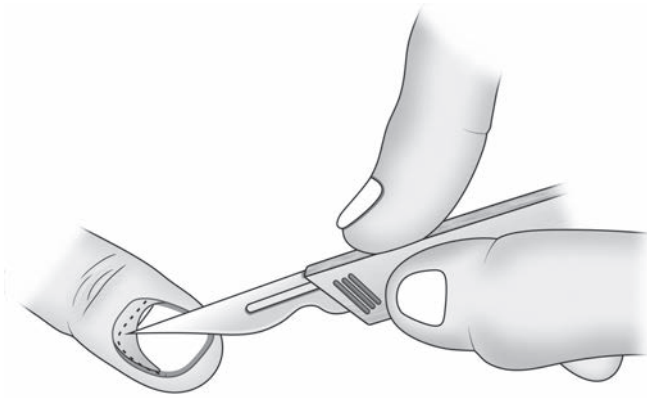


Fig. 8: Drainage of paronychia

the eponychium (cuticle), enable bacteria to invade the overlying soft tissues. Infection tends to occur adjacent to the eponychium, where blood supply is most tenuous and recurrent microtrauma is greatest. It then spreads circumferentially around the nail. Advanced paronychia may extend proximally and deep to the nail base. It is the most common hand infection in children. Children are particularly prone to paronychia due to a relatively thin eponychium, finger-sucking and play resulting in local trauma. Chronic paronychia occurs largely in adults whose hands are constantly exposed to moisture, e.g. dishwashers. The indications for drainage of paronychia are the failure of this infection of the soft tissue along the edges of the nail to respond to medical treatment. The complications of procedure of drainage may include bleeding and scar formation.

Procedure

Restrain the child appropriately for age. Prepare the site for the surgical procedure with povidone-iodine solution and cover with sterile disposable drapes. Inject 1 percent lidocaine for a digital block or spray the skin locally with ethyl chloride for anesthesia. Using a No. 11 surgical blade, incise the skin at its junction with the nail. Extend the incision along the base of the nail to permit adequate drainage. If the paronychia is only on one side of the nail bed distal to the cuticle. Dress the wound and instruct the patient to use warm compresses.

REMOVAL OF A SUBUNGUAL SPLINTER

Core Facts

A foreign body located underneath the nail, usually after playing with tree branches or an old wooden structure such as a deck, staircase, etc. Usually an unsuccessful effort has already been made to remove the object. Minor infections such as a subungual abscess or cellulitis may develop if the patient or family delays presentation for care. The minor

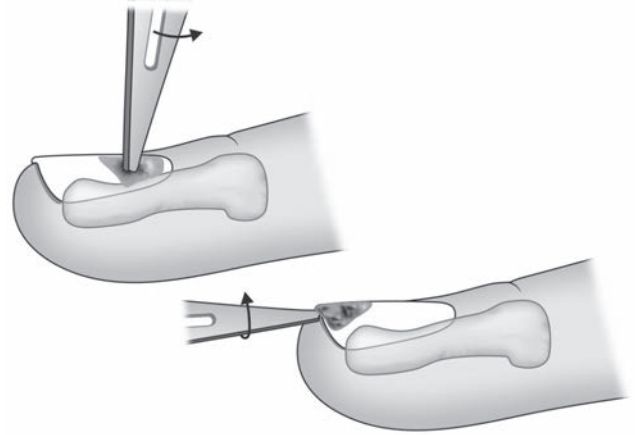


Fig. 9: Removal subungual splinter

complication of the procedure may include bleeding and infections if not done properly under aseptic precautions.

Procedure

Restrain the child's hand with the fingers extended and perform a digital block, using 1 or 2 percent lidocaine without epinephrine. Now do sterile preparation of distal phalanx with a povidone-iodine solution. Trim the nail as close to the nail bed as possible using surgical scissors and blunt tweezers or forceps. The further steps depend on the location and size of the foreign body. Foreign body embedded underneath the nail, extending beyond the distal margin of the nail bed. Trap the splinter against the undersurface of the nail using a scalpel tip (number 11 surgical blade) or 25-gauge needle and stroke the splinter toward the distal end of the underside of the nail to dislodge it and dress the wound. If the above method fails or the splinter is embedded underneath the nail, extending close to but not beyond the distal margin of the nail bed. Using blunt dissection with tweezers, elevate the surrounding nail from the nail bed enabling tweezers/forceps removal of the splinter and dress the wound.

If the above method fails or the splinter is deeply embedded and not extending close to the distal margin of the nail bed. Cut a V-shaped wedge in the nail with the proximal point 1 mm proximal to the foreign body and the wide portion at the distal nail edge. Removal of the wedge of nail reveals the entire visible foreign body, leaving the proximal nail intact. Remove the foreign body with a wet sterile gauze or fine tweezers and dress the wound.

REMOVAL OF RINGS

Core Facts

The tight rings can get stuck on the finger and if not removed in time, it can lead to vascular compromise and even gangrene in neglected cases. Children with strangulating ring on a digit are brought to ER only when mother

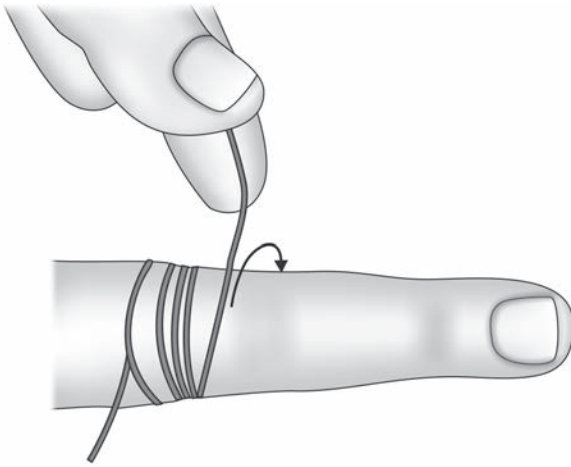


Fig. 10: String method of ring removal

has failed in removing the ring by lubricating or other domestic methods. There are few simple procedures, which can be conducted in pediatric office practice or ER to remove the strangulating rings on the digit. The complications are few and may include vascular compromise and trauma to digit.

Procedure

String compression of skin: Explain the procedure and position the patient comfortably. Cleanse the area and consider a digital block. Use string or 3-0 silk suture and wrap the suture around the finger, starting at the distal edge of the ring. Continue to wrap the string tightly until it covers the proximal interphalangeal joint. Grasp the ring, and while exerting a back and forth twisting movement, pull the ring over the suture and off the finger. Pull the string around and off the finger at the proximal end to draw the ring off the finger distally. After the ring is off, remove the suture. Cleanse the digit and apply sterile dressing as needed.

String pull: Explain the procedure and position the patient comfortably. Cleanse the area and consider a digital block. Use a string or heavy suture. Place one end of the string under the ring. Pull the string through. Place a small amount of lubricating ointment at the distal end of the ring. Grasp both ends of the suture 5 to 10 cm from the ring. Pull the suture in a circular motion. Continue slipping the suture around the ring as it gradually moves along the finger.

Ring cutting: Often it is preferable to try technique No. 2 or 3 if edema distal to ring is minimal in an attempt to avoid cutting the ring. Explain the procedure as appropriate to the child and parent/ guardian. Position the patient supine or sitting. Cleanse the area with povidone-iodine solution or substitute. Insert the ring cutter guard between

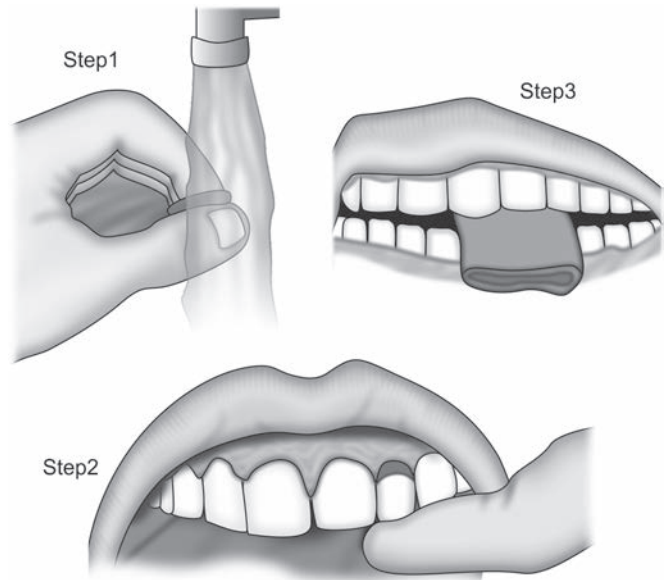


Fig. 11: Re-implantation of completely avulsed permanent tooth

the ring and the finger. Place the blade on the ring. Grasp the handle of the ring cutter and apply pressure while rotating the blade. If the ring is made of hard metal, cutting may be difficult and friction will cause the ring to heat up. If this occurs, stop until the metal cools. After the ring is completely cut through, pull the ring apart manually or with a hemostat and remove from the digit. Occasionally when the child finds the procedure painful, digital block may be necessary to complete ring cutting. Cleanse the digit and apply sterile dressing as necessary. After the ring is removed, cleanse the digit and apply sterile dressing as needed.

REIMPLANTING AN AVULSED PERMANENT TOOTH

Core Facts

Avulsion is complete displacement of the tooth from the supporting socket. Avulsed teeth may be ingested or aspirated, and some effort should be made to find them. Replacement should be done within 30 to 60 minutes to offer the best chance for survival of permanent teeth. Avulsed primary teeth should not be replaced. Since the ED physician does not provide definitive treatment and time is an important factor in outcome.

Procedure

Always handle tooth by its crown and inspect it for fractures. Cleanse tooth by gently swirling it in normal saline solution or a commercial medium. Locate empty socket; for better visualization, lightly suction or swab surrounding area. Position tooth at socket opening and reinsert it

smoothly, applying firm but gently pressure. Hold tooth in place manually or have child bite on gauze pad until dentist arrives. It is important to note that reimplantation is only indicated for an avulsed permanent tooth, not for a deciduous (primary) tooth. The tooth must be reimplanted immediately. Delay reduces the chance of success. If the physician cannot reimplant the tooth, it should be stored in milk. The tooth must always be handled by its crown. The root should never be touched. The dentist should be consulted as soon as the physician is notified about the case.

REDUCTION OF AN INCARCERATED INGUINAL HERNIA

Core Facts

At least 80 percent of incarcerated hernias can be reduced nonoperatively. Emergent operative reduction has a greater morbidity than elective repair. Successful reduction is the goal of the acute care physician. Presence of an inguinal hernia is suggested by a mass in the inguinal area that may extend to the scrotum. In a female the mass appears in the groin or labia majora. Symptoms of incarceration include irritability, poor feeding, abdominal or inguinal pain, and vomiting. Older children report groin discomfort. Signs of incarceration include edema, erythema, tenderness, and/ or bluish discoloration from venous engorgement of the involved area. It may be difficult to distinguish incarceration from strangulation. Strangulated hernia should never be reduced. The perioperative complication rate is 20 to 30 percent in emergent surgery compared to 1 to 2 percent in elective surgical repair of an inguinal hernia. This emphasizes the benefit of nonoperative reduction. The purpose of reduction of incarcerated hernia is to prevent strangulation of incarcerated bowel, ovary, or other organs; and to allow for edema to resolve in order to permit a less hazardous, semi-elective repair of the hernia.

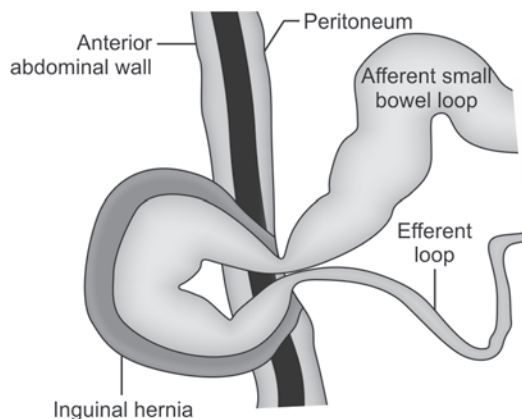
The complications of the manual reduction of incarcerated hernia are not common but may include compression damage of the bowel or other incarcerated organ or tissue; and increased edema with pain.

Procedure

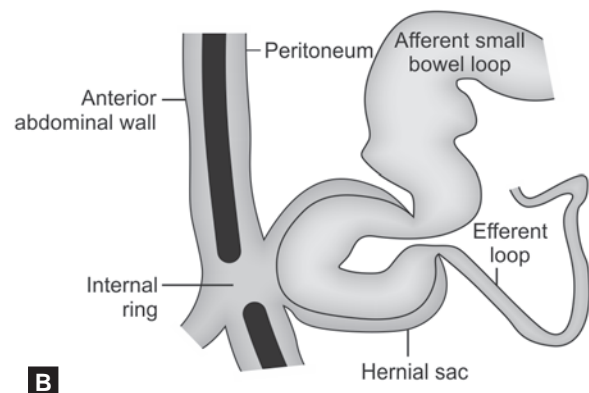
Place the patient supine in a mild Trendelenburg position to decrease edema in the incarcerated tissue. The primary principle of reduction is to reduce the contents of the bowel first, following which the edematous bowel itself may then be coaxed back into the abdominal cavity. To do this, apply bimanual pressure along the entire inguinal canal so that there is uniform pressure on the incarcerated bowel. Begin to apply pressure gently with slightly increased pressure in the distal canal compared to the proximal canal to encourage reduction of intestinal contents into the bowel within the abdomen. Apply a sustained, moderate pressure for up to 5 minutes or until reduction is achieved.

If reduction has not occurred at this point, it may be due to patient discomfort and tensing of the abdominal wall. The patient should then be sedated with 0.1 mg/kg of morphine sulfate and allowed to fall asleep. After a half an hour, reposition the patient gently in Trendelenburg position and apply the same maneuver of sustained pressure along the inguinal canal. If sustained pressure is successful, a gurgling sensation will first be felt as the intestinal contents move back into the intra-abdominal bowel, following which the bowel loop itself may begin to move and finally slide up the inguinal canal and in through the internal ring into the abdomen. When manual reduction, even with sedation, is not successful, it usually is in those situations in which the incarcerated bowel and/or ovary is outside the external ring. Another mass within the inguinal canal, which does not lend itself to ready reduction, is hydrocele, which simulated incarcerated bowel. If reduction is not successful after 5 or 10 minutes' effort with the benefit of sedation, prepare the patient for surgery.

Sagittal section at the site of internal ring (semi-diagrammatic)



Reduction enmasse of inguinal hernia



Figs 12A and B: Reduction of an incarcerated inguinal hernia

RECTAL PROLAPSE

Core Facts

The prolapse may involve only the mucosa; or may be termed procidentia, which is a complete prolapse of all layers of the rectum. Rectal prolapse is most common in children under age 3 years, in whom it is most often idiopathic. It is hypothesized that this is because these children have recently assumed the erect position, and their musculature is weak, while they begin to take control of defecation. Most children with rectal prolapse have chronic constipation (28%) or acute diarrheal disease (20%, especially shigellosis, *Clostridium difficile*, enterocolitis, etc.). It is idiopathic approximately 20 percent of the time. Cystic fibrosis is identified in nearly 12 percent of cases. Anatomic abnormalities, such as repair of imperforate anus and rectal polyp, or neurologic abnormalities, such as myelomeningocele, account for most of the remainder. Rectal prolapse occurs in 18 to 23 percent of cystic fibrosis patients, often before the definitive diagnosis is made. The diagnosis of rectal prolapse is made by history and physical exam. A history of 1 to 2 centimeter, painless protrusion from the anus during or after defecation is reported, which typically resolves spontaneously. Older children may complain of discomfort or a constant urge to defecate. Blood or a mucosal discharge may be noted from the anus. Manual reduction of rectal prolapse is necessary when it is prolonged, fails to reduce spontaneously or when associated with passive congestion and/

or hemorrhage. Complications of this procedure are extremely rare but occasionally there may be bleeding.

Procedure

In the anxious child (peak age 1-3 years), consider administration of mild sedation (i.e. chloral hydrate) before attempting reduction of a prolapsed rectum. The child should lie prone on his or her knees. Lubricate your gloves with petrolatum (Vaseline) and hold the prolapsed edges with 4 × 4 inch gauze. Then, bimanually apply pressure on alternate sides to reduce the prolapse. Have the patient lie on his or her side afterward. Be sure to address the primary problem.

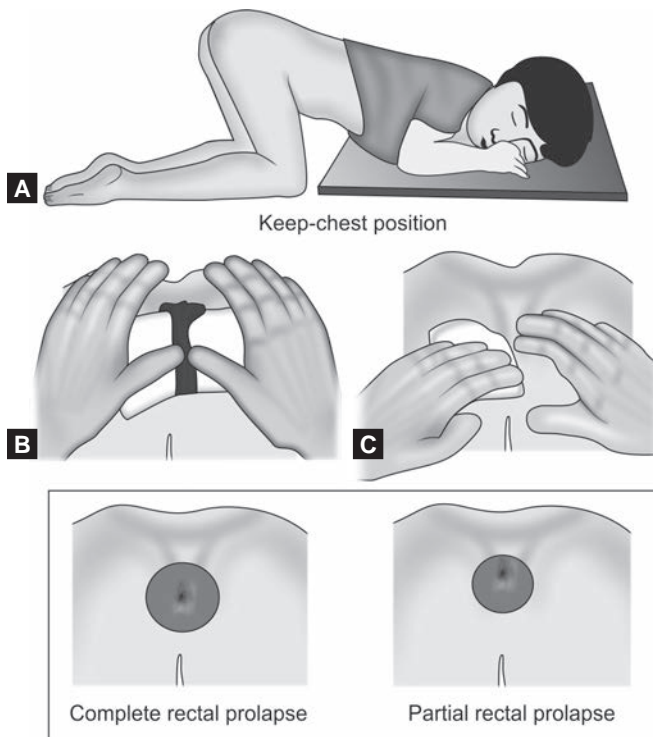
MANUAL DETORSION OF THE TESTES

Core Facts

Torsion of the testicle is defined as ischemia and infarction of the testicle following twisting of the spermatic cord. Venous obstruction initially leads to venous thrombosis, then impairment of arterial circulation, and eventually infarction. There is essentially no viable testicular function 24 hours after the onset of symptoms. Torsion of the testicle is estimated to occur in 1/4,000 males, and occurs most commonly in males 13 to 25 years of age. Torsion of the testicle occurs more frequently on the left side. There are two peak incidences: Extravaginal torsion occurs primarily within the first few months of life; intravaginal torsion peaks at puberty and may be because of the increase in size and weight that the testicle undergoes at puberty.

The first sign is sudden, severe scrotal pain, often followed by nausea and vomiting and later with erythema and swelling of the scrotum. The patient may have had several brief episodes of testicular pain that spontaneously resolved within the previous few days or weeks. These may represent partial or intermittent torsion. Fever is very uncommon. The testicle often has a horizontal lie, and the cremasteric reflex is absent. Most cases of torsion are idiopathic, although some have an antecedent history of trauma, athletic activity, or sexual activity. So the clinical diagnostic triad of acute scrotal pain, high-riding testis, and absent cremasteric reflex suggests testicular torsion. If there is any suspicion that the patient has torsion of the testicle, obtain a pediatric surgery consult immediately. Always seek urologic consultation for initial assessment and follow-up. Manual detorsion may be successful and of value in first 8 to 12 hours of symptoms. Administer intravenous conscious sedation and/or perform spermatic cord block as indicated.

Torsion almost always occurs with inward or internal rotation-rotate testis within scrotum in outward direction one or two 360 turns. Prompt relief of pain and return to normal position in scrotum suggest successful detorsion. Following successful detorsion, surgical exploration and orchiopexy should proceed as soon as possible.



Figs 13A to C: Reduction of a prolapsed rectum

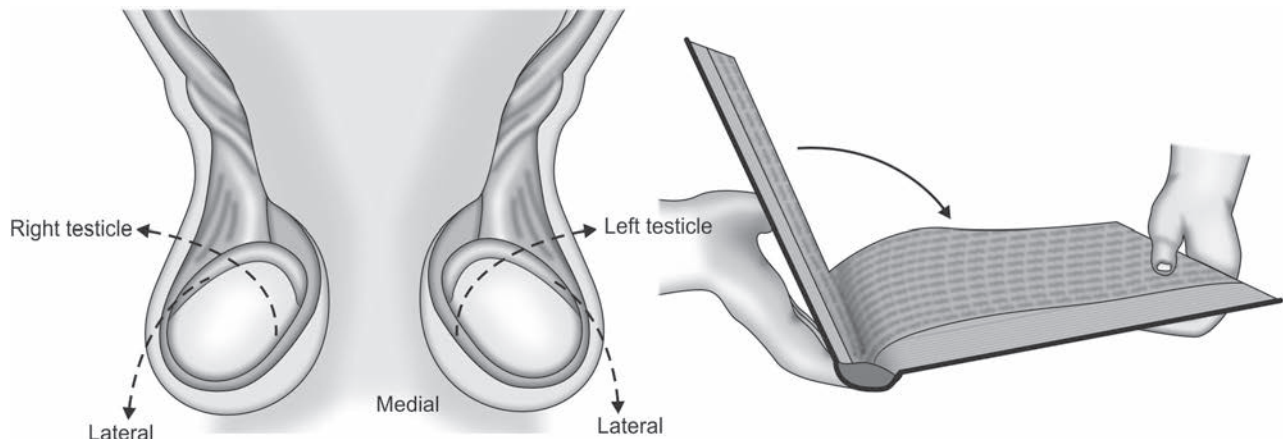


Fig. 14: Detorsion of testicular torsion

Procedure

The patient requires rapid transport to the ED because delays decrease the testicular survival rate. Proper analgesia may improve the clinical examination, but analgesia or local anesthesia in the ED is not advised unless a decision has been made to go to the operating room immediately, since it will be impossible to determine if the patient has untorted. A urologist should be consulted before giving any pain medicine. The patient should be NPO for emergent surgery. Manual detorting the testicle may be tried in the ED, particularly if duration has been 4 to 6 hours or more since the onset of pain and there is a chance of regaining viability, or the patient needs to be transferred to another facility, and there will be a delay in surgery. Manual detorsion may be successful and of value in first 8 to 12 hours of symptoms. Administer intravenous conscious sedation and/or perform spermatic cord block as indicated. Most torsions rotate the testicle medially. Therefore, twisting the testicle from medial to lateral will return the testicle to a normal anatomic position and permits blood flow. When standing at the patient's feet, twist the left testicle clockwise and the right testicle counterclockwise, e.g. "opening a book." This maneuver should only be attempted once. Do not continue to twist the testicle in an effort to untort it. Even if the procedure is successful, the urologist should be consulted for further management. Detorsion is only a time buying procedure before the patients arrive in a facility which can handle the situation.

PARAPHIMOSIS REDUCTION

Core Facts

Paraphimosis results from a constricted ring of retracted foreskin causes obstruction of the arterial, venous and lymphatic flow. This in turn leads to edema of the foreskin and underlying glans. The usual cause is failure to reduce the foreskin back over the glans after manually retracting it for penile cleaning or catheterization. The foreskin is retracted,

engorged, edematous, and usually very tender. The entrapped prepuce can be erythematous; rarely cyanotic and/or necrotic after prolonged entrapment. The glans may also become edematous and tender, usually inferior or immediately adjacent to the constricted foreskin. There is usually a clear margin between the swollen retracted foreskin and the proximal glans of the penis. The penis is flaccid proximal to the level of foreskin engorgement. If the proximal phallus is more diffusely edematous and tender, an infectious etiology (balanoposthitis, which is a local cellulitis) becomes more likely. Parents of uncircumcised boys should be cautioned not to forcibly retract the foreskin. Uncircumcised boys with retractable foreskin should be taught to return it to the normal position after cleaning.

Procedure

Pediatricians in the pediatric emergency room or in pediatric offices can reduce most of the paraphimosis. Prompt reduction of paraphimosis obviates later difficult reduction of the extremely swollen foreskin and glans penis. Prolonged and painful attempts at reduction must be avoided. With more difficult cases urological consultation should be sought early. Following is a simple stepwise approach for paraphimosis reduction.

Step 1: If necessary, dorsal penile nerve block can be performed in 3 ways:

For single injection nerve block, first palpate the pubic symphysis and then vertically advance a 22-gauge needle at the base of the penis until it comes in contact with the inferior border of the symphysis pubis. Then, withdraw the needle slightly and advance it parallel to the pubic symphysis until there is a loss of resistance, indicating penetration of Buck's fascia. This usually occurs approximately 5 mm beyond the anterior border of the pubic symphysis. A single injection of lidocaine or bupivacaine may be given, after ensuring that the needle is not in a blood vessel. For bilateral injection nerve block, follow the same steps as above until penetration of Buck's fascia.

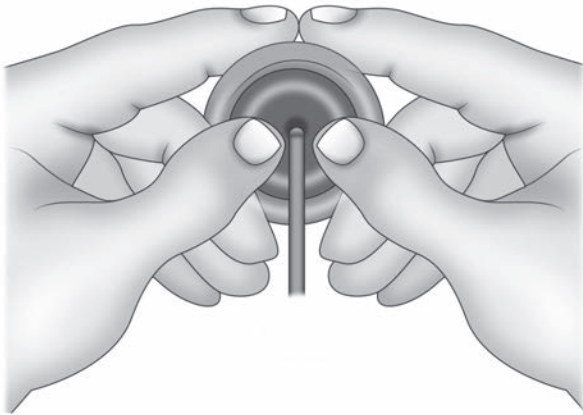


Fig. 15: Manual reduction of paraphimosis

Instill 1 percent lidocaine on either side of the midline at 10 o'clock and 2 o'clock positions. Alternatively one can infiltrate lidocaine subcutaneous in a concentric ring around the base of the penis. Complications of nerve blocks include:

- i. Ischemia if epinephrine is used,
- ii. Hematoma,
- iii. Intravascular injection

Step 2: Manual compression: Encircle the foreskin with a gloved hand and apply pressure for 5 to 10 minutes.

Step 3: Manual reduction: Using both hands, place the index finger at the dorsal aspect of the foreskin, the thumbs at the tip of the penis, and the other fingers on the ventral aspect of the foreskin. Then push the glans inward with the thumbs while applying traction to the foreskin to pull it over the glans.

Alternative Methods

Place the entire palm of the hand around the foreskin and apply traction while pushing the glans in with the thumb of the other hand. Fill half of size 8 latex surgical gloves with ice and water. Push in the thumb of the glove. Apply lubricant to the penis. Place the penis inside the thumb of the glove. This step helps reduce edema and causes vasoconstriction. After this step, re-attempt manual reduction as outlined in step 3.

Babcock clamp method: If manual reduction in step 3 fails, hold the phimotic ring of foreskin with 6 to 8 Babcock clamps and apply traction slowly pulling the foreskin slowly over the glans. Do not use serrated (Allis) clamps. Complications may include tearing of the foreskin. In this case, urology should be consulted to perform operative dorsal slit of the foreskin.

Dorsal slit of the foreskin: If the Babcock clamp method fails, this may be attempted in the ED, if urology is not available for any reason. Use 1 percent lidocaine local infiltration in a line at the 12 o'clock position along the constricted ring.

Begin infiltrating 0.5 cm proximal to the constriction making a line 0.5 cm distal to it. Then make a small circumcision along the line of anesthetic infiltration, passing through the skin, subcutaneous layer, and the constricting ring. The proximal and distal edges of this incision should be brought together with 4.0 chromic sutures using a continuous suture technique. Bleeding is the most common complication of manual reduction, and may be treated with a compression dressing. One can consider emergency circumcision if all other methods fails.

ZIPPER ENTRAPMENT INJURIES

Core Facts

The key to treatment of zipper entrapment is to avoid further manipulation of the zipper. Take the fastening device apart by cutting the median bar. Zipper injuries occur most commonly when the uncircumcised male zips up his pants too quickly and entraps the foreskin of the penis in the zipper mechanism. Children with foreskin entrapment are frequently in a great deal of pain and are very anxious. Two types of zipper entrapment are generally seen: a) The most common type presents with the foreskin stuck in the moveable part of the zipper, b) Less commonly, the foreskin may be caught between the teeth of the zipper, the moveable part having been pulled beyond the foreskin. The foreskin may be caught between the teeth of the zipper or is frequently wedged between the engaged zipper teeth and the casing of the slide fastener. The foreskin may be swollen.

Procedure

- In most cases, no local anesthetic is necessary to remove the zipper as it is a painless procedure. However, in the highly anxious or uncooperative child, a restraint device, local infiltration with Xylocaine®, or sedation may be required.

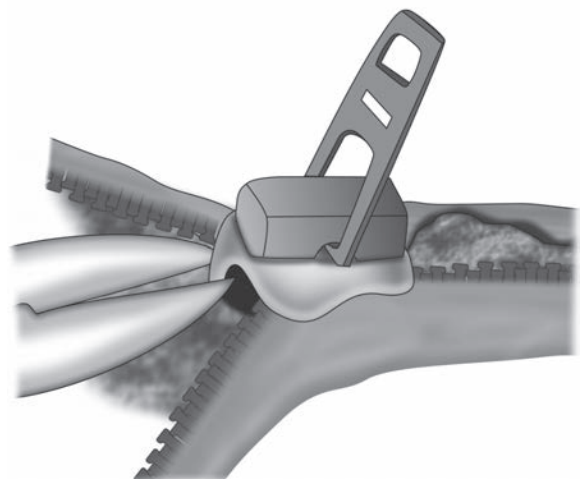


Fig. 16: Release of foreskin during zipper injuries

- In the situation where the foreskin is entrapped in the zipper sliding mechanism, the median bar of the zipper can be cut with a wire or bone cutter. This will permit the two halves of the zipper to fall apart, releasing the entrapped skin.
- In the less common situation where the entrapment of foreskin is between the teeth of the zipper alone, simply cutting across the zipper with a scissors below the entrapment will allow the teeth to separate and release the foreskin.

PULLED ELBOW OR NURSEMAID ELBOW

Core Facts

It is one of the most common subluxation seen in the children. The most common mechanism is a fall on an outstretched hand. Subluxation of the radial head occurs after a pull on the forearm in a young toddler, mainly 1 to 3 years of age. In many cases, there is no clear or recalled history of a pull. On examination, the forearm is held pronated, with partial flexion at the elbow. There is no deformity or ecchymosis, but there may be tenderness at the wrist, elbow or shoulder. Reduction of the subluxation, which may be done without radiographic studies before or after, is curative. Technique is simple and can be easily performed by pediatricians in their offices.

Procedure

The reduction of pulled elbow can be done without any sedation analgesia by the pediatricians in their offices. The diagnosis is clinical and radiography is not needed to confirm the diagnosis. Make the child to sit in the lap of mother with elbow held posteriorly, to prevent the child from running away during the reduction. The child's hand is grasped in a hand-shaking gesture, and then rapidly rotated externally and flexed simultaneously. There is often

a palpable "click" or "pop" as the radial head reduces, accompanied by a sharp cry from the infant. If a pop is not felt, the maneuver may be repeated once. If still unsuccessful, a radiograph of the forearm should be obtained. If there has been a palpable pop, the child should have a return to normal movement in 5 to 15 minutes. If unsuccessful, and subsequent radiographs are negative, the arm should be placed in a sling, and parents instructed to follow-up the next day with their primary care provider or orthopedist.

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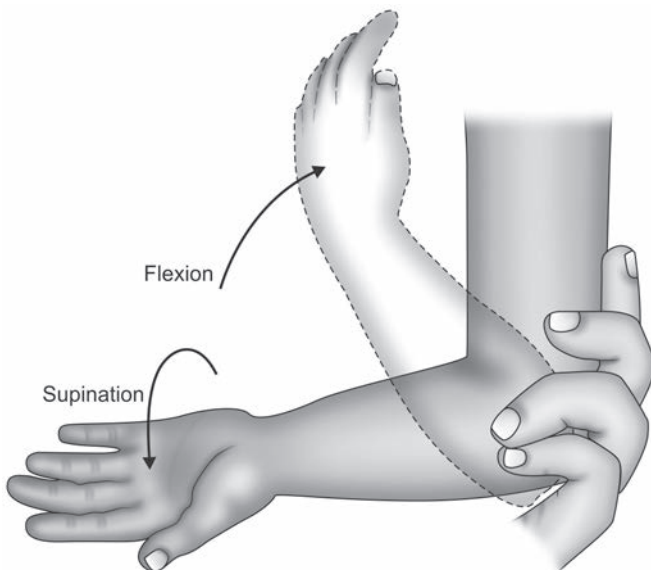


Fig. 17: Reduction of pulled elbow (nursemaid's elbow)

Pain and Palliative Care for the Pediatric Patient

Veronique Dinand, Tulika Seth

BACKGROUND

A growing number of children live with chronic life-limiting conditions, leading to impaired quality of life. Life-threatening diseases in childhood such as neurologic, rheumatological and genetic disorders, cancers and acquired immunodeficiency syndrome (AIDS), require palliative care. With steady improvement in the management of these diseases over the years, longer survival has been achieved in many of these conditions, but quality of life remains a major challenge. The vital role of pain management and palliative care in these children has received increased attention and importance.

Palliative care is the art and science of patient- and family-centered care aimed at attending to suffering, promoting healing and improving quality of life. It provides relief of physical, emotional, social and spiritual suffering. Palliation begins when illness is diagnosed and continues until cure or death.

PALLIATIVE MODEL OF CARE

Palliative care is an interdisciplinary care that aims to relieve suffering and improve quality of life for patients with advanced illness and their families. The WHO defined quality of life as “Individuals perception of their position in life in the context of the culture, value systems in which they live; their goals, expectations, standards, and concerns”.¹ Health-related quality of life is related to physical function and mobility, cognitive function, self-care, emotional status, sensory function and pain.² The primary goal in palliative care is relief of suffering, whereas the primary goal in modern medicine is to cure, and death is seen as an ultimate failure. In a palliative model of care, enabling a patient to live fully and comfortably until death

is a success. The palliative model of care recognizes the importance of cure as well as control and relief of suffering. Thus palliative care is not restricted to ‘End of Life’ care and is offered simultaneously with all other appropriate medical treatment, from the time of initial diagnosis. All four fields of palliative care, i.e. support, comfort, dignity and team approach, can be established more easily in pediatric practice than in adults. Palliative care is provided both within specific structures such as the hospital (palliative care unit, intensive care unit, pediatric department, pediatric oncology unit) or palliative care hospice and outside through home visits.

Palliative care is not doctor-centered but involves allied health professionals: physicians, social workers, palliative care-trained nurses, psychologists, occupational therapists and child-life specialists. All have an equally important part in an interdisciplinary rather than multidisciplinary approach. Adequate support requires a holistic approach, treating the whole person in its physical, emotional, spiritual and social dimensions.³

COMMUNICATION

Collaborative communication between health care takers and the patient and relatives is fundamental at all points of patient care: initial diagnosis, curative treatment and palliative care.⁴ Collaborative communication involves the family. It is especially delicate when faced with the issue of communicating bad news. Communicating the truth builds the physician-patient relationship, fosters collaboration, permits the family to plan and cope (Table 1). When language is a barrier, it is important to involve a skilled translator who is used to medical terminologies and is not a part of the patient’s family.

Table 1: The six-step protocol to reveal bad news (adapted from Robert Buckman⁷)

<i>Steps</i>	<i>Do's</i>	<i>Don'ts</i>
1. Getting ready	<ul style="list-style-type: none"> Plan what to say Conducive environment (proper room, tissues, etc.) Adequate time, blocking at least 30-60 minutes Body language: sit down, eyes at their level Ask who else parents would like to be present 	<ul style="list-style-type: none"> No interruptions by cell phone/pager Body language: don't look at watch Avoid family members as primary translators
2. Establish what the parents know	<ul style="list-style-type: none"> "What are you expecting to happen? How specific do you want me to be?" Assess ability to comprehend bad news Reschedule if they are unprepared 	<ul style="list-style-type: none"> Do not assume parents understand about the disease, prognosis or treatment
3. Establish how much they want to know	<ul style="list-style-type: none"> If they decline to know, say "this is what I have to do" If the parents don't want the child to be told, ask why Wait for their informed consent to tell the child: "We will talk to the child together" 	<ul style="list-style-type: none"> Don't allow one parent to hide the diagnosis from the other Don't lie to the child
4. Sharing the information	<ul style="list-style-type: none"> Say it in small pieces Pause frequently, check for understanding. Allow silence for them to reflect or dialogue Use clear words to make them understand diagnosis and prognosis (e.g. "cancer", "HIV", "death") You may acknowledge that you are sorry (e.g. "this must be very difficult for you") 	<ul style="list-style-type: none"> Avoid medical jargon Avoid euphemisms about death and dying (e.g. "terminal," "critical," "not doing well," "unresponsive to treatment") Avoid "I know how you feel" because no one can
5. Responding to the feelings of the patient and his/her family	<ul style="list-style-type: none"> Broad range of reactions: affective (tears, anger, sadness), cognitive (denial, blame, guilt) or basic psycho-physiological (flight to fight) Listen, use non-verbal communication (holding hands) 	<ul style="list-style-type: none"> Do not be cold and distant Do not be afraid to show emotion or distress
6. Planning, follow-up	<ul style="list-style-type: none"> Explain further plan of care Goal setting: treatment objectives and expectations There is hope for a pain-free and symptom-free life Emphasize the quality of life 	<ul style="list-style-type: none"> Don't say "there is no hope"

The physician reveals the truth to the patient's family first, giving them some time (a day or more) to face and comprehend the situation and then reveal it to the child. Using an age-appropriate way of revealing the illness, a child as young as 7-year-old may be told about the prognosis truthfully and tactfully. In the Indian scenario parents are unwilling to discuss or inform even older children about the diagnosis of a life threatening disease and poor prognosis.⁵ However, many children and teenager wish to understand their underlying disease and prognosis, as well as to take part in therapeutic decisions. All children intuitively know about the outcome of their illness.⁶ Honesty with the child promotes trust. Building trust may take time, but it is essential in the management of children suffering from chronic conditions.

PAIN MANAGEMENT

In the developed world, the major sources of pain in children are due to diagnostic and therapeutic procedures. In the developing world, most chronic pain is disease-related and most children are under-treated for pain. The multidimensional character of pain, i.e. psychological, social, spiritual and physical, requires a multidimensional approach. Determining the type of pain is important since response to treatment will depend on the type of pain.

Types of Pain

- Nociceptive or physiological pain is caused by the stimulation of sensory receptors (nociceptors) in the tissues, with normal nerve system. There are two types of nociceptive pain:

1. Somatic pain is usually well localized to the skin and superficial structures
 2. Visceral pain is usually difficult to localize
- Neuropathic pain is caused by peripheral or central nervous system injury. The injured nerves either react abnormally to stimuli or discharge spontaneously, causing dysesthesia (described as burning, tingling) or shooting pain (described as an electric shock). Neuropathic pain is less responsive to non-opioid and opioid analgesics and responds better to adjuvant analgesics, particularly anticonvulsants.
 - Sympathetic pain is caused by damage to sympathetic nerves. It is characterized by burning pain, increased sensitivity and sympathetic dysfunction (erythema, pallor, edema, sweating, trophic changes). It responds poorly to analgesics, but responds well to regional sympathetic nerve block.
 - Psychogenic pain in which no physical basis can be found to explain the pain. Since all chronic physical pain is associated with some degree of psychological distress, primary treatment of the cause of physical pain is fundamental. Psychological pain requires psychological therapies.

Pain Assessment

Pain assessment starts with a complete evaluation.

- Assess the child: QUESTT
 - Q – Question the child
 - U – Use pain rating scales
 - E – Evaluate child's behavior
 - S – Secure parent's involvement

T – Take cause of pain into account

T – Take earliest action

- Conduct physical examination
- Determine primary cause of pain
- Evaluate secondary causes (environmental and internal)
- Develop treatment plan: Analgesic drugs and non-analgesic therapies
- Implement Plan
- Assess regularly and revise plan as necessary

Documentation of pain score with the time of observation should form a part of routine pediatric charting. There are multiple pain assessment scales adapted to diverse age groups.⁸ Observation methods based on behavioral response are used to assess pain in preverbal and nonverbal children. The FLACC Behavioral Pain Assessment Scale (Table 2) has been validated in children aged 2 to 7 years.⁹

Self-report pain scales facilitate communication from verbal children about pain, such as the Wong Faces Pain Scale, validated in children above 4 years (Fig. 1)^{10, 11} and the Visual Analogue Scale (Fig. 2). Always remember that pain is what the child says it is.

Analgesic Therapy

Drug treatment is the main stay in pain management. Placebo plays no role in the treatment of chronic pain in palliative care. Analgesic therapies should be combined with appropriate psychosocial, physical and supportive approaches, since pain is multidimensional. The 3-step WHO analgesic ladder (Fig. 3) forms the basis of pain control in palliative care.

Table 2: FLACC behavioral pain assessment scale (face legs activity cry consolability scale)⁹

FLACC		Scoring		
Score	Indicators	0	1	2
0: Relaxed and comfortable	Face	No particular expression or smile	Occasional grimace or frown; withdrawn, disinterested	Frequent to constant frown, clenched jaw, quivering chin
1-3: Mild discomfort	Legs	Normal position or relaxed	Uneasy, restless, tense	Kicking or legs drawn up
4-6: Moderate pain	Activity	Lying quietly, normal position, moves easily	Squirming, shifting back and forth, tense	Arched, rigid or jerking
7-10: Severe discomfort or pain or both	Cry	No cry (awake or asleep)	Moans or whimpers, occasional complaint	Crying steadily, screams or sobs; frequent complaints
	Consolability	Content, relaxed	Reassured by occasional touching, hugging or being talked to; distractable	Difficult to console or comfort

Instructions for Usage

In patients who are awake: observe for 1-5 min or longer. Observe legs and body uncovered. Reposition patient or observe activity. Assess the body for tenseness and tone. Initiate consoling interventions if needed.

In patients who are asleep: observe for 5 min or longer. Observe legs and body uncovered. If possible, reposition patient. Touch the body and assess for tenseness and tone.

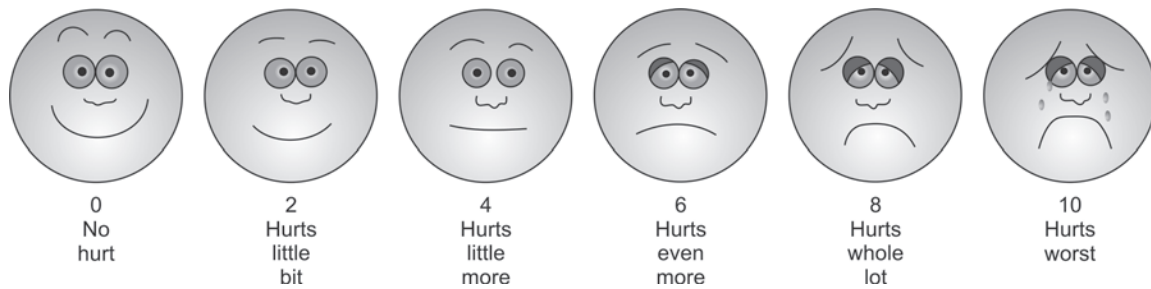


Fig. 1: Pain assessment scale in children over 4 years of age – The Wong Baker faces pain rating scale (with permission, from <http://www.wongbakerfaces.org>)

Instructions for Usage

Explain to the child that each face is for a person who has no pain (hurt), or some, or a lot of pain.

"Face 0 doesn't hurt at all. Face 2 hurts just a little bit. Face 4 hurts a little more. Face 6 hurts even more. Face 8 hurts a whole lot. Face 10 hurts as much as you can imagine, although you don't have to be crying to have this worst pain." Ask the child to choose the face that best describes how much pain he/she has.



Fig. 2: Pain assessment scale in teenagers—visual analogue pain scale

Instructions for Usage

The child should be able to verbalize a number, > 9 years old.

Ask the child: "On a scale of 0 to 10, with 0 meaning 'no pain' and 10 meaning the worst pain you can imagine, how much do you hurt right now?"

Various degrees of pain are equivalent to 0-no pain, 2-annoying, 4-uncomfortable, 6-dreadful, 8-horrible and 10-unbearable pain.

In case of chronic pain, the medical person assessing pain should have knowledge of the patient's baseline level of pain to appreciate efficacy of analgesic therapy.

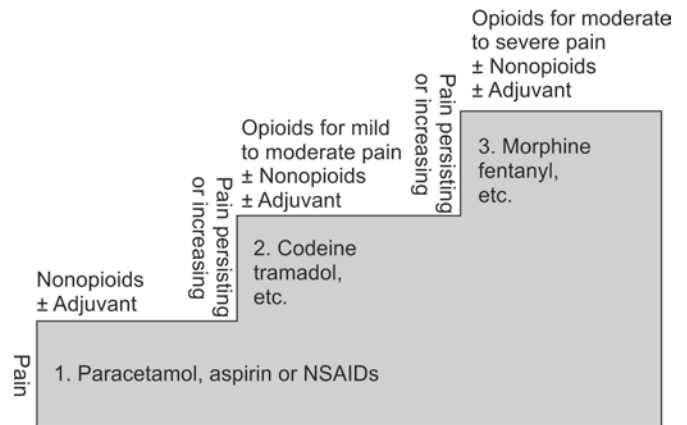


Fig. 3: The 3-step WHO analgesic ladder

Whenever one drug provides no relief, then a drug combination or a change of drug is required. Analgesic therapy is given "by the ladder, by the clock, by the appropriate route, by the child", i.e. choice of analgesics guided by the analgesic ladder; analgesics given at a regular schedule, not as required; choosing the least invasive route of administration, easily accepted by the child; analgesic therapy individualized to the child (Table 3).

Mild to Moderate Pain

Mild pain is treated by nonopioid analgesics: paracetamol and nonsteroidal antiinflammatory drugs (NSAIDs). Nonsteroidal anti-inflammatory drugs are contraindicated in children with thrombocytopenia. Weak opioids (codeine and dextropropoxyphene) can be added to nonopioid analgesics at the second step of the analgesic ladder, i.e. mild to moderate pain. Codeine is used at twice the antitussive dose. If pain control is insufficient, codeine plus paracetamol are a good option.

Severe Pain

Strong opioids are required for moderate to severe pain, in association with step 1 nonopioids. Since narcotics are prohibited drugs, they can be dispensed only with a license. A special prescription is required on an official form of prescription (form DD7) provided by the chemist, or on the doctor's letterhead, with his/her State Medical Council number and stamp. The prescription should mention the name, address and description of the person to whom the prescription is issued, so as to reduce the risk of misuse.

Although India is a major opium exporting country, there is minimal access to opioids, due to regulatory and opioid availability issues.¹² Efforts at improvement of stringent laws on opioid use led to Amended Narcotic Rules (1999), which has approved "Recognized Medical Institutions" providing palliative care and allots them an opioid quota. Few chemists provide narcotics in metropolitan cities. Opioids that are available in India are codeine,

Table 3: Analgesic medications in children above 6 months of age

<i>Drug classification</i>	<i>Analgesic</i>	<i>Dose</i>	<i>Formulation</i>
Non-opioid analgesics	Paracetamol	10–15 mg/kg po q6h	Tab 500 mg, Syrup 125 mg/5 ml, Drops 100 mg/ml, Suppositories 80 mg, 125 mg, 250 mg
	Ibuprofen	10–20 mg/kg po q6h	Tab 200 mg, 400 mg, 600 mg, syrup 100 mg/5 ml
	Diclofenac	1 mg/kg po q8h to q12h	Tab 25 mg, 50 mg
	Naproxen	10 mg/kg po q12h	Tab 250 mg, 500 mg
Weak opioids	Codein	Start at 0.5 mg/kg, increase to 1–3 mg/kg q4h	Linctus codein syrup (codein-10 mg/5 ml)
	Tramadol	6–12 yr: 1 tab q6h >12 yr: 2 tab q6h	Tab tramadol 37.5 mg + Paracetamol 325 mg
	Dextropropoxyphene	1–2 mg/kg q12h	Tab 65 mg + Paracetamol 400 mg
Strong opioids	Fentanyl	IV bolus 1–2 µg/kg IV infusion 1–3 µg/kg/hr Transcutaneous	Inj 50 µg/ml, 100 µg/2 ml Transdermal patch 25 µg/h, 50 µg/h, 75 µg/h, 100 µg/h for 24h or 72 h
	Morphine	0.15–0.3 mg/kg po (opioid-naïve child) ^a 30–60 µg/kg/hr SC	Tab ^b 5 mg, 10 mg, 20 mg, 30 mg, 60 mg CR ^c Tab 10 mg, 30 mg, 60 mg Inj 15 mg
	Buprenorphine	IV/IM 3–6 mg/kg Sublingual 5–7 mg/kg	Inj 0.3 mg/ml, 0.6 mg/2 ml SL Tab 0.2 mg
	Pethidine ^d	IV 0.5–1 mg/kg	Pethidine inj 50 mg/1 ml, 100 mg/2 ml

Note: (a) 0.05–0.1 mg/kg in infants <6 months. (b) Immediate release. (c) Controlled release. (d) Never as continuous infusion (neurotoxicity)

Table 4: Opioid equianalgesic doses

<i>Opioid</i>	<i>Equianalgesic dose (mg)</i>	
	<i>Intravenous</i>	<i>Oral</i>
Morphine	10	30
Fentanyl	0.1–0.2	Not available

pethidine, morphine, fentanyl and tramadol. Substitution of an opioid for another in case of poor pain control or significant side effects may result in improved analgesia and fewer adverse effects. Fentanyl has rapid onset and short duration of action. It is the opioid of choice in hepatorenal dysfunction. Buprenorphine, with its longer duration of action than morphine, is both safe and effective. When switching to an alternative opioid, use equianalgesic doses (Table 4).¹³ When substituting intravenous fentanyl with oral morphine, fentanyl should be titrated only after starting the latter.

Oral morphine is preferred route for patients who require morphine chronically, e.g. children with progressive cancer. Short acting morphine elixir (currently not available in India) or 5 mg tablets are used initially; tablets may be crushed and mixed with 5 ml of any beverage for administration to young children. The dose is titrated to attain pain control, increasing by 50 percent everyday till total pain control, after which the patient is switched to

12 hourly slow release morphine tablets (MST preparation), available through the IAPC. Opioid-tolerant children require dose escalation at the end of life, with no maximum acceptable dose to control severe oncological pain. Fentanyl transdermal patches of various strengths offer a 1-day or 3-day pain relief with easy administration (Table 4). Once-daily morphine (MXT preparation) and fentanyl oral preparation are not available in India.

Expected side effects of opioids include nausea/vomiting and constipation by reducing gastrointestinal motility. Thus antiemetics and laxatives are prescribed routinely for the prevention of constipation (Table 5). Itching is another common complication, usually tackled with oral anti-histaminics and skin emollients provide some relief. Contrary to cetirizine and hydroxyzine hydrochloride, loratadine leads to minimal sedation. However, intractable itching may require a change of opioid, e.g. fentanyl, or continuous morphine infusion along with low-dose infusion of naloxone at 1–2 µg/kg/h, feasible only in hospital setting.

Opioid-induced respiratory depression can only occur in case of accidentally high dose of or sudden hepatic or kidney failure in children. Hypotension, bronchospasm and chest wall rigidity are never seen with oral morphine. Somnolence is common, and judicious balance between a pain-free and over-sedated child needs to be found in concert with the family. In case of over-sedation, switching

Table 5: Adjunctive therapy to opioid prescription

Indication	Drug classification	Drug	Dose	Formulation
Prevention of constipation	Softening agent	Lactulose	5–15 mL q8h Upto 1 ml/kg per dose	Syrup 10 g/15 ml
Nausea	Dopamine antagonist	Domperidone	0.2–0.4 mg/kg q4h to q8h	Tablet 5 mg, 10 mg Syrup 5 mg/5 ml Drops 10 mg/ml
Excessive sedation	Piperidine	Methylphenidate	0.3–2 mg/kg/day Start with 5 mg before breakfast and lunch and increase	Ritalin® Tab 5 mg, 10 mg, 20 mg Ritalin LA® cap 20 mg, 30 mg, 40 mg Concerta® tab 18 mg, 27 mg, 36 mg
Itching	Antihistaminic	Cetirizine	2–6 yrs: 2.5 mg BD or 5 mg OD >6 yrs: 5 mg BD or 5 mg OD	Syrup 5 mg/5 ml Tab 5 mg, 10 mg
		Hydroxyzine	0.5 mg/kg q6h	Syrup 10 mg/5 ml, Drops 6 mg/ml Tab 10 mg
		Loratidine	2–6 yrs: 2.5 mg OD 6–12 yrs: 5 mg >12 yrs: 10 mg OD	Syrup 5 mg/5 ml Tab 10 mg
Opioid over-dose		Naloxone	0.1 mg/kg per dose IV. Max 2 mg. Repeat after 2-3 min if needed	Inj 0.02 mg/ml Inj 0.4 mg/ml

Table 6: Adjuvant analgesic medications in children

Indication	Drug classification	Drug	Dose	Formulation
Neuropathic pain	Anticonvulsant	Gabapentin	5 mg/kg po at bed time, increase q12h than q8h till effective analgesia (max 60 mg/kg/day)	Cap 300 mg, 400 mg
		Carbamazepine	3–10 mg/kg q8h	Syr 100 mg/5 ml Tab 100 mg, 200 mg, 400 mg
		Clonazepam	0.01–0.03 mg/kg/day q8h–q12h. Max dose 0.2 mg/kg/day	Tab 0.25 mg, 0.5 mg, 1 mg, 2 mg
Anxiety, muscle spasm	Benzodiazepine	Lorazepam	0.025–0.05 mg/kg q6h, max 2 mg per dose	Tablet 1 mg, 2 mg
Depression	Tricyclic antidepressant	Imipramine	0.5 mg/kg q8h initially. Increase by 1–1.5 mg/kg/day (maximum 5 mg/kg/day)	Tab 25 mg Cap 25 mg, 75 mg

to another drug is useful. Addition of methylphenidate is an alternative; however, this expensive psychostimulant is a controlled drug that can only be prescribed by psychiatrists.

Adjuvant Analgesic Therapy

Adjuvant therapy to analgesics includes antidepressant, anticonvulsants, corticosteroids and muscle relaxants (Table 6). Their judicious use is adjusted to the type and cause of pain (Table 7).

Alongside pharmacological measures, non-pharmacological analgesic measures are very useful to reduce pain. They include behavioral, psychological, physical and

cognitive approaches. Behavioral measures are relaxation therapy, deep breathing exercises, etc. Psychological support is needed for both children and parents, with particular need to relieve anxiety. Physical approach to pain may be occupational therapy, acupuncture, massages, etc. Cognitive interventions, such as imagining an enjoyable item or experience, help focus the attention to other thoughts than discomfort and pain.¹⁴

Interventional Pain Management

When pain is not relieved by the 3-step WHO ladder, patients should be referred to an interventional pain management physician. Intractable pain described as an

Table 7: Types of pain and management in children with cancer

<i>Type of pain</i>	<i>Cause</i>	<i>Management</i>
Nociceptive pain	Soft tissue	Nonopioid \pm opioid analgesics
	Bone	Nonopioid \pm opioid analgesics Steroids
	Visceral	Nonopioid \pm opioid analgesics
Neuropathic pain	Nerve compression	Steroids \pm Opioid analgesics
	Shooting/lancinating pain (Nerve infiltration/damage)	Opioids Anticonvulsants \pm Antidepressants
Sympathetic pain		Sympathetic nerve block
Other pain	Headache caused by intracranial tumor	Steroids
	Muscle spasm	Muscle relaxant
		Nonpharmacological analgesic measures

electric shock, stabbing or burning, suggests persistent pain caused by damage to the peripheral or central nervous system. In addition, these patients often show signs of paralysis and pain hypersensitivity. Neurolytic block or epidural/intrathecal infusion of morphine is indicated. Use of fixed program devices such as patient-controlled analgesia infusion pump for intrathecal drug delivery is ideal and should ideally be used when life expectancy is greater than 6 months.

MANAGEMENT OF OTHER SYMPTOMS

Nausea and Vomiting

Pharmacological Measures

An initial evaluation is required to identify the underlying cause of vomiting, since treatment of the cause may be more effective than antiemetics alone. Common causes are raised intracranial pressure, gastritis, opioids, partial or complete bowel obstruction. Phenothiazines, lorazepam, or dexamethasone may be effective in treating nausea and vomiting.

Serotonin antagonists (e.g. ondansetron, metoclopramide) are very good antiemetics even for non-chemotherapy related vomiting, such as opioid-induced nausea. Diphenhydramine (Benadryl®) along with metoclopramide is an effective combination. Metoclopramide at low dose enhances motility. Anxiety exacerbates nausea and vomiting and should be addressed. Anticipatory nausea is effectively managed with anxiolytic drugs.

Nonpharmacological Measures

Nonpharmacological measures to control nausea and vomiting include keeping the child in a calm environment, away from the smell of food, and giving small feeds frequently.

Nutrition

Assessing the Cause for not Eating

A child may not eat because he or she is not hungry, or because of other causes prevent the hungry child from

eating. A child with a minimum of appetite only needs to be helped to feed and drink. An anorexic child with short prognosis should not be forced to feed, since it would only cause suffering but without prolonging life.¹⁵ Treatable causes of poor feeding, such as mouth ulcers, oral thrush, dysphagia, nausea and vomiting, severe constipation, dyspnea, pain, chronic infections, etc. need proper management, and will often result in an increased appetite. Drugs causing anorexia should be changed e.g. opioids, metronidazole, etc.

Oral Feeding

Enteral feeding should be encouraged as much as possible, even if the child is not able to take by mouth. As long as possible, the child should take orally nutrient-rich foods and fluids providing a well-balanced diet, within the child's favourite dishes and preferences with easily tolerated food and drink. If preparing or getting the request food will take more than an hour, the child is likely to no longer want it. The child should not be forced, but may want to eat it at the next meal or snack. Attendants should also be ready to adjust to changes in taste.

Being flexible with timings is important, while trying to stick to normal family mealtime habits as much as possible helps maintain a near-normal life. For instance, three meals and three snacks a day encourages feeding in a child with poor appetite. These small frequent feeds are helpful to complement small meals, with high-calorie and high-protein food and homemade drinks and shakes. Commercial liquid nutritional supplements can be advised when food is refused. If only liquid diet is tolerated, one may vary the type of liquids, e.g. soups, juices, curd and coconut water. Daily supplementation with vitamin C, pyridoxine, thiamine, the fat-soluble, D, E, K and folic acid are easily provided with a multivitamin preparation.

Tube Feeding

If oral intake does not meet calorie and nutrient requirements, feeding by nasogastric tube can be easily managed

by mothers at home, with minimal training. Initially, tube feed can be tried at night while sleeping, so that the child may eat during the day. As anorexia progresses, feeds are given every 3 to 4 hours. Regular mouth rinsing and brushing is still required while on tube feed. Feeds may consist of milk or home-made food mixed and liquefied. Tube feeding by gastrostomy or jejunostomy is justified in case of upper gastrointestinal obstruction. Caregivers need to be educated about daily skin care of the gastrostomy or jejunostomy site with antibacterial soap and bolus feeding.

Parenteral nutrition is rarely indicated in children with intractable vomiting, such as intestinal obstruction or uncontrolled vomiting or diarrhea. In India, parenteral nutrition can only be given in hospital or hospice setting.

Cachexia

Cancer-related or AIDS-related cachexia is characterized by lack of appetite, weight loss due to fat and skeletal muscle wasting, anemia, fatigue and edema. It can only be improved with treatment of the underlying condition leading to the release of cytokines responsible for this syndrome. Cachexia usually improves with antiretroviral therapy in case of AIDS, but this is usually not possible in the case of terminal cancer. Parents need to be told that it is not associated with hunger or thirst, and does not improve with forced feeding or hydration.

Cyproheptidin and megestrol acetate are commonly used to improve appetite and increase weight in cancer-associated and AIDS-associated anorexia, cachexia or unexplained weight loss. Significant weight gain can be obtained with cyproheptidin (0.25–0.5 mg/kg/day in 2 or 3 divided doses) and megestrol acetate (7.5–10 mg/kg/day in divided doses) in children with cancer-related and HIV-related cachexia.¹⁶ However, caution is required, with possibly glucocorticoid stress coverage, since a transitory or severe secondary adrenal suppression may occur.¹⁷

Constipation

Inactivity, decreased mobility, poor oral intake and drugs predispose to constipation. Such common drugs include opioids, antidiarrheals, anticholinergics drugs, antispasmodics, 5-HT₃ receptor antagonists, vincristine. Other causes may be related to complications of the underlying illness itself (e.g. bowel obstruction, involvement of the sacral nerve roots, etc.).

Constipation may be prevented by increased food intake, dietary fiber and fluid intake, greater mobility and exercise, and establishing regular patterns of defecation after meals. Treatment of constipation is usually with both a stool softener (lactulose) and a stimulant (polyethylene glycol). Enema is contraindicated in neutropenic patients, due to the risk of intestinal perforation. Bowel obstruction may require a colostomy.

Neurogenic bowel is a distinct cause of constipation.

- In case of spinal cord lesion (spastic bowel, hypertonic anal sphincter and intact sacral reflexes) rectal suppositories help for sphincter relaxation, in addition to fluid/fiber intake. Laxatives causing excessive softening should be avoided.
- Neurogenic bowel due to a sacral nerve root lesion shows reduced peristalsis, flaccid sphincter and absent sacral reflexes. Management includes straining, abdominal massage, laxatives, suppositories and increased fluid and fiber intake.

Diarrhea

Try and identify treatable causes of diarrhea e.g. enteral infection (bacterial, viral, parasitic), non-enteral infection (otitis media, pneumonitis, urinary tract infection), malabsorption, constipation with overflow or drug-induced diarrhea (antibiotics, excessive laxative use, chemotherapy-induced mucositis). Counselling about contaminated food, poor hand-washing technique and the use of contaminated toys needs to be reinforced. Management of diarrhea includes hydration, correction of electrolyte and acid-base imbalance, dietary modifications. Antibiotics are usually not required except in case of documented bacterial or parasitic infection.

Dyspnea

Breathlessness is a frequent symptom in the palliative care of children with cancer and AIDS. It may be:

- Related to the underlying disease: effusion, consolidation, ascites, Kaposi's sarcoma, lymphangitis, lymphoid interstitial pneumonitis.
- Related to treatment, e.g. post-radiation fibrosis.
- Infective: bacterial pneumonia, pneumocystis carinii pneumonitis (PCP), CMV pneumonitis, tuberculosis
- Others: anemia, encephalopathy asthma, cardiac failure.

Nonpharmaceutical Measures

Dyspnea generates anxiety, which in its turn exacerbates dyspnea in a vicious cycle fashion. Thus non-pharmacological measures aiming at reducing anxiety are very important: sitting the child up, with appropriate ventilation, reassuring words relaxation and distraction techniques.

Pharmaceutical Measures

Severe dyspnea requires adequate sedation with morphine and/or benzodiazepine (e.g. oral, rectal or parenteral diazepam). Morphine dose is to be increase by one-third in children who are already receiving morphine.

Specific symptoms will require different management:

- *Acute stridor*: Try and clear airway, oxygen administration, adrenaline nebulization, high dose IV dexamethasone. Tracheostomy may be considered in a hospital setting if the overall prognosis allows it.

- Pneumothorax is treated symptomatically, unless drain is required.
- *Pleural effusion:* Pleural drainage brings immediate relief, but malignant effusions will recur soon after pleural tab, unless pleurodesis is done. Talc is the most effective sclerosing agent.¹⁸
- *Bronchospasm:* Oxygen, bronchodilator nebulization, steroids.
- *Cardiac failure:* Oxygen, diuretics, morphine.
- *Pneumonia in a child with AIDS:* Antibiotics; if PCP then give high-dose cotrimoxazole, steroids and high-dose oxygen; in case of lymphoid interstitial pneumonitis, give pulsed steroids, bronchodilators, physiotherapy, oxygen and ART.

Hiccup

Hiccup is a common cause of distress, causing interruption to normal activity, sleep and feeding disturbances.¹⁹ Possible mechanisms are phrenic nerve or diaphragmatic irritation (tumor or chest infection), vagus nerve irritation (gastro-oesophageal reflux, oesophagitis, hiatus hernia, ascites or liver tumor), metabolic imbalance (uremia, hyponatremia), brainstem tumor or drugs (benzodiazepines, corticosteroids and barbiturates).

Nonpharmaceutical Measures

- Pharynx stimulation (swallowing some food and drinking cold drinks)
- Vagal stimulation (breathing through a paper bag)
- Small frequent meals to reduce gastric distension.

Pharmaceutical Measures

- Prokinetics (domperidone or metoclopramide)
- Antacids and antiflatulents
- Smooth muscle relaxation (nifedipine or baclofen)
- Central suppression (chlorpromazine, promazine or haloperidol)

Psychological Distress

Psychological counselling is very important for compliance. Children react to the distress and emotions of adults. The family has different phases of reactions, from denial, anger, grief that may require time to reach acceptance of the situation. When the child is told about the disease and is allowed to talk about it, they will understand their distress and be in a better emotional state. On the contrary, when relatives don't want the child to be told, it leads to isolation, depression, anger and abnormal reactions.

Anxiety

Symptoms of anxiety include subjective feeling of apprehension, feeling tense, worried or restless, irregular or fast heartbeats, chest pain, rapid, difficult breathing,

or sweating, feeling of suffocation, difficulty in concentrating. Anxiety in parents and in the child needs to be addressed by empathetic listening, psychotherapy, relaxation therapy (music, etc.). A mild anxiolytic may be indicated in moderate to severe anxiety.

Depression

Chronic and terminally ill children are at risk of depression. Manifestations of depression in children range from sadness to suicidal ideation. Change in appetite or weight, sleep disturbance, fatigue and loss of energy, diminished ability to think or concentrate, lack of reactivity, feelings of hopelessness and worthless. One should assess situational factors and previous psychiatric history or treatment. The mainstay of depression management is psychological counselling. This interaction itself may be therapeutic. Promoting the child's autonomy, drawing on their strength rather than focusing on growing limitations and dependency; discussing short-term goals is a positive concrete step. Cognitive behavioral therapy, i.e. talking with patients about their feelings and reframing their ideas, is a helpful approach. Pharmaceutical measures are only required if counselling is not entirely effective: tricyclic antidepressants, benzodiazepines and stimulants may be used.

Weakness and Fatigue

Weakness and fatigue are commonly encountered symptoms among children on palliative care. Energy depletion makes the child sleep during the day instead of the night, leading to insomnia. Such sleep cycle disturbance should be addressed by having a timetable for meals, activities, sleep and dealing with the child as with the other siblings. The importance of play needs to be emphasized, since it enables the child to relax and to lead a near-to normal life. Readjustment to school in this phase of the disease would lead to excessive stress. However, home schooling is to be encouraged, preferably by a third person. Bringing a non-relative into the child's life can give a break to the family.

Insomnia

When insomnia is related to uncontrolled pain, adequate pain relief is the mainstay. Insomnia is often a manifestation of anxiety and depression, which need proper pharmacological and psychological management, with particular emphasis on listening to the child's fears and feelings. Children who picture death as a deep sleep may fear sleep when they reach the terminal phase of their disease. Simple nonpharmacological measures include providing the child with a comfortable mattress and posture, avoiding coffee, tea and alcohol before bedtime, avoiding loud noises near the room. Drinking warm milk at bedtime may be beneficial.

Skin Conditions

Pruritus is a common side effect of morphine, which may be replaced by another opioid. Other causes of pruritus include dry skin, atopic dermatitis, contact dermatitis, chicken pox, scabies (disseminated scabies in HIV positive children) and obstructive jaundice. Simple skin care consists of avoiding overheating, sweating and prolonged hot baths, washing no more than once daily and frequent application of skin moisturizer or oily calamine lotion. Scratching should be discouraged, finger nails kept short and smooth. Slightly sedating systemic anti-histaminics may help.

In children with AIDS, the management of seborrheic dermatitis, psoriasis, bacterial and fungal infection, Herpes zoster, etc. requires specific local and systemic treatment. It may include palliative radiotherapy in condylomata accuminata and kaposi sarcoma (particularly if fungating tumor).

ALTERNATIVE MEDICINE

Most patients in terminal part of disease go for alternative medicine. Alternative treatment options, such as ayurvedic medicine, homeopathy, etc. should not be disregarded for symptom relief. Patients should be allowed to continue allopathy in parallel with any other alternative therapy opted for. Acupressure and acupuncture are particularly effective for nausea, vomiting and pain relief.

PALLIATIVE RADIATION THERAPY

Radiation therapy is an important nonpharmacologic modality in the palliative care management of incurable, loco-regionally advanced and metastatic childhood cancers.²⁰ An average 40 to 60 percent symptom response can be achieved with palliative radiation therapy in children. The radiation dose needed to achieve palliation is much lower than therapeutic radiotherapy, with no or minimal radiation-induced morbidity.^{21,22} Three-dimensional conformal radiotherapy (3D CRT), intensity-modulated radiotherapy (IMRT) and image-guided radiotherapy (IGRT) allow treatment of the loco-regional tumor site without damaging normal tissues and organs. Conditions amenable to radiotherapy are:

- Bone metastases or spinal cord compression causing pain and immobility: a single fraction of 5 to 8 Gy may be sufficient for symptom relief; or 15 to 30 Gy in 5 to 15 fractions.
- Brain tumor or metastases causing headache, vomiting and neurological deficit: 18 to 30 Gy are administered in 10 to 15 sittings.
- Advanced Wilms' tumor, neuroblastoma, rhabdomyosarcoma may manifest as respiratory distress, dysphagia, intestinal or urinary obstruction: 12 to 30 Gy in 10 to 15 fractions.

- Solid tumors or metastatic hematologic malignancies causing compression, bleeding or fungation required 10 to 30 Gy in 2 to 10 fractions.

Adjuvant antiemetic, steroid, diuretic, laxative and antispasmodic drugs may be required by radiation-induced cellular and vascular edema.

HOME-BASED PALLIATIVE CARE

Palliative care at home enables to take care of the child in a friendly and familiar environment. It is provided by a complete home-care team (physician, nurse and counsellor) able to provide physical, psychological, social and spiritual care as well as advising, training and supporting the family. Home care visits are to be made at least weekly, in plain clothes and not in hospital vehicle so as to avoid social stigma, which may be a concern for the family. Siblings should contribute to the care of the sick child, which will not traumatize them but help them cope better with their sibling's departure.

END OF LIFE CARE

Even though the family may be well aware of the life-threatening illness and may understand that there is progression of the disease or relapse, the death of a child is particularly traumatic. Emotional expression enables to avoid dysfunctional reactions. Communication may be compromised by the anxiety and dread many physicians face when discussing impending death.^{23,24}

Communication

Good doctor patient communication is essential at this time. Terminally ill patients experience less stress and unwanted aggressive medical care if they have end-of-life discussions with their healthcare team. Aggressive care is associated with worse patient quality of life and worse bereavement adjustment.²⁵ Discussing what choices the family has at this time allows them some autonomy and control during this process. Many families will now have fewer resources to cope, e.g. financial, emotional and other support systems. A detailed discussion of beliefs and any necessary rituals at the time of death may be needed in case the treating team is unfamiliar with them.

When a child is dying, the child should have discussions with the doctors and treating team to answer their fears and questions in an age-appropriate manner. Many children will have heard of the death of fellow patients, they understand that things are not going well by their own health or the response of grief stricken parents. An unmet need of pediatric cancer patients includes a paucity of information and discussion about death.⁵ Honesty, compassion and reassurance of making things as pain free as possible are of assistance. The team can facilitate communication between the family members, this is important

in the case of teenage children, where their autonomy and wishes need to be expressed. This may stimulate sharing of emotions, facilitate in saying farewells and be a meaningful time for the family.

The grieving process as outlined by Kübler-Ross starts again at this time, i.e. denial, anger, bargaining, depression and acceptance.²⁶ The way in which families grieve depends on the personality of the individual, relationship, circumstances and experience of cancer, cultural and religious beliefs, coping skills, past experiences, support systems, and even socioeconomic status.²⁷ Siblings of cancer patients are an important group who should receive bereavement counselling along with the parents and preferably separately as well.²⁸

Symptom Control

Most children in the terminal phase of cancer or AIDS develop devastating physical symptoms for weeks to months before death, e.g. pain, breathlessness, fever and bleeding. Patients with more severe symptoms usually present to a new tertiary care hospital or return to their treating centres. Medical challenges in treating symptoms towards the end of life include alteration of drug pharmacokinetics due to malnutrition, low albumin, impaired liver and kidney function. The child should be frequently assessed for relief of symptoms and development of side effects of multiple drugs and opioids.²⁹

It is often difficult for families to maintain adequate blood and blood component therapy. Judicious use of platelet transfusions and addition of medications like tranexemic acid and local measures may decrease hemorrhage. Occasional packed red cell transfusions as per the discretion of the physician may improve quality of life and activity in a dying child. Towards the end, family members should accept anorexia and aversion to food, not forcing food or fluids since this can lead to aspiration. Allowing gentle massage helps the family stay in touch and provide care. Supplemental nutrition may be beneficial in the treatment of advanced cancer, where the quality of life would otherwise suffer and death would be caused by malnutrition or dehydration rather than the underlying disease.³⁰

Supportive measures should be maintained till the end. But it is important for patients and families to understand that the decision to start or withhold resuscitation (interventions that provide cardiovascular, respiratory, and metabolic support to maintain and sustain the life) is theirs and should be taken before any acute event occurs. "Do not resuscitate" orders should be written and signed by the parents in advance.

Place of Care

The decision on where to care for a dying patient depends on choice, home situation, beliefs and finances. All the options should be discussed with the child, if old enough,

and family. The aim is to provide a secure and comforting environment and provide measures to provide comfort and relief at the end of life. Home care is an option for children where the family or additional staff can provide care at home. In larger cities of India, palliative home care teams are present which provide free home visits, symptom management, psychological support and bereavement counselling. Unfortunately, these are not yet available in rural areas. Hospice care services ensure good quality of life in a few institutions and clinics with good community networks in several states of India. Inpatient care may be an option for some families if the child needs round-the-clock care for symptom management or if hospice like care cannot be given at home.

Palliative Sedation

Palliative sedation has been an area of debate, even among palliative care providers, due to its double effect. Under the principle of double effect, the intended effect (relieving suffering) would be considered allowable as long as any risks or negative effects (i.e. shortened survival) are unintended by the health care professional. Palliative sedation is used to alleviate pain and symptoms, mainly delirium and dyspnea. Sedation in these circumstances is often on a temporary basis and reversible in about one fourth of patients.³¹

Recognizing when Death is Near

Patients may withdraw emotionally or sleep more, they may be confused and unable to recall recent events. The child's skin may become mottled, cold or pale. The heart rate may become irregular, urine output may decrease or even stop. Respiration may be labored or Cheyne-Stokes respiration – very shallow breaths and alternating periods of apnea and deep, rapid breathing, may occur. As the end draws the child may experience more symptoms such as restlessness, which is distressing to the family. Hence frequent communication is needed to provide updates on the condition of the child, as well as revision of treatment for new or exacerbating symptoms.

When death occurs, expressions of grief by those at the bedside vary greatly, and are dictated by culture and preparedness for death. The healthcare team needs to be empathetic and supportive of the family. They should help with hospital formalities and provide bereavement counselling. Care and understanding at this time assists the family in coping with grief and makes them feel that their child was loved and cared for in the best possible way.

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Procedural Sedation and Analgesia in Pediatric Emergency Room

Suresh Gupta

INTRODUCTION

Pain and anxiety are common problems in pediatric emergencies. Most of the diagnostic and therapeutic procedures are associated with pain. Inadequate relief of pain associated with procedures may have acute and long-term consequences. By providing pain relief, the emergency provider will face a less anxious and more co-operative child, resulting in better outcome. Failure to co-operate during management is likely to result in a sub optimal outcome. But still, children continue to receive less pain medications as compared to adults.^{1,2}

Procedural sedation is a term that describes these interventions. Conscious sedation is another term that is sometimes used. However, because effective sedation often alters consciousness, this term is less accurate. Analgesia and/or sedation should be used any time a child complains or experiences pain and anxiety. Physicians caring for children are often faced with the difficult task of separating pain from anxiety and deciding which the predominant contributor to child's state is. But very often, anxiety amelioration is needed along with pain reduction. The clinical situation decides the method of pain management. No single drug or drug combinations in any fixed doses will be successful in every child for a given procedure. It is often necessary to titrate the medication doses according to desired level of analgesia and sedation. This article intends to review the current trends in the safe and effective methods for analgesia and sedation in children.

PHYSIOLOGY OF PAIN

International Association for the Study of Pain has defined the pain as "unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in such terms of damage". The physiologic basis of pain is now well understood.³

Tissue damage initiates the release of local mediators, such as bradykinin, substance P, prostaglandins, and potassium. These mediators heighten nociception and facilitate the communication of painful sensations to the spinal cord and the brain. Tissue injury also leads to release of histamine and serotonin, which results in increased pain sensitivity in areas surrounding the site of initial injury. Pain is multifactorial and subjective. There are several factors, which affect the nature of pain a child experiences. The developmental age, cognitive and emotional level, underlying medical condition, previous painful events, culture and environment of child greatly influence the pain process. Physician's attitude, experience and competence can greatly affect the pain management process.⁴ The response to pain differs with the level of development. Treatment strategies should account for these developmental changes.⁵

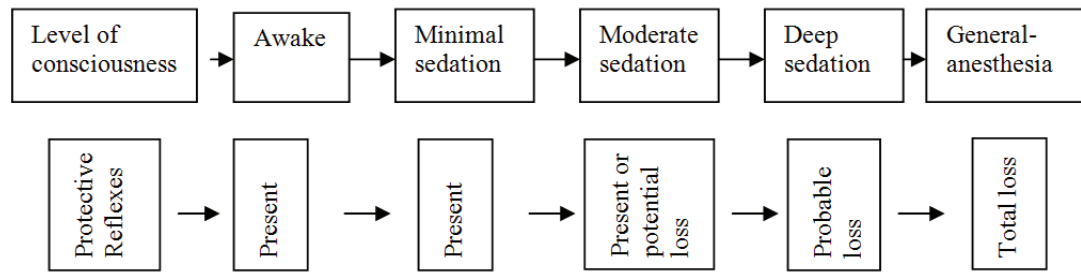
- *Less than six months:* Infants do not express anticipatory fear. Their level of anxiety reflects that of the parent.
- *6 to 18 months:* Infants begin to develop fear of painful experiences and withdraw when pain is anticipated.
- *18 to 24 months:* Children express pain with words, such as "hurt" or "boo boo."
- *Three years:* Children more reliably assess the pain they feel. They begin to localize pain and identify external causes. However, they depend upon a visual injury or cause for adequate localization and are unable to understand a reason for pain.
- *Five to seven years:* Children in this age group have improvements in understanding of pain, the ability to localize internal pain, and co-operation.

TERMINOLOGY

Procedural sedation and analgesia is a continuum which may progress from mild sedation to general anesthesia.⁶

Table 1: Levels of sedation and clinical response

	<i>Verbal response</i>	<i>Pain response</i>	<i>Airway response</i>	<i>Breathing</i>	<i>Circulation</i>
Anesthesia overdose	0	0	0	0	0/+
Anesthesia	0	0	0	0/+	++
Deep sedation	0	+	+	++	+++
Moderate sedation	+	++	+++	++++	+++++
Minimal sedation	+++	++++	++++	+++++	+++++
No sedation	+++++	+++++	+++++	+++++	+++++

**Fig. 1:** Continuum of depths of sedation

Following are the commonly used terms to define the level of sedation and analgesia (Table 1 and Fig. 1).

- *Analgesia:* Relief of pain without intentionally producing a sedated state. Altered mental status may be a secondary effect of medications administered for analgesia.
- *Minimal sedation:* The patient responds normally to verbal commands. Cognitive function and co-ordination may be impaired, but ventilatory and cardiovascular function is unaffected.
- *Moderate sedation/analgesia:* The patient responds purposefully to verbal commands either alone or accompanied by light touch. Patient is able to maintain airway and adequate ventilation without intervention. Cardiovascular function is also maintained.
- *Deep sedation/analgesia:* The patient cannot be easily aroused but responds purposefully to noxious stimulation. Patient may require assistance to maintain airway and adequate ventilation. Cardiovascular function is usually maintained.
- *General anesthesia:* The patient cannot be aroused. Often requires assistance to maintain airway and positive pressure ventilation. Cardiovascular function may be impaired.
- *Dissociative sedation:* Dissociative sedation is a trance-like cataleptic state in which the patient experiences profound analgesia and amnesia, but retains airway protective reflexes, spontaneous respirations, and cardiopulmonary stability. Ketamine is the pharmacologic agent used for procedural sedation that produces this state.

While providing pain and anxiety relief is important, the safety of the child during procedural sedation should never be compromised.⁵ The clinician must determine the appropriate level of sedation and/or analgesia required for a particular procedure. In addition to medications, verbal reassurance, distraction techniques, and hypnosis may be helpful. The purpose of sedation and analgesia for painful procedures are to:

- Maintain patient safety and welfare
- Minimize physical pain and discomfort
- Control anxiety, minimize psychological trauma, and maximize amnesia
- Control behavior to allow safe performance of procedures
- Ensure safe discharge.

INDICATIONS FOR SEDATION

Sedation should be considered for any procedure, which provokes distress in a child. The route of administration may include intravenous (IV), intramuscular (IM), transmucosal (intranasal, sublingual), per rectal (PR), per oral (PO), or inhalational. It is easy to titrate the dose with intravenous route but with intramuscular route the dose cannot be titrated. With oral, rectal and intranasal agents, the onset, depth and duration are less predictable than parenterally administered drugs. It is better to start with the lowest recommended dose and then incremental doses can be given at 2 to 5 minutes intervals till the desired level of sedation is obtained. Each institution should have its own guidelines for assessment and monitoring of

pediatric patients during and after sedation. The pediatric procedural sedation and analgesia can be divided into three phases (i) Preprocedure phase, (ii) Intraprocedure phase and (iii) Postprocedure phase.

Preprocedure Phase

Assessment

Patients should be evaluated prior to the procedure for their suitability for sedation.⁵ Before sedating any child a complete history and physical examination should be done and the American Society of Anesthesiologists (ASA) class is assigned to the patient (Table 2). AMPLE is good mnemonic for assessment purpose for pediatric sedation.

- Allergies
- Medications
- Past medical history
- Last meal (time of solids and liquids taken)
- Events leading to need for sedation.

American Society for Anesthesiologists (ASA) has assigned categories to the patient for sedation purposes. Suitability for sedation ranges from excellent to extremely poor for patients in class I through class V. Children with ASA classes I and II are generally reasonable candidates for mild, moderate, and deep sedation outside of the operating room. For those with ASA classes III and IV, special needs, or airway abnormalities, consultation with an anesthesiologist or subspecialist is recommended. The balance of risks and benefits must be weighed for each individual.

Equipment

To handle any emergency arising during the procedure, following monitoring and resuscitation equipment should be ready at the bedside:

- Oxygen source
- Intubation tray
- Oral airway
- A source of suction
- Cardiorespiratory monitor
- Resuscitation medications (Injection epinephrine, atropine, hydrocortisone)
- Pharmacological reversal agents like naloxone and flumazenil.

Personnel

The minimum personnel during sedation should include a physician and a nursing staff trained in pediatric advanced life support (PALS).⁷ The person should be well versed with the drugs, which are going to be used on that patient. It is important that the person responsible for sedation and monitoring is not doing the procedure. Any time the patient gets unstable, the procedure should be withheld and stabilization should be done first.

Fasting Guidelines

Before providing sedation, the fasting for adequate period should be ensured to prevent pulmonary aspirations.^{7,8} It's always better to plan and conduct procedure

Table 2: American Society of Anesthesiologists (ASA) classification

ASA class	Description	Examples
1	A normal, healthy patient, without organic, physiologic, or psychiatric disturbance	Healthy with good exercise tolerance
2	A patient with controlled medical conditions without significant systemic effects	Controlled hypertension, controlled diabetes mellitus without system effects, cigarette smoking without evidence of chronic obstructive pulmonary disease (COPD), anemia, mild obesity, age less than 1 or greater than 70 years, pregnancy
3	A patient having medical conditions with significant effects intermittently associated with significant functional compromise	Controlled congestive heart failure (CHF), stable angina, old myocardial infarction (MI), poorly controlled hypertension, morbid obesity, bronchospastic disease with intermittent symptoms, chronic renal failure
4	A patient with a medical condition that is poorly controlled, associated with significant associated with significant dysfunction and is a potential threat of life	Unstable angina, symptomatic COPD, symptomatic CHF, hepatorenal failure
5	A patient with a critical medical condition that is associated with little chance of survival with or without the surgical procedure	Multiorgan failure, sepsis syndrome with hemodynamic instability, hypothermia, poorly controlled coagulopathy
6	A patient who is brain dead and undergoing anesthesia care for purposes of organ donation	
E	This modifier is added to any of the above classes to signify a procedure	

Table 3: ASA fasting guidelines for procedural sedation

<i>Ingested material</i>	<i>Minimum fasting period</i>
Clear liquids	2 hours
Breast milk	4 hours
Infant formula	6 hours
Non-human milk	6 hours
Light meal	6 hours

on elective basis. The recommendations given by ASA, for fasting during an elective situation are given in Table 3. Fasting periods apply to healthy patients of all ages who are undergoing elective procedure. Those with gastroesophageal reflux (GER), obesity, may require appropriate pharmacological intervention. In emergency settings patients are rarely fasting. Therefore if possible, it is always better to delay the procedure. Should the procedure be conducted, lightest possible sedation should be given.

Important factors that may increase the risk for aspiration include possibility of a difficult airway, conditions predisposing to esophageal reflux (i.e. elevated intracranial pressure, gastritis, bowel obstruction, or ileus), Extremes of age (e.g. <6 months or >70 years), severe systemic disease with functional limitation (ASA class ≥ 3) and altered mental status. Fasting is not needed for minimal sedation, sedation with nitrous oxide (in oxygen) alone and moderate sedation where the child maintains verbal contact.

Checklist

The team providing sedation ensures following before doing the procedure under sedation. A checklist will reduce the possibility of missing or omitting an important component.

- Patient's medical history has been obtained
- Pre-procedure laboratory testing (at the discretion of Physician)
- Informed consent
- Functioning I/V line
- Patient clinical condition should be appropriate for sedation
- Child and parents must be explained the procedure, and about the sedation
- There should be written order for sedation by the consultant in the case sheet
- An accurate weight is documented
- Vitals signs are recorded and trends should be followed closely any change in the base line vitals should be addressed immediately
- Airway assessment in non-intubated patients
- General neurological status.

Monitoring

It is an important component of pediatric procedural sedation and analgesia. A proper monitoring will not only

ensure patient safety but will also help in providing effective sedation and avoid sedation disasters.⁹ Monitoring includes visual observation, determination of vital signs, and pulse oximetry. The face and mouth and movement of the chest wall should be observed continuously. Heart rate and oxygen saturation (pulse oximeter) should be monitored and recorded continuously. Vital signs are recorded at the beginning of the procedure, after administration of the drug, when the procedure is completed, during early recovery, and when recovery is completed. Patients undergoing deep sedation or patients with underlying illness should have vital signs measured at least every five minutes. End-tidal CO₂ (ETCO₂) monitoring is increasingly available in critical care settings for nonintubated patients and is useful to assess ventilation during sedation and analgesia.¹⁰ The ETCO₂ is more sensitive for detecting hypoventilation than clinical assessment. Increases in ETCO₂ will detect respiratory depression before hypoxemia occurs, particularly in those who are receiving supplemental oxygen.

Complications are most likely to occur within 5 to 10 minutes of intravenous drug administration and immediately postprocedure when stimuli associated with the procedure have gone. So monitoring becomes more significant during these periods.

Intraprocedure Phase

Whenever drugs for sedation are considered for a procedure, safety and welfare of the patient is always a priority. The goal of sedation is to minimize pain, discomfort, and anxiety and maximize the co-operation. Sedation is a continuum. A child can easily slip from minimal or moderate sedation into deep sedation where the chances of losing airway protective reflexes become high. In addition to this child may also develop cardiorespiratory depression. It highly suggested the physicians interested in providing sedation to children should be trained in pediatric advanced life support and sedation techniques.

The drugs to be used during sedation should have been thought well in advance depending on the age, condition and type of procedure being conducted. For painless procedures like CT scan or MRI, only sedation without analgesia is required. Midazolam or propofol are good agents to provide sedation under these circumstances. On

Table 4: Ramsay score for level of sedation

<i>Ramsay scale</i>	<i>Level of sedation</i>
I	Anxious, agitated or restless
II	Cooperative, oriented and tranquil
III	Responds to verbal command
IV	Responds to gentle shakily
V	Responds to noxious stimuli
VI	No response to noxious stimuli

the other hand, the painful procedures like bone marrow aspiration or kidney biopsy, one needs deep sedation with analgesia. A trained person should continuously monitor the patient vitals and act immediately any time complication occurs. Consultant should prescribe the drug and dosage. Adequate sedation should be obtained before starting the procedure. Never cover face during procedure; it hinders the physician watching the patient. Monitor vital signs pulse, blood pressure (BP), respiratory rate (RR), Saturation, level of consciousness (Ramsay Score-Table 4) every 15 minutes during conscious sedation, every 5 min during deep sedation in all the hemodynamically unstable patients irrespective of degree of sedation.^{9,11}

During the procedure, any question concerning the adequacy of patient airway, ventilation or hemodynamic status should be addressed immediately and all other things are only second priority.

Postprocedure Phase

To facilitate smooth recovery from the effect of sedation following steps are very useful:

- Should be quiet with dim lights
- All the equipment needed to deal with any emergency arising, should be available
- A physician who is adept at airway management should be immediately available
- NPO status must be maintained till the patient is fully awake oriented and the vital signs have returned to the baseline
- Drapes should be placed in such a way that airway and chest motions can be visualized all the time.

Vital signs (pulse rate and volume, SpO₂, BP) should be monitored every 15 minutes during minimal sedation

and every 5 minutes during deep sedation for at least 60 minutes and the patient should not be left alone. Monitoring should continue until the child meets criteria for safe discharge. The post sedation "Aldrete Score" should be 8-10 before the patient is discharged from the procedure area (Table 5).¹² The important components of discharge criteria are:⁷

- Airway patency and stable cardiovascular function
- Easy arousability with intact protective reflexes
- Ability to talk (if age-appropriate)
- Ability to sit up unaided (if age-appropriate)
- Adequate hydration with management of any nausea or vomiting
- Appropriate management of any continued pain
- Young infants or children who are handicapped should return to the level of responsiveness observed before sedation.

NONPHARMACOLOGICAL APPROACHES

Both nonpharmacologic and pharmacologic interventions are used to manage acute pain.

Nonpharmacological methods for reducing distress in the child are as important as using the sedatives and analgesics. The use of these methods reduces need and doses of the sedation drugs. Every emergency room should have people who are trained in these nonpharmacological methods.

Psychological Preparation and Relaxation

Psychological preparation of the child and parents may dramatically reduce distress. These should be age specific and may include careful explanation, distraction, hypnosis and reassurance. The environment should be as relaxing as possible.¹³

Parental Presence

The decision of parental presence in the procedure room depends on the age of the child, needs of the child and the ability of the parents to remain calm.¹⁴ School going and young children may feel more relaxed if their parents are on their side during painful procedures. Informed parents rarely interfere with the procedure. But, a parent who moans and groans during the procedure will disrupt any chances of relaxation. For such parents, it may be better that they wait outside the treatment area.

Behavior Therapy

Children should always be encouraged to express their feelings and emotions.¹⁵ It is always better not to lie or downplay a child's perception of pain. Consistent positive enforcement and emphatic tone of physician can make the child more comfortable.

Table 5: Aldrete score for discharge following procedural sedation

Activity	Able to move 4 extremities	2
	Able to move 2 extremities	1
	Able to move 1 extremities	0
Respiration	Able to deep breath/cough freely	2
	Dyspnea/limited breathing	1
	Apnea	0
Circulation	BP + 20% of basal BP	2
	BP + 20-50% of basal BP	1
	BP + 50% of basal BP	0
Consciousness	Fully awake	2
	Arousable on calling	1
	Not responding	0
Color	Pink	2
	Pale, dusky, blotchy	1
	Cyanotic	0

Total Aldrete Score

Hypnosis

Hypnosis can be very useful in those children who are hypersuggestible. Guided imagery is used to facilitate pain control during procedure. The type of hypnotic approach depends on the developmental age of the child. It is most effective when used in a quiet and comfortable environment. However, most emergency physicians prefer nonhypnotic pain coping strategies because hypnosis is difficult to provide in busy emergency department.¹⁵

Restraint

In spite of best efforts of physician to relax the child, some kind of restraint is often needed to conduct the procedure. It is always preferable to provide a short period of effective restraint on a papoose board rather than an extended period of struggling with an uncooperative and immobilized child.¹⁶ But using a restraint does not mean that other techniques of pain control are not required. Psychological and pharmacological techniques should be used in conjunction with restraint. Though immobilization decreases struggling by negative feedback, inadequate restraint may encourage struggling by positive feedback.

PHARMACOLOGICAL APPROACHES FOR SEDATION

The American College of Emergency Physicians has developed a clinical policy describing an evidence-based approach to the pharmacologic agents used for sedation and analgesia of children in the emergency department. A wide range of short-acting sedative-hypnotic and analgesic medications are available.¹⁷⁻¹⁹ Many of these agents have multiple routes of administration. The choice of drug is based upon the type of procedure and the patient's underlying medical condition. Procedures that are not painful but require the child to remain still can generally be performed with sedation alone. Children undergoing painful procedures typically require analgesia as well as sedation. Table 6 provides the list of pharmacological interventions used for pediatric procedural sedation and analgesia. The commonly used sedation protocols are: (i) Ketamine dissociative sedation, (ii) Fentanyl-midazolam sedation, (iii) Propofol sedation and (iv) Nitrous oxide sedation (Figs 2 to 4). Table 7 provides the suggested methods for sedation-analgesia for procedures in pediatric emergency room.

Table 6: Suggested methods for sedation-analgesia for procedures in pediatric emergency room*

<i>Procedure</i>	<i>Local anesthetics</i>	<i>Sedation</i>
IV Catheter placement	Buffered lidocaine, SC or Saline with benzyl alcohol, SC or EMLA and sometime	Nitrous oxide for significant or Midazolam, PO (anxiolysis)
Lumbar puncture	Buffered lidocaine EMLA	Nitrous oxide or Midazolam (PO/IN/PR) or Fentanyl/midazolam, IN or Ketamine, PO/IV/IM
Intensely painful procedures	Buffered lidocaine	Ketamine-midazolam, IV/IM or Fentanyl midazolam, IV
CT Scan/MRI		Midazolam (PO/IN/IM/PR) or Pentobarbitone (IM/IV) or Propofol (IV)

*Parental presence, comforting, and distraction should be encouraged during all procedures

EMLA = Eutectic mixture of local anesthetics, SC = Subcutaneous, PO = Per oral, IN = Intranasal, PR = Per rectal, IV = intravenous, IM = Intramuscular

Definition of dissociative sedation

A trance like cataleptic state induced by the dissociative agent ketamine, characterized by profound analgesia and amnesia, with retention of protective airway reflexes, spontaneous respirations, and cardiopulmonary stability.

Characteristics of the ketamine "Dissociative State"

- *Dissociation:* After administration of ketamine, the patient passes into a fugue state or trance. The eyes may remain open, but the patient does not respond.
- *Catalepsy:* Normal or slightly enhanced muscle tone is maintained. On occasion, the patient may move or be moved into a position that is self-maintaining. Occasional muscular clonus may be observed.
- *Analgesia:* Analgesia is typically substantial or complete.
- *Amnesia:* Total amnesia is typical.
- *Nystagmus:* Nystagmus is typical.
- *Maintenance of airway reflexes and cardiovascular stability.*

Contd...

Indications		
Short, painful procedures, especially those requiring immobilization (e.g. facial laceration, burn debridement, fracture reduction, abscess incision and drainage, central line placement, tube thoracostomy).		
Contraindications: Absolute (Risks essentially always outweigh benefits)		
<ul style="list-style-type: none"> Age younger than 3 months (higher risk of airway complications) Known or suspected schizophrenia, even if currently stable or controlled with medications (can exacerbate condition) 		
Contraindications: Relative (Risks may outweigh benefits)		
<ul style="list-style-type: none"> Major procedures stimulating the posterior pharynx (e.g., endoscopy) increase the risk of laryngospasm, whereas typical minor ED oropharyngeal procedures do not. History of airway instability, tracheal surgery, or tracheal stenosis Active pulmonary infection or disease, including upper respiratory infection or asthma (higher risk of laryngospasm) Known or suspected cardiovascular disease, including angina, heart failure, or hypertension Avoid ketamine in patients who are already hypertensive Central nervous system masses, abnormalities, or hydrocephalus (increased intracranial pressure with ketamine) Glaucoma or acute globe injury, porphyria, thyroid disorder, or thyroid medication 		
Ketamine Administration: General		
<ul style="list-style-type: none"> Frame the dissociative encounter as a positive experience. Encouraging children to “plan” specific, pleasant dream topics in advance of sedation (believed to decrease unpleasant recovery reactions). Ketamine is administered when the physician is ready to begin the procedure. Ketamine is initially administered as a single IV loading dose or IM injection. IV Ketamine: IV route is preferable because recovery is faster and there is less emesis. Administer a loading dose of 1.5 to 2.0 mg/kg IV in children over 30–60 seconds. Additional incremental doses of ketamine may be administered (0.5 to 1.0 mg/kg) if initial sedation is inadequate or to accomplish a longer procedure. IM Ketamine: The IM route is especially useful if IV access cannot be consistently obtained. IV access is unnecessary for children receiving IM ketamine. Administer ketamine 4 to 5 mg/kg IM in children and repeat ketamine dose (full or half dose IM) if sedation is inadequate after 5 to 10 minutes (unusual) or if additional doses are required. 		
Route of administration	IV	IM
<i>Advantages</i>	<i>Ease of repeated dosing; less vomiting, slightly faster recovery</i>	<i>No IV access necessary</i>
Peak concentrations and clinical onset	1 minute	5 minute
Typical duration of effective dissociation	5–10 minute	20–30 minute
Typical time from dose to discharge	50–110 minute	60–140 minute
Coadministered medications		
<ul style="list-style-type: none"> Prophylactic anticholinergics are no longer recommended. Prophylactic benzodiazepines are no longer recommended for children; however, they should be available to treat rare, unpleasant recovery reactions, should they occur. Prophylactic ondansetron can slightly reduce the rate of vomiting (number needed to benefit 9 or more). 		
Procedure		
Adjunctive physical immobilization may be occasionally needed to control random motion. Adjunctive local anesthetic is usually unnecessary when a dissociative dose is used. Occasional repositioning of the head or suctioning of the anterior pharynx may be indicated for optimal airway patency.		
Potential adverse effects		
<ul style="list-style-type: none"> Airway misalignment requiring repositioning of head (occasional) Transient laryngospasm (0.3%) Transient apnea or respiratory depression (0.8%) Hypersalivation (rare) Emesis, usually well into recovery (8.4%) Recovery agitation (mild in 6.3%, clinically important in 1.4%) Muscular hypertonicity and random, purposeless movements (common) Clonus, hiccapping, or short-lived nonallergic rash of face and neck 		

Fig. 2: Ketamine dissociative sedation

Indications
<ul style="list-style-type: none"> Brief, painful procedures for which deep sedation is indicated, including fracture and dislocation reductions, incision and drainage of abscesses, cardioversion, tube thoracostomy, and central line placement.
Contraindications
<ul style="list-style-type: none"> Absolute (Risks essentially outweigh benefits): Known or suspected allergy to soy or eggs. Higher relative risk patients: Patients >55 years of age, debilitated, or with significant underlying illness (i.e. ASA physical status score 3 or 4)

Contd...

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Propofol Administration: General
<ul style="list-style-type: none"> Propofol induces sedation approximately 30 seconds after bolus injection, with typical resolution of clinical effects within 6 minutes. The most common ED dosing is with an initial bolus dose of 1 mg/kg followed by 0.5 mg/kg every 2–3 minutes as needed to achieve or maintain the desired level of sedation. This dosing applies to both adults and children. Propofol is typically titrated to slurring of speech and/or lid ptosis depending on the depth of sedation and degree of relaxation needed for the procedure.
Potential adverse effects
<ul style="list-style-type: none"> Respiratory depression or apnea leading to assisted ventilation (0%–3.9%). Transient hypotension (2.2–6.5%). Emesis (0–0.5%). Pain with injection (2–20%).

Fig. 3: Deep sedation with propofol

Caveats
<ul style="list-style-type: none"> Individual response to the drugs is variable and dependent upon the patient's underlying physiologic state and the presence of concomitant drugs/ medication. Maximum drug effect occurs 2–3 minutes after administration. Proceed slowly and patiently, allowing the medication to take full effect before giving the next dose. Have naloxone and flumazenil immediately available for over sedation and/or respiratory depression
Contraindications
<ul style="list-style-type: none"> Absolute (Risks essentially always outweigh benefits): Active hemodynamic instability or active respiratory distress or hypoxemia. Relative (Risks may outweigh benefits): Respiratory depression or altered level of consciousness or anticipated difficulty if ventilatory assistance should become necessary (e.g. facial deformity or trauma, small mandible, large tongue, trismus).
Procedure
<ul style="list-style-type: none"> Establish IV access Midazolam dose: IV (0.5–5 yr): Initial 0.05– 0.1 mg/kg, then titrated to max 0.6 mg/kg. IV (6–12 yr): Initial 0.025– 0.05 mg/kg, then titrated to max 0.4 mg/kg. Fentanyl Dose IV: 1 µg/kg/dose, may repeat q3min, titrate to effect The order of the drugs is one of personal preference. The ratio of analgesia to sedation is determined by the nature of the procedure. Some procedures require primary analgesia and secondary anxiolysis/ sedation (e.g. abscess incision and drainage, bone marrow aspiration, arthrocentesis, burn debridement, central catheter placement). In this case, administer fentanyl first. Others require primary anxiolysis/ sedation with secondary analgesia (e.g. lumbar puncture, simple foreign body removal); administer midazolam first. Administer local anesthesia if indicated after procedural sedation is initiated (this often serves to help gauge effectiveness of systemic analgesia). Perform the procedure. Additional doses of fentanyl or midazolam may be required if further pain or anxiety are noted based on the response and length of the procedure. If hypoxemia, over sedation, or slowed respirations are seen during or after the procedure, the patient should be first stimulated while oxygen is applied and the airway repositioned. If the patient's response is insufficient, assist ventilations with a bag-valve-mask. Reversal agents should be considered if there is not a prompt response to assisted ventilation.

Fig. 4: Moderate to deep sedation with intravenous midazolam and fentanyl

ADVERSE SEDATION EVENTS

Adverse events occur with all routes of administration and classes of medication, including those considered to have minimal effect on breathing. Poor outcomes also have been associated with excessive doses, drug interactions, administration by personnel without medical training, and, after discharge, drugs with long half-lives. The consequences of an adverse event that is not immediately recognized and treated can be devastating. In one retrospective report describing adverse sedation events in children, permanent neurologic injury or death was associated with adverse events that occurred in nonhospital-based facilities and with those for which resuscitative efforts were

inadequate.²⁰ Other factors that contributed to adverse events were:

- Inadequate and inconsistent physiologic monitoring
- Inadequate medical evaluation before sedation
- No independent observer
- Medication errors
- Inadequate recovery procedures.

Adverse events associated with procedural sedation for children are unlikely when standardized safe practices are observed. It has been suggested that implementation of hospital-wide guidelines for procedural sedation and analgesia may decrease the incidence of adverse events. This was demonstrated in a report describing 30,037

Table 7: Pharmacological agents used for procedural sedation and analgesia in children

Agent	Dose	Onset of Action	Duration of action	Remarks
Benzodiazepines				
Midazolam	IV: 0.05 mg/kg, maximum single dose 5 mg; may be repeated up to maximum total dose of 0.4 mg/kg	1-2 min	30-60 min	Sedative and hypnotic agents with potent amnestic effects. May suppress ventilation when used in combination. Occasionally cause a paradoxical excitatory reaction. For hemodynamically unstable patients, decrease dose by 50%.
	IM: 0.1-0.2 mg/kg	5-15 min	30-60 min	
	IN: 0.2-0.4 mg/kg			
	PR: 0.5-1 mg/kg	5-10 min	30-60 min	
	PO: 0.25-0.5 mg/kg; maximum total dose 20 mg	10 min	1-2 hours	
Lorazepam	IM, IV: 0.05-0.1 mg/kg maximum single dose 4 mg	IV: 3-5 mins	2-6 hours	
	PO: 0.05-0.1 mg/kg maximum single dose 2 mg	IM: 10-20 mins	2-6 hours	
		PO: 60 mins	2-8 hours	
Diazepam	IV: 0.1-0.2 mg/kg	2-3 mins	30-90 mts	
	PR: 0.3-0.5 mg/kg	5-15 mts	2-4 hours	
Barbiturates				
Pentobarbital	IV: 1-3 mg/kg, may be repeated up to 6 mg/kg	1-5 mins	15-60 min	Short acting sedative-hypnotic agents. None has analgesic properties. Typically the sedative of choice for patients with head-trauma, status epilepticus or suspected increased intracranial pressure. Side effects include dose-dependent myocardial depression and hypotension. Other adverse effects include bronchospasm, laryngospasm, cough and anaphylaxis.
	IM: 2-5 mg/kg	5-15 min	2-4 hours	
	PO: 2-3 mg/kg	15-60 min	2-4 hours	
Thiopental	PR: 25 mg/kg	5-15 min	60-90 min	
Methohexital	PR: 20-30 mg/kg	5-15 min	30-90 min	
Narcotics				
Morphine	IV: 0.05-0.1 mg/kg	5-10 min	2-4 hours	Remain the gold standard for treatment of severe pain. Codeine is less potent and efficacious than morphine. Fentanyl, a synthetic narcotic, is 50-100 times more potent than morphine. An unusual complication associated with its use is chest-wall rigidity (with larger doses, given rapidly usually >5 mcg/kg, especially in infants.) The most common adverse effects of narcotics are hypoventilation, apnea and hypotension.
Fentanyl	IV: 1-4 mcg/kg	2-3 mins	20-60 min	
Codeine	0.5-1.0 mg/kg	15-60 min	4-6 hours	
Other agents				
Ketamine	IV: 0.5-2 mg/kg	1-2 mins	15-60 min	Ketamine produces potent analgesia and rapid sedation. Preserves respiratory drive, airway protective reflexes when used in appropriate dosages. Lower dose of ketamine is advocated for hemodynamically compromised patients.
	IM: 3-4 mg/kg	3-10 min	15-60 min	

Contd...

Ketamine may decrease or protect against bronchospasm and improve ventilation in asthmatics. Ketamine adverse effects include increased systemic, intracranial, and intraocular pressures, hallucinogenic emergence reactions, laryngospasm and excessive airway secretion. Chloral hydrate (hypnotic agent) may have paradoxical excitatory effect. Propofol may decrease cardiac output and cause severe hypotension. It is contraindicated in patients with history of allergy to egg or soybean. Nitrous oxide is most useful in cooperative patients (>6-8 years). Side effects include hypoxemia after its discontinuation; all patients should breath 100% O₂ for at least 5 min. after its discontinuation. It is relatively contraindicated in patients with air-leak syndromes like (pneumothorax) or closed air spaces (bowel obstruction).

Chloral hydrate	PO, PR: 25-100 mg/kg; max 2 gms.	15-30 min	2-3 hours
Ketorolac	IV, IM: 0.5-1 mg/kg	10-15 min	3-6 hours
Propofol	IV: 0.5-1 mg/kg; may be repeated in 0.5 mg/kg boluses; may be given as a titrated continuous infusion of 25-100 mcg/kg/min	1-2 min	3-5 min
Nitrous-oxide	25-50% of NO with O ₂		

prospectively collected hospital-based pediatric sedation/anesthesia encounters in which 77 percent of the sedations were performed by anesthesiologists, emergency physicians, or intensivists. The incidence of adverse events (primarily transient oxygen desaturation, vomiting, and excessive secretions) was three percent. There were no deaths. One patient was successfully resuscitated from cardiac arrest.²¹

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Assessment and Triage of a Sick Child in Emergency Room

Suresh Gupta

There are many reasons for which a sick child may visit pediatric office or pediatric emergency room. Assessment of pediatric patients presents a unique challenge whose size may vary from the newly born through adolescence. In a general emergency department (ED), the pediatric patients account for 25 to 30 percent of the total visits. Although most pediatric visits to the ED may not be life-threatening but significant number of children may have serious or potentially serious underlying disease. There are wide varieties of etiology which can lead to these serious and life-threatening pediatric emergencies. The management of these sick children requires a basic understanding of the unique age specific anatomic, physiologic, immunologic, and developmental differences on the part of health care provider. Moreover, the emergency care does not stop or start at the ED level, ED is only one of the important components of integrated emergency medical system. Most of the sick children are initially seen in small community hospitals and for definitive care at tertiary hospitals, inter-facility transport system is required.

Respiratory emergencies and trauma are the most common causes for visits to an ED. The common problems include acute respiratory infection, fever, otitis media and other head and neck infections, enteritis, and minor cuts and contusions. Trauma is one of the most common causes of serious morbidity and mortality in children younger than 15 years. Most of these injuries are unintentional injuries, predictable and preventable. Irrespective of the underlying etiology, the care of critically ill or injured children should always focus on two physiologic events: shock and respiratory failure. This chapter focuses on the role of the emergency physician in recognizing, assessing and triaging children needing emergency care.

ANATOMICAL, PHYSIOLOGICAL AND DEVELOPMENTAL ISSUES IN ASSESSMENT

The assessment of a child requires attention to a variety of anatomic, physiologic, and developmental differences that vary with the age. For example, the infant have large surface area-to-weight ratio, making them more prone to temperature instability and highlights the importance of a neutral thermal environment during assessment and management. The relatively large head-to-body ratio and the small, weak neck make the children more prone to head injuries. Soft and pliable growing ribs of children allow the blunt trauma to cause injury to internal organs of chest and abdomen with negligible or no external signs. Growth plates are the weakest part of growing bones rather than surrounding ligaments. So, in a growing child, the sprains are uncommon and physeal fractures are more common. The smaller airways of infants and young children are more prone to obstruction from secretions with resultant more rapid respiratory distress to failure. Compensatory mechanisms of young children provide them extra protection from decompensated shock. Recognition and justification for abnormal vital signs is one of the keys to success in the treatment of the ill patient. It is crucial for the provider to be familiar with these different values of the vital signs as these vary with age. Moreover the vital signs at one given point in time may be quite difficult to interpret. Repeated serial measurement of vital signs will provide a more accurate assessment of the physiologic status of child.

The assessment of any sick child should always take into account the age-related differences in motor function, problem-solving, language, and social/adaptive milestones. During the neonatal period the discomfort is

usually nonspecific, and the cause of the irritability or crying may be difficult to interpret. A mother's "sense" of her child is often accurate and should be considered seriously. By 2 to 3 months, an infant has a social smile and responds to a friendly voice. Lack of appropriate social interaction can be worrisome. An infant with a glassy-eyed, "nobody home" stare can be easily distinguished. Normal behavior for a 6 month old baby includes any expression of curiosity or anxiety, such as crying. If a 6 month baby does not acknowledge your presence, it is a matter of concern. Children older than 6 months will exhibit stranger anxiety. So, the children at this age should preferably be examined in the lap of the caregiver. During the toddler and preschool age, child has more extensive receptive language than expressive language and can pick up fears and concerns. Praise, reassurance and allowing the child to control some part his experience will help in maintaining the rapport with the child. As child reaches school age, the power of reasoning and negotiating become more mature. So, it is important to explain procedures, answer questions, and address fears and concerns honestly. With adolescence comes independence and autonomy but may not anticipate consequences. Privacy and confidentiality should always be respected and should be involved in decision making.

EMERGENCY ASSESSMENT OF PEDIATRIC PATIENTS

Emergency assessment focuses on identification of children at risk for decompensation and deterioration. The initial assessment begins with examination of respiratory effort, circulation of the skin and mental status of the child to make a first impression whether the child is "sick or not sick" The pediatric assessment triangle (PAT) (Fig. 1) is one of the simple clinical tools which can be used to assess children of all ages, identify abnormal cardiopulmonary physiology, and define the urgency and need for lifesaving interventions.

THE INITIAL ASSESSMENT: PEDIATRIC ASSESSMENT TRIANGLE

The initial assessment of the child condition is made by observing the child from a distance for visual and auditory hints even before touching him/her. The three arms of this initial assessment or PAT are: (1) A: appearance, (2) B: work of breathing, and (3) C: circulation to the skin. This quick assessment in first few seconds will help the health care provided in making a sense whether the child is sick or not sick.

Appearance: By looking at the child from a distance, one can make out whether the child is irritable, drowsy, lethargic, or interacting with the surrounding normally. The commonly used mnemonic TICLS: Tone, Interactiveness, Consolability, look/gaze, and speech/cry is a good way

to be more objective for this assessment. The abnormal assessment can result from inadequate brain perfusion like in shock or hypoxia due to respiratory problem or due to primary neurological insult which may be traumatic or nontraumatic. A normal appearance indicates that ventilation, oxygenation, and brain perfusion are at least adequate.

Work of breathing: Very often, observing the child from a distance will provide better clue regarding work of breathing rather than examining a crying child. The type of audible abnormal airway sounds such as grunting, wheezing, stridor, and snoring will help in deciding the underlying cause of respiratory distress. Observing for other abnormalities like sniffing position, tripod position, nasal flaring, head bobbing, see-saw breathing, presence of inter-costal, supraclavicular, and substernal retractions will also be useful to infer the cause and severity of airway obstruction.

Circulation to the skin: Visual examination of the skin can be used quickly to assess the peripheral perfusion. A pale skin with rapid heart rate is strongly suggestive of shock or blood loss or severe anemia. Mottling of skin reflects loss of small vessel integrity and is an ominous sign. It is important not to confuse cutis marmorata with mottling in young infants. Cyanosis is an indication of respiratory failure or decompensated shock unless the child is cyanotic as a result of chronic primary cardiopulmonary problems or congenital heart disease.

By integrating the information gained through this pediatric assessment triangle (appearance, work of breathing and circulation to skin), an initial impression regarding physiological status of the child can be made and acuity of the problem may also be judged (Table 1).

Primary Assessment

After a quick initial evaluation through the pediatric assessment triangle, the health provider begins the primary assessment. This part of evaluation focuses on following components in an orderly and stepwise fashion.

- A: Airway
- B: Breathing
- C: Circulation
- D: Disability
- E: Exposure
- F: Family

While interpreting the vital signs in children, one should always keep in mind the age appropriate standards of vital parameters and trends are more important than individual single reading. Assessment of the airway involves checking for the patency and the ability to maintain independently or with airway adjuvant. Breathing evaluation focuses on respiratory rate and efforts and oxygenation. The health care provider must resolve issues related to each step before progressing to the next one. The AVPU (alert, verbal, painful, unresponsive) scale is

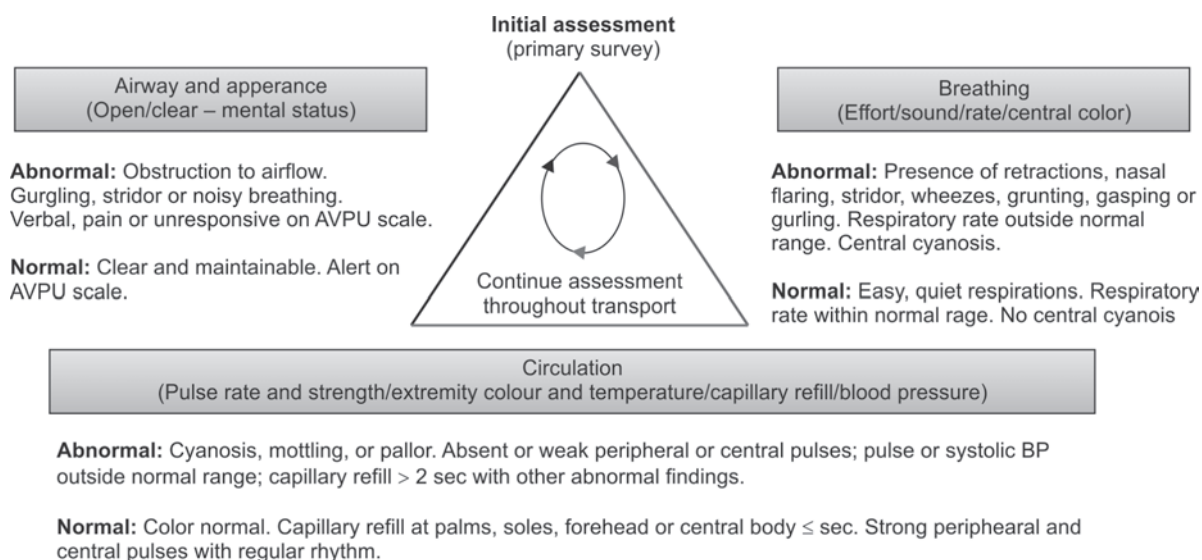


Fig. 1: Pediatric assessment triangle (PAT)

Table 1: Pediatric assessment triangle and its interpretation

<i>Physiological status</i>	<i>Appearance</i>	<i>Work of breathing</i>	<i>Circulation to skin</i>
Respiratory distress	Normal	Abnormal	Normal
Respiratory failure	Abnormal	Abnormal	Normal/abnormal
Compensated shock	Normal	Normal	Abnormal
Decompensated shock	Abnormal	Normal/abnormal	Abnormal
Brain injury/dysfunction	Abnormal	Normal	Normal
Cardiopulmonary failure	Abnormal	Abnormal	Abnormal

a simple clinical tool to assess the disability or neurological status whether the child is alert, responsive to verbal commands, responsive only to painful stimuli, or unresponsive. Exposure of children should be done with the parent's assistance while maintaining the modesty and respect for the child. A neutral thermal environment should be maintained to avoid hypothermia and heat loss.

Secondary and Tertiary Assessment

After primary assessment and initial stabilization, a more detailed examination of the child is done from head to toe. At the same time, a brief history is obtained from the family or the available care provider. A mnemonic of this brief history is SAMPLE: Signs/symptoms, allergies, medications, past medical problems, last meal and events preceding the injury/illness. Interviewing a child and parents in emergency room is an art as the parents who bring children to an ED for care usually perceive that their child has an emergency. So, it is important to treat the family with respect, gentleness, and kindness to ensure trusting patient-doctor relationship. In an emergency setting, the chief complaint and present illness are the main focus for

information gathering, so always begin the interview by asking "What brings you and your child to the emergency department today?" The examination of a child should be performed in the least hurtful manner while concentrating on most important components initially and doing fear-provoking part at the end of examination. There is no need to follow a stepwise fashion from head to toe. Infants and toddlers are always most comfortable and cooperative when examined in the parent's lap.

SPECIFIC SITUATIONS AND CHILDREN WITH SPECIAL HEALTH CARE NEEDS

Trauma is a special situation where initial assessment starts with a primary survey that includes careful assessment of the airway, adequacy of oxygenation and ventilation, as well as a search for signs of circulatory compromise. The most important priority in these cases is to identify life-threatening abnormalities and start appropriate resuscitation efforts. After this, a careful and detailed secondary trauma survey is necessary to identify subtle but potentially life-threatening injuries. Evaluation of the cervical spine is a critical part of pediatric trauma assessment to look

for the risk of spinal injury. While the secondary trauma survey is systematically performed, continued attention is maintained on the PAT and primary survey to identify any ongoing bleeding or progressing respiratory problems.

Another group of children who need evaluation in a different manner are those with special health care needs. These children account for a large number of emergency and urgent ED visits. Clinical assessment can be difficult in a child with developmental delay or significant neurologic problems. In such cases pediatric assessment triangle has its own limitation. In these children, the healthcare provider should take the help of the caretaker to know the baseline neurological status of the child. The subtle observation made the caretaker usually provide important clues to a potentially serious illness or complications. It is always better to seek specialty consultation from providers who are familiar with children who have special health care needs.

PEDIATRIC EMERGENCY TRIAGE

Large numbers of children visit the general or pediatric emergency department. Providing the medical care to these pediatric patients in the order of attending may lead to long waiting times for seriously ill patients and increased risk of morbidity and mortality. So, it is important to prioritize patients who are seriously ill and would be at increased risk of morbidity or even mortality due to delay in the initiation of treatment. The aim of triage is to determine and classify the clinical priority of patients visiting the ED. During a short assessment the nurse will identify signs and symptoms that determine the patient's

urgency. The physician will see the patients in order of their urgency level. Patients requiring immediate care are identified. Moreover, patients are identified who can safely wait longer or who can be seen by another caregiver such as the general practitioner or nurse practitioner. Triage systems are developed by expert opinion with the lowest level of evidence, and are mainly based on the adult population visiting the ED. Several studies have investigated the reliability and validity of triage systems in children. The Pediatric Canadian Triage and Acuity Scale (PedC-TAS) was especially modified for the pediatric population. Although different criteria per triage system are used, they all sort patients into five urgency categories except for the WHO triage which divides the children in three categories (Table 2).

The commonly used triage systems in pediatric emergency include:

- Manchester triage system (MTS)
- Emergency severity index (ESI)
- Pediatric Canadian Triage and Acuity Score (pedC-TAS)
- Australasian triage scale (ATS)
- The triage suggested by WHO manual of emergency care of children.

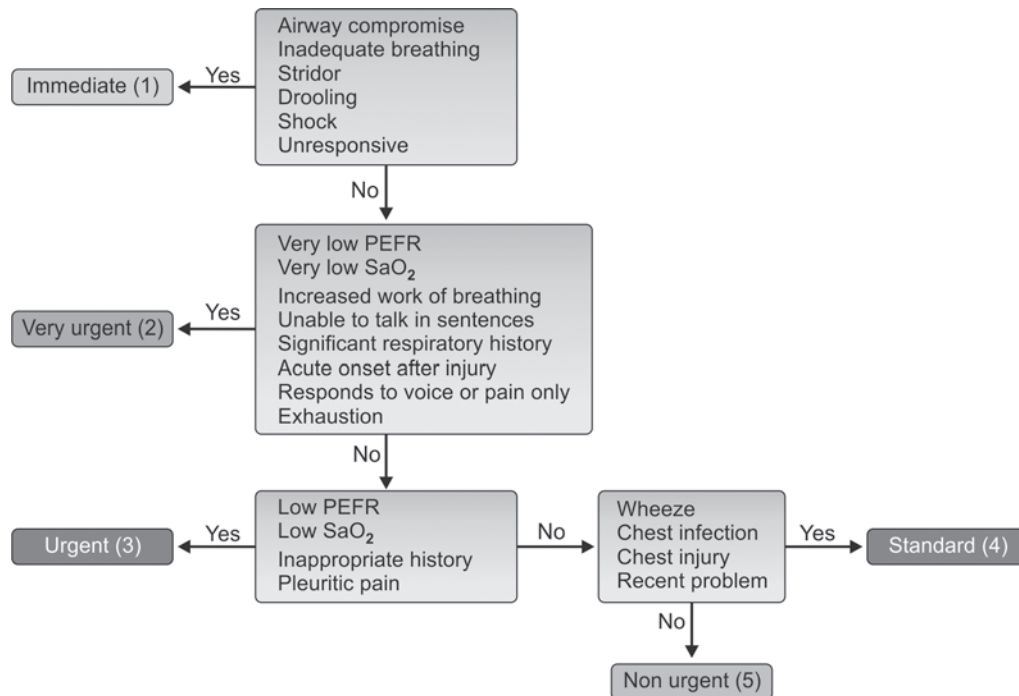
Manchester triage system (MTS): The first version was published in 1997 followed by second version in 2006 (Flow chart 1). The MTS contains 52 flow charts presenting different presenting problems. Some flowcharts are specific for children, such as 'Worried parent', 'Abdominal pain in children', 'Crying baby', 'Shortness of breath in children', 'Limping child', 'Unwell child' and 'Irritable child'. The

Table 2: Triage systems and the level of acuity of emergency

<i>System and countries</i>	<i>Triage levels</i>	<i>Patient should be seen within</i>
Australasian triage scale (ATS) formerly National triage scale of Australia (Australia, New Zealand)	Level 1: Resuscitation	Level 1: 0 minutes
	Level 2: Emergency	Level 2: 10 minutes
	Level 3: Urgent	Level 3: 30 minutes
	Level 4: Semiurgent	Level 4: 60 minutes
	Level 5: Nonurgent	Level 5: 120 minutes
Manchester triage scale (England, Scotland)	Level 1: Immediate (Red)	Level 1: 0 minutes
	Level 2: Very Urgent (Orange)	Level 2: 10 minutes
	Level 3: Urgent (Yellow)	Level 3: 60 minutes
	Level 4: Standard (Green)	Level 4: 120 minutes
	Level 5: Nonurgent (Blue)	Level 5: 240 minutes
Canadian triage and acuity scale (CTAS) (Canada)	Level 1: Resuscitation	Level 1: 0 minutes
	Level 2: Emergent	Level 2: 15 minutes
	Level 3: Urgent	Level 3: 30 minutes
	Level 4: Less Urgent	Level 4: 60 minutes
	Level 5: Nonurgent	Level 5: 120 minutes

(Australasian College for Emergency Medicine, 2002; Manchester triage group, 1997; Canadian Association of Emergency Physicians, 2002)

Flow chart 1: Manchester triage system flow chart shortness of breath in children



flow charts contain general as well as specific discriminators, which are presenting signs or symptoms of the patient. General discriminators are life threat, pain, hemorrhage, conscious level, temperature and acuteness. Specific discriminators are related to the presenting problems such as 'Increased work of breathing' (flow chart 'Shortness of breath in children') or 'Persistent vomiting' (flow chart 'Abdominal pain in children'). The selected discriminator leads to an urgency level. Medical care should be delivered immediately for level 1, within 10 minutes for level 2, within 60 minutes for level 3, within 120 minutes for level 4 and within 240 minutes for level 5. Some of the studies have found low validity for a subgroup of patients such as young patients, patients with a nontraumatic presenting problem and older patients with fever.

Canadian triage and acuity scale (CTAS): In 2001, a specific guideline to triage children was added to the CTAS, (pedCTAS). Per presenting problem, specific criteria are provided to allocate patients to different urgency levels. For example, children presenting with respiratory distress, for level 1 signs are: inability to speak, cyanosis, lethargy or confusion, tachycardia or bradycardia, and hypoxemia with $SpO_2 < 90$ percent. For level 2, the signs audible stridor, intermittent respiratory distress and audible wheezing, tachypnea, or cough are listed in order to select patients with respectively upper respiratory distress, congenital vascular anomalies and foreign bodies or lower airway concerns. Level 3 is for patients with moderate respiratory distress such as patients with pneumonia, bronchiolitis or croup. Level 4 and 5 do not contain criteria for

patients with respiratory distress. Medical care should be delivered immediately for level 1, within 15 minutes for level 2, within 30 minutes for level 3, within 60 minutes for level 4 and within 120 minutes for level 5. Table 3 lists the 10 most common causes for triage level I and level II visits in children hospital at Colorado.

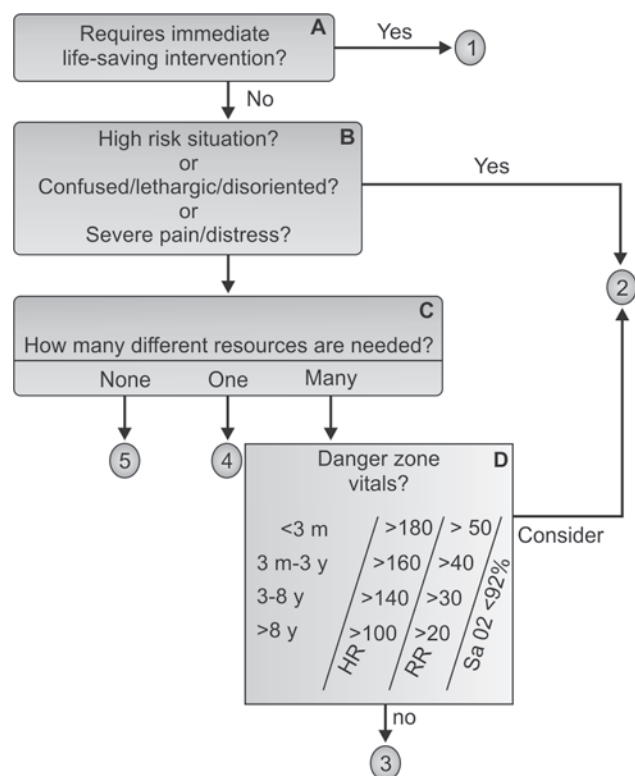
Emergency severity index (ESI): The ESI is a 5-level triage system, developed in the United States. Level 1 stands for the highest acuity level and level 5 for the lowest acuity. Patients requiring immediate lifesaving interventions are allocated into level 1 and must be seen immediately. Patients in a high risk situation, who are confused, lethargic, disoriented, have severe pain or distress or have deviated vital signs/PO are attributed to level 2. A physician should see these patients within ten minutes. Level 3 is for patients who are expected to require two or more resources. Level 4 is attributed if one resource is expected to be required and 5 if no resources are expected to be required. Resources can be diagnostics (for example, lab tests, ECG, X-rays, CT scan etc), treatment (for example IV fluids, laceration repair) or specialty consultation. Patients triaged as level 3 to 5 can safely wait for several hours (Flow chart 2).

In the fourth version of the ESI, a specific flowchart for children with fever was added. It uses age, the height of fever, the cause of fever and whether the child is immunized to determine urgency. Children younger than 28 days with a temperature $> 38.0^\circ\text{C}$ are allocated to level 2. Children with fever aged 28 days – 3 months are assigned to level 2 or 3, depending on the hospital's institutional

protocol. Children aged 3 to 36 months who are under immunized or who have no obvious source of fever and a temperature $>39.0^{\circ}\text{C}$ are allocated to level 3.

Australasian triage scale (ATS): This was formerly known as the National Triage Scale. The ATS provides criteria per urgency level. Most criteria are general but three criteria are specific for children: shocked child/infant should be allocated to level 1, all 'stable neonates' are allocated to level 3 as well as 'children at risk'.

Flow chart 2: Emergency severity index (ESI): Triage algorithm



WHO pocket book of hospital care for children: This manual also provides a simple and rapid method of screening sick children soon after their arrival in hospital. The children are categorized in three groups: (1) Children with emergency signs, (2) Children with urgent signs and (3) Non-urgent cases

Those with emergency signs: These children require immediate emergency treatment. The emergency signs include:

- Obstructed breathing
- Severe respiratory distress
- Central cyanosis
- Signs of shock (cold hands; capillary refill longer than 3 seconds; weak, fast pulse)
- Coma
- Convulsions
- Signs of severe dehydration in a child with diarrhea (lethargy, sunken eyes, very slow return after pinching the skin—any two of these).

Children with emergency signs require immediate treatment to avert death. Any child coming to the hospital should be checked immediately of any emergency signs. Checking for emergency signs is done in two steps:

- *Step 1:* If there is any airway or breathing problem, start immediate treatment to restore breathing.
- *Step 2:* Quickly determine if the child is in shock or unconscious or convulsing, or has diarrhea with severe dehydration.

If emergency signs are found, call an experienced health professional to help if available, but do not delay starting the treatment. Stay calm and work with other health workers who may be required to give the treatment, because a very sick child may need several treatments at once. The most experienced health professional should continue assessing the child, to identify all underlying problems and develop a treatment plan. Carry out

Table 3: Ten common causes of triage level 1 and Triage level 2 in a children

Triage level 1	Triage level 2
Trauma	Respiratory distress
Seizures	Suspected sepsis/meningitis
Respiratory failure	Trauma/injury
Altered consciousness	Sickle cell disease complications
Sepsis	Diabetes complications
Cardiac problem	Genitourinary complaints
Diabetic ketoacidosis	VP shunt complications
Toxic ingestion	Seizures
SIDS/CPR	Hypovolemic dehydration
Hypovolemic shock	Oncology patient with fever

CPR, cardiopulmonary resuscitation; SIDS, sudden infant death syndrome; VP, Ventriculoperitoneal

emergency investigations (blood glucose, blood smear, hemoglobin). Send blood for typing and cross-matching if the child is in shock, or appears to be severely anemic, or is bleeding significantly. After giving emergency treatment, proceed immediately to assessing, diagnosing and treating the underlying problem.

Those with priority signs: If no emergency signs are found, check for priority signs. The priority signs identify children who are at higher risk of dying. These children should be given priority while waiting in the queue so that they can be assessed and treated without delay. The priority signs include:

- Tiny baby: any sick child aged under 2 months
- Temperature: child is very hot
- Trauma or other urgent surgical condition
- Pallor (severe)
- Poisoning
- Pain (severe)
- Respiratory distress
- Restless, continuously irritable, or lethargic
- Referral (urgent)
- Malnutrition: visible severe wasting
- Edema of both feet
- Burns (major).

The above can be remembered with the help of “3TPR MOB”. These children need prompt assessment (no waiting in the queue) to determine what further treatment is needed. Move the child with any priority sign to the front of the queue to be assessed next. If a child has trauma or other surgical problems, get surgical help where available.

Nonurgent cases: The children having neither emergency nor priority signs are categorized as nonurgent cases.

These are to be attended by after taking care of children having emergency or priority signs.

Various studies have tried to compare the validity and reliability of these triage systems for children. A recent review article based on search in Pubmed and Cochrane on studies on reliability and validity of triage systems in children concluded that the MTS and pedCTAS both seem valid to triage children. Available studies show that reliability of the MTS is good, is moderate to good for the ESI, moderate for the pedCTAS and poor to moderate for the ATS.

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Emergency Cardiopulmonary Resuscitation

Suresh Gupta

When cardiac arrest or life-threatening emergencies occur, prompt and skillful response can make the difference between life and death and between intact survival and debilitation. Since 2000, researchers from the International Liaison Committee on Resuscitation (ILCOR) member councils have evaluated resuscitation science in 5-year cycles. The conclusions and recommendations of the 2005 International Consensus Conference on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care with Treatment Recommendations were published at the end of 2005. The most recent International Consensus Conference was held in Dallas in 2010. This article is based on the current recommendations and guidelines for pediatric basic life support (BLS) and pediatric advanced life support (PALS). Pediatric advanced life support always begins with a good basic life support which is continued from out of hospital settings to the emergency room. The core concepts of BLS are outlined first before discussing the PALS.

BASIC LIFE SUPPORT IN CHILDREN

Introduction

Early recognition and treatment of sudden cardiac arrest improves survival for children and adults.¹⁻³ Basic life support (BLS) involves a systematic approach to initial patient assessment, activation of emergency medical services, and the initiation of cardiopulmonary resuscitation (CPR), including defibrillation. Key components of effective CPR include adequate ventilation and chest compressions. BLS can be performed by trained lay persons, as well as by health care providers. Bystander CPR has been associated with a greater than 70 percent chance of neurologically intact survival after respiratory arrest in children and is a key component to achieving optimal survival following a sudden witnessed cardiac collapse due to

a ventricular arrhythmia.⁴ Based upon extensive review of clinical and laboratory evidence, the American Heart Association (AHA) and the ILCOR published updated guidelines for pediatric BLS in 2010.⁴⁻⁷ For the purposes of these guidelines, a newborn is defined as from birth to hospital discharge, an infant is younger than one year of age, and a child is from one year to start of puberty. The guidelines are designed to be simple, practical, and effective. Changes for infants and children from the previous basic life support guidelines of 2005 include new criteria for the initiation of CPR, compressions prior to airway and breathing for infants and children in cardiac arrest (CAB instead of ABC), and evidence-based reaffirmation of conventional cardiopulmonary resuscitation (CPR) as preferred to compression only CPR (Table 1).

BASIC LIFE SUPPORT SEQUENCE

Before beginning basic life support (BLS), rescuers must ensure that the scene is safe for them and the victim. The next steps in BLS are activating emergency medical services (EMS), getting an automated external defibrillator (AED), and starting cardiopulmonary resuscitation (CPR). *Activate EMS:* For activating EMS, the guidelines recommend the following in infants and children for health care providers⁴⁻⁷:

- If two or more rescuers present
 - For unwitnessed and witnessed cardiac arrests with two or more rescuers present, initiation of CPR, activation of the emergency response system, and getting an automated external defibrillator (AED) occur simultaneously. CPR should be performed for two minutes (five cycles) before using an AED in a patient with an unwitnessed arrest based on limited evidence in adults that even for prolonged arrest from ventricular fibrillation (VF), an initial

Table 1: 2010 American Heart Association Guidelines for CPR and key changes in basic life support

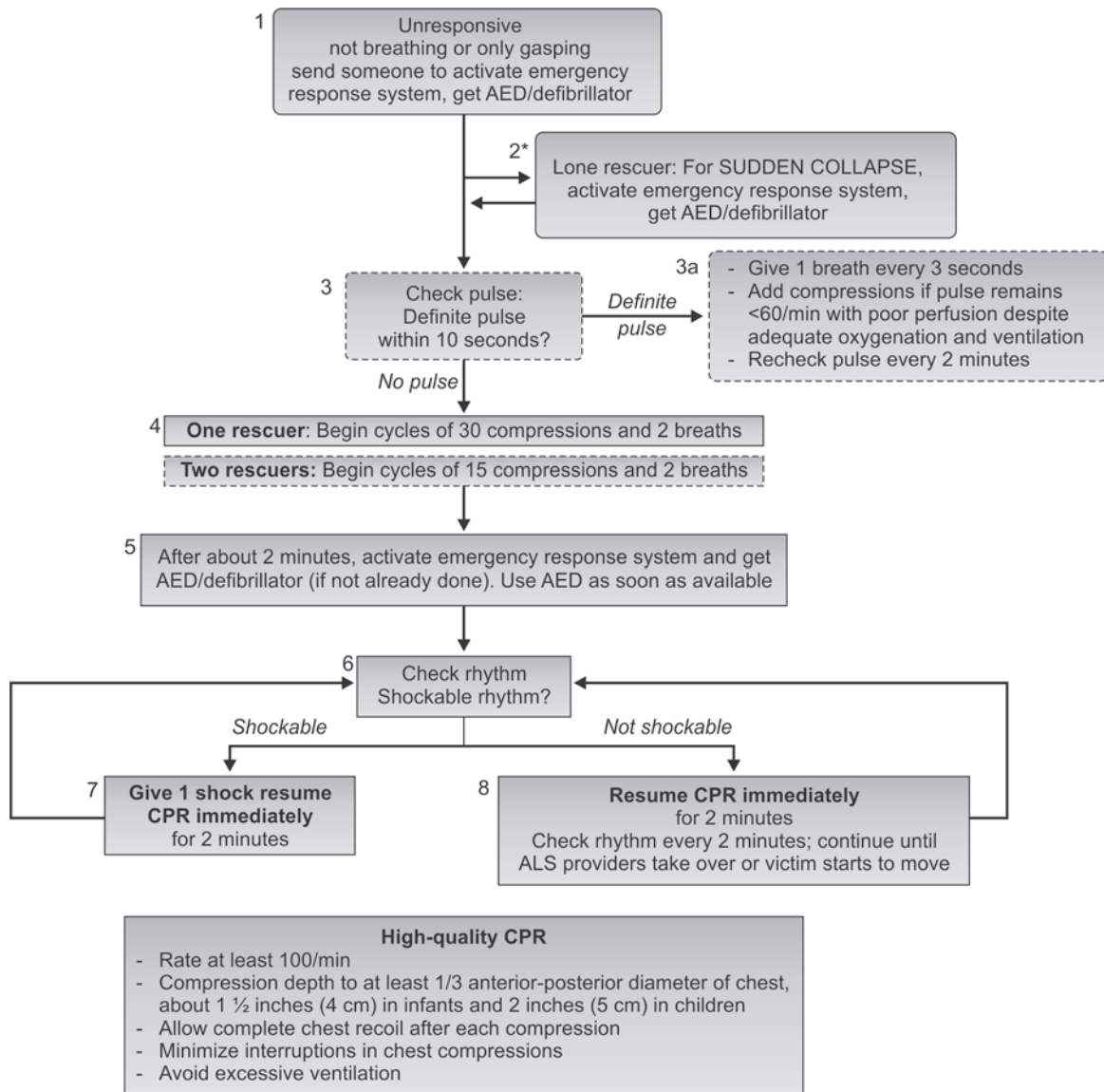
<i>2010 Recommendation</i>	<i>2005 Recommendation</i>	<i>Explanation</i>
<i>Pediatric basic life support</i>		
Initiate CPR for infants and children with chest compressions rather than rescue breaths (C-A-B) rather than A-B-C). CPR should begin with 30 compressions (any lone rescuer) or 15 compressions (for resuscitation of infants and children by two health care providers) rather than with two ventilations.	Cardiopulmonary resuscitation was initiated with opening of the airway and the provision of 2 breaths before chest compressions.	This proposed major change in CPR sequencing to compressions before ventilations (C-A-B) led to vigorous debate among experts in pediatric resuscitation. Because most pediatric cardiac arrests are asphyxial, rather than sudden primary cardiac arrests, both intuition and clinical data support the need for ventilations and compressions for pediatric CPR. However, pediatric cardiac arrests are much less common than adult sudden (primary) cardiac arrests, and many rescuers do nothing because they are uncertain or confused. Most pediatric cardiac arrest victims do not receive any bystander CPR, so any strategy that improves the likelihood of bystander action may save lives. Therefore, the C-A-B approach for victims of all ages was adopted with the hope of improving the chance that bystander CPR would be performed. The new sequence should theoretically only delay rescue breaths by about 18 seconds (the time it takes to deliver 30 compressions) or less (with 2 rescuers).
To achieve effective chest compressions, rescuers should compress at least one third of the anterior-posterior diameter of the chest. This corresponds to approximately 1½ inches (about 4 cm) in most infants and about 2 inches (5 cm) in most children.	Push with sufficient force to depress the chest approximately one-third to one-half the anterior-posterior diameter of the chest.	Evidence from radiologic studies of the chest in children suggests that compression to one half the anterior-posterior diameter may not be achievable. However, effective chest compressions require pushing hard, and based on new data, the depth of about 1½ inches (4 cm) for most infants and about 2 inches (5 cm) in most children is recommended.
For infants, a manual defibrillator is preferred to an AED for defibrillation. If a manual defibrillator is not available, an AED equipped with a pediatric dose attenuator is preferred. If neither is available, an AED without a pediatric dose attenuator may be used.	Data have shown that AEDs can be used safely and effectively in children 1 to 8 years of age. However, there are insufficient data to make a recommendation for or against using an AED in infants < 1 year of age.	Newer case reports suggest that an AED may be safe and effective in infants. Because survival requires defibrillation when a shockable rhythm is present during cardiac arrest, delivery of a high-dose shock is preferable to no shock.

period of CPR improves the likelihood of successful defibrillation. This approach is the same as for adults with cardiac arrest.

- If the lone rescuer, the sequence varies:
 - If the cardiac arrest is witnessed, the lone rescuer should first activate the emergency response system, obtain an AED, and then start CPR. This approach is the same as for adults with cardiac arrest.
 - If the cardiac arrest is unwitnessed, the lone rescuer should first perform two minutes of CPR, activate the emergency response system, and then obtain an

AED. CPR is recommended initially for infants and children with an unwitnessed cardiac arrest being cared for by a lone rescuer because most pediatric arrests are likely to be asphyxial. This approach differs from that recommended for adults.

- Initiate CPR—The steps of cardiopulmonary resuscitation (CPR) are opening the airway, providing ventilations (rescue breaths), and performing chest compression. The sequence of the actions of CPR for infants and children should be performed by health care providers is as follows (Flow chart 1):

Flow chart 1: Pediatric BLS algorithm for health care providers: 2010 guidelines

AED: Automated external defibrillator; BLS: Basic life support; CPR: Cardiopulmonary resuscitation.

* The boxes bordered by dotted lines are performed by health care providers and not by lay rescuers. Source Pediatric Basic Life Support: 2010. American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. © 2010 American Heart Association, Inc.

- Initiate CPR in an infant or child who is unresponsive and not breathing (or only gasping).
 - If there is no pulse or it is not definitively identified within 10 seconds, then start compressions before performing airway or breathing maneuvers. After 30 compressions (15 compressions if two rescuers) open the airway and give two breaths.
 - If a definite pulse is found within 10 seconds, provide ventilation only
 - If the pulse is ≥ 60 beats per minute (bpm), continue ventilation
 - If the pulse is < 60 bpm, add chest compressions to ventilation
- High quality CPR focuses on the effective delivery of chest compressions and avoidance of excessive ventilation.

VENTILATION

Ventilations can be provided with mouth-to-mouth, mouth-to-nose, or with a bag and mask. Evidence in adults and animals suggest that hyperventilation is associated with increased intrathoracic pressure and decreased coronary and cerebral perfusion. Based on these data following recommendations are made.^{4,8}

- Each rescue breath should be delivered over one second.
- The volume of each breath should be sufficient to see the chest wall rise.
- A child with a pulse ≥ 60 bpm who is not breathing should receive one breath every three to five seconds (12 to 20 breaths per minute).
- Infants and children who require chest compressions should receive two breaths per 30 chest compressions for a lone rescuer and two breaths per 15 chest compressions for two rescuers.
- Intubated infants and children should be ventilated at a rate of 8 to 10 breaths per minute without any interruption of chest compressions.

CHEST COMPRESSIONS

The new guidelines emphasize the importance of hard and fast chest compression, with full chest recoil and minimal interruptions.⁵ Chest compressions should be performed over the lower half of the sternum.^{4,6,9} Compression of the xiphoid process can cause trauma to the liver, spleen, or stomach, and must be avoided. The effectiveness of compressions can be maximized by attention to the following:

- The chest should be depressed at least one-third of its anterior-posterior diameter with each compression (approximately 4 cm (1 ½ inches) in most infants and 5 cm (2 inches) in most children).
- The optimum rate of compressions is at least 100 per minute. Each compression and decompression phase should be of equal duration.
- The sternum should return briefly to its normal position at the end of each compression, allowing the chest to recoil fully.
- A smooth compression-decompression rhythm, with minimal interruption, should be developed.
Infants — Chest compressions for infants (younger than one year) may be performed with either two fingers or with the two thumb-encircling hands technique.
- Two fingers technique: This is recommended when there is a single rescuer.^{4,7} Compressions are performed with index and middle fingers, placed on the sternum just below the nipples. Because of the infant's large occiput, slight neck extension and the placement of a hand or rolled towel beneath the upper thorax and shoulders may be necessary to ensure that the work of compression is focused on the heart.

- Two thumb-encircling hands technique: It is suggested when there are two rescuers.⁴ The thorax is encircled with both hands and cardiac compressions are performed with the thumbs. The thumbs compress over the lower half of the sternum, avoiding the xiphoid process, while the fingers are spread around the thorax.^{4,7}

Children: For children (from one year until the start of puberty), compressions should be performed over the lower half of the sternum with either the heel of one hand or with two hands, as for adult victims.

COMPRESSION TO VENTILATION RATIO

Chest compressions in infants and children should always be accompanied by ventilation for infants and children who remain pulseless after the initial sequence of compressions.⁴⁻⁷ However, every effort should be made to avoid excessive ventilation and to limit interruptions of chest compressions to less than ten seconds.

- For lone rescuers, two ventilations should be delivered during a short pause at the end of every 30th compression.
- For two rescuers, two ventilations should be delivered at the end of every 15th compression. The compression to ventilation ratio for newborns is 3 to 1.
- Once the trachea is intubated, ventilation and compression can be performed independently. For infants and children, ventilations are given at a rate of 8 to 10 per minute. Compressions are delivered at a rate of 100 per minute without pauses. Compression to ventilation ratios of 30 to 2 and 15 to 2 are recommended to minimize interruption and for ease of teaching and retention.^{4,5} Coordination of compression and ventilation may be facilitated by counting compressions aloud rousing an audio-prompted rate guide.¹⁰

Conventional versus compression-only CPR: Although compression-only CPR (COO-CPR) for bystanders is suggested in limited situations in adults with cardiac arrest, conventional CPR is recommended in infants and children, because cardiac arrest in this population is more commonly due to hypoxia when compared to adults.⁴⁻⁶

AUTOMATED EXTERNAL DEFIBRILLATOR

According to newer guidelines, if a manual defibrillator is not available, an automated external defibrillator (AED) is used as soon as possible for infants and children who experience a witnessed cardiac arrest.⁴⁻⁷ For patients with unwitnessed arrest, CPR should be performed for two minutes (five cycles) prior to using an AED. For infants and children <8 years of age, an AED with a pediatric dose attenuating system should be used whenever possible. However, if a manual defibrillator or an AED with a pediatric dose attenuating system is not available, then use of an AED without a dose attenuator is advised.^{4,7}

PEDIATRIC ADVANCED LIFE SUPPORT

Introduction

The American Heart Association (AHA) pediatric advanced life support (PALS) program provides a structured approach to the assessment and treatment of the critically ill pediatric patients.¹¹ The AHA guidelines for pediatric resuscitation were updated in year 2010 to include the new evidence from a variety of sources ranging from large clinical trials to animal models¹² (Table 2). The components of pediatric advanced life support include

- Overview of assessment
- Recognition and management of respiratory distress and failure

- Recognition and management of shock
- Recognition and management of cardiac arrhythmias
- Recognition and management of cardiac arrest
- Post resuscitation management of patients with pulmonary and cardiac arrest
- Review of pharmacology

Overview of Assessment

A rapid assessment facilitates rapid evaluation and intervention for life-threatening conditions. In infants and children, most cardiac arrests result from progressive respiratory failure and/ or shock. The rapid assessment aims at recognizing the respiratory failure before progression to cardiac arrest. The evaluation includes:

Table 2: 2010 American Heart Association Guidelines for CPR and key changes in pediatric advanced life support		
2010 Recommendation	2005 Recommendation	Explanation
<i>Pediatric advanced life support</i>		
Specific resuscitation guidance has been added for management of cardiac arrest in infants and children with single-ventricle anatomy, Fontan or hemi-Fontan/bidirectional Glenn physiology, and pulmonary hypertension.	These topics were not addressed in the 2005 guidelines.	Specific anatomical variants with congenital heart disease present unique challenges for resuscitation.
Although there have been no published results of prospective randomized pediatric trials of therapeutic hypothermia, based on adult evidence, therapeutic hypothermia (to 32°C to 34°C) may be beneficial for adolescents who remain comatose after resuscitation from sudden witnessed out-of-hospital VF cardiac arrest. Therapeutic hypothermia (to 32°C to 34°C) may also be considered for infants and children who remain comatose after resuscitation from cardiac arrest.	Based on extrapolation from adult and neonatal studies, when pediatric patients remain comatose after resuscitation, consider cooling them to 32°C to 34°C for 12 to 24 hours.	Additional adult studies have continued to show the benefit of therapeutic hypothermia for comatose patients after cardiac arrest, including those with rhythms other than VF. Pediatric data are needed.
The new guidelines have added this topic: When a sudden, unexplained cardiac death occurs in a child or young adult, obtain a complete past medical and family history (including a history of syncopal episodes, seizures, unexplained accidents/drowning, or sudden unexpected death at <50 years of age) and review previous ECGs. All infants, children, and young adults with sudden, unexpected death should, where resources allow, have an unrestricted complete autopsy, preferably performed by a pathologist with training and experience in cardiovascular pathology. Tissue should be preserved for genetic analysis to determine the presence of channelopathy.	This was not addressed in the previous guidelines.	There is increasing evidence that some cases of sudden death in infants, children, and young adults may be associated with genetic mutations that cause cardiac ion transport defects known as channelopathies. These can cause fatal arrhythmias, and their correct diagnosis may be critically important for living relatives.

Contd....

Suctioning immediately after birth should be reserved for babies who have an obvious obstruction to spontaneous breathing or require positive-pressure ventilation.

The person assisting delivery of the infant should suction the infant's nose and mouth with a bulb syringe after delivery of the shoulders but before delivery of the chest. Healthy, vigorous newly born infants generally do not require suctioning after delivery. When the amniotic fluid is meconium stained, suction the mouth, pharynx, and nose as soon as the head is delivered (intrapartum suctioning) regardless of whether the meconium is thin or thick.

There is no evidence that active babies benefit from airway suctioning, even in the presence of meconium, and there is evidence of risk associated with this suctioning. The available evidence does not support or refute the routine endotracheal suctioning of depressed infants born through meconium-stained amniotic fluid.

The recommended compression-to-ventilation ratio for newborns remains 3:1. If the arrest is known to be of cardiac etiology, a higher ratio (15:2) should be considered.

There should be a 3:1 ratio of compressions to ventilations.

The optimal compression-to-ventilation ratio remains unknown. The 3:1 ratio for newborns facilitates provision of adequate minute ventilation, which is considered critical for the vast majority of newborns who have an asphyxial arrest. The consideration of a 15:2 ratio (for 2 rescuers) recognizes that newborns with a cardiac etiology of arrest may benefit from a higher compression-to-ventilation ratio.

There is increasing evidence of benefit of delaying cord clamping for at least 1 minute in term and preterm infants not requiring resuscitation. There is insufficient evidence to support or refute a recommendation to delay cord clamping in babies requiring resuscitation.

No recommendation.

- *General assessment:* It is done using pediatric assessment triangle (brief visual and auditory observation of child's overall condition to focus on A: appearance, B: work of breathing and C: circulation)
- *Primary assessment:* It is rapid evaluation of cardiopulmonary and neurologic function to include A: Airway, B: Breathing, C: Circulation, D: Disability and E: Exposure
- *Secondary assessment:* It is focused medical history using sample mnemonic S: Signs and symptoms, A: Allergies, M: Medications, P: Pastmedical history, L: Last meal, E: Events leading to current illness and thorough head to toe physical exam
- *Tertiary assessment:* It includes laboratory, radiographic, and other ancillary studies.

- Upper airway obstruction (e.g. croup)
- Lower airway obstruction (e.g. bronchiolitis, status asthmaticus)
- Lung parenchymal disease (e.g. bronchopneumonia)
- Disordered control of breathing (e.g. seizure, coma, muscle weakness)

Initial management aims to support airway, breathing, and circulation:

- *Airway:* Key steps in basic airway management include i) providing 100 percent inspired oxygen, ii) allowing the child to assume position of comfort or manually open airway, iii) Clearing airway (suction) or use of oropharyngeal airway or nasopharyngeal airway if consciousness impaired
- *Breathing:* One should assist ventilation manually in patients not responding to basic airway maneuvers and at the same time monitor oxygenation by pulse oximetry and ventilation by end-tidal CO₂ if available, and administer medications like salbutamol or epinephrine as needed. Children who cannot maintain their airway, oxygenation, or ventilatory requirements need an artificial airway, usually via endotracheal intubation or a laryngeal mask airway.

Respiratory Distress and Failure

Early detection and treatment of respiratory distress and failure result in improvement of overall outcome. There are many causes of acute respiratory compromise in children. The clinician should attempt to categorize the cause of respiratory distress or failure into one or more of the following:

- Circulation key interventions include monitoring heart rate and rhythm and establishing vascular access .

Shock

Early recognition and categorization of the type of shock is important to prioritize treatment options. Early management of shock may prevent the progression to cardiopulmonary failure. Shock results from the inadequate delivery of oxygen to the tissues relative to tissue metabolic demand, usually characterized by inadequate perfusion. Shock may occur with normal, increased, or decreased systolic blood pressure. Shock in children is usually related to low cardiac output, but some patients may have high cardiac output, such as with sepsis or severe anemia.

Severity of shock is usually classified by its effect on systolic blood pressure:

- Compensated shock occurs when compensatory mechanisms maintain a systolic blood pressure within a normal range.
- Hypotensive shock (or decompensated shock) occurs when compensatory mechanisms fail to maintain systolic blood pressure.

In children 1 to 10 years of age, hypotension is defined as:

- Systolic pressure (5th percentile) $<70 \text{ mmHg} + (\text{child's age in years} \times 2)$
- For infants 1 to 12 months of age, hypotension is defined by systolic pressure $<70 \text{ mmHg}$, and, in term infants 0 to 1 month of age, systolic pressure $<60 \text{ mmHg}$.¹² Systolic blood pressure $<90 \text{ mmHg}$ indicates hypotension in children over 10 years of age.

Shock Categorization

There are four major categories of shock based on pathophysiology.

- *Hypovolemic shock:* It is characterized by inadequate circulating blood volume like in diarrhea or burns
- *Distributive shock:* It is characterized by inappropriately distributed blood volume typically associated with decreased systemic vascular resistance like in septic shock, anaphylactic shock
- *Cardiogenic shock:* It refers to impairment of heart contractility like in congenital heart disease, myocarditis and cardiomyopathy
- *Obstructive shock:* Here the shock arises because of obstructed blood flow to the heart like in cardiac tamponade or tension pneumothorax

Any given patient may suffer from more than one type of shock. For example, a child in septic shock may develop hypovolemia during the prodrome phase, distributive shock during the early phase of sepsis, and cardiogenic shock later in the course.

Shock Management

The approach to undifferentiated shock in children requires careful attention to history and physical examination in order to arrive at the type of shock present. Goals of management are to improve oxygen delivery and to reduce oxygen consumption. Specific measures include increasing circulating volume, increasing cardiac contractility, improving distribution of cardiac output, and reducing oxygen demand. Depending on the severity and cause of shock, one or more of the following measures are needed to manage a child with shock.

- Administration of high concentration of oxygen and support of respirations to decrease the work of breathing
- Rapid intravenous administration of fluids (e.g., boluses of normal saline 20 mL/ kg up to three times or more as needed for persistent hypotension)
- Administration of vasoconstrictors and/ or inotropes in selected patients
- Reversal of identified obstructions and other adjunct methods including treatment of underlying infection, fever, pain and anxiety, and treatment of metabolic derangements (hypoglycemia, hypocalcemia, hyperkalemia, metabolic acidosis)

CARDIOPULMONARY FAILURE

Respiratory failure and hypotensive shock are the most common conditions foregoing cardiac arrest. The patient in cardiopulmonary failure will progress rapidly to cardiac arrest without aggressive intervention. The following physical findings often herald cardiopulmonary failure:

- *Airway:* Possible upper airway obstruction secondary to decreased level of consciousness or anatomic obstruction from foreign body or infection
- *Breathing:* Bradypnea, irregular, ineffective respiration, gasping
- *Circulation:* Bradycardia, capillary refill >5 seconds, weak central pulses, no peripheral pulses, hypotension, cool extremities, mottled/cyanotic skin
- *Disability:* Diminished level of consciousness.

The management of cardiopulmonary failure includes positive pressure ventilations with 100 percent oxygen, chest compressions for heart rate <60 beats per minute in patients with poor perfusion, and administration of intravenous fluids and medications tailored to treat the underlying cause are indicated.

Approach to Cardiac Arrhythmias

Arrhythmias are classified as bradyarrhythmias, tachyarrhythmias, and pulseless arrest. Assessment of arrhythmias depends on the age related heart rate and baseline rhythm as well as level of activity and clinical condition.^{5,6,8}

Bradyarrhythmias

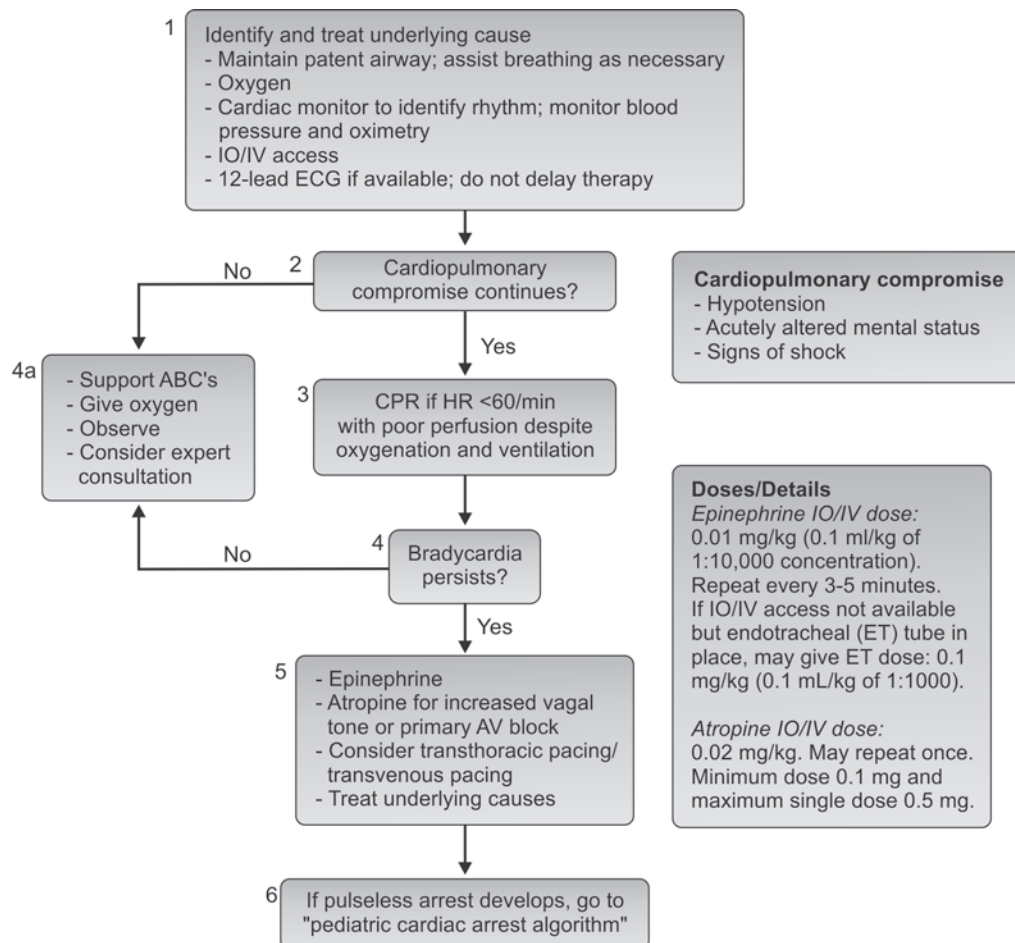
Bradycardia is defined as a heart rate that is slow compared with normal heart rates for the patient's age. Primary bradycardia results from congenital and acquired heart conditions that directly slow the spontaneous depolarization rate of the heart's pacemaker or slow conduction through the heart's conduction system. Secondary bradycardia is the result of conditions that alter the normal function of the heart, including hypoxia, acidosis, hypotension, hypothermia, and drug effects. Bradyarrhythmias are common pre-arrest rhythms in children and are often due to hypoxia. In emergency settings, the management of bradycardia focuses on reestablishing or optimizing oxygenation and ventilation, supporting circulation with chest compressions if needed, and using medications to increase heart rate and cardiac output (Flow chart 2). If these measures

fail, transcutaneous pacing can be attempted; however, the same factors that are producing refractory bradycardia (e.g. hypoxia, hypothermia, electrolyte disturbance, drug overdose) may prevent effective electrical capture.

Tachyarrhythmias

Tachyarrhythmias are fast abnormal rhythms originating in the atria or the ventricles. Relative tachycardia is a heart rate that is too fast for the child's age, level of activity, and clinical condition. In children, sinus tachycardia usually represents hypovolemia, fever, physiologic response to stress or fear, or drug effect (such as with beta agonists). Certain arrhythmias, such as supraventricular tachycardia and ventricular tachycardia, can lead to shock and cardiac arrest. Unstable rhythms lead to poor tissue perfusion with a fall in cardiac output, poor coronary artery perfusion,

Flow chart 2: Pediatric bradycardia algorithm (with a pulse and poor perfusion): 2010 PALS guidelines



PALS: pediatric advanced life support; CPR: cardiopulmonary resuscitation; IO: intraosseous; IV: intravenous; HR: heart rate; AV: atrioventricular; ABCs: air way, breathing, circulation. Source: Pediatric Advanced Life Support: 2010. American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. © 2010 American Heart Association, Inc.

and increased myocardial oxygen demand, which can all lead to cardiogenic shock. Management depends on differentiating between tachycardia with narrow QRS complex (sinus tachycardia, supraventricular tachycardia, atrial flutter) and wide QRS complex tachycardias (ventricular tachycardia, supraventricular tachycardia with aberrant intraventricular conduction).

Sinus tachycardia: Typical ECG findings in patients with sinus tachycardia include:

- Heart rate is usually <220/min in infants, <180/min in children, and exhibits beat to beat variability in rate
- P waves are present with normal appearance
- PR interval is constant and exhibits a normal duration for age
- R-R interval is variable
- QRS complex is narrow

Supraventricular tachycardia: Supraventricular tachycardia (SVT) can be defined as an abnormally rapid heart rhythm originating above the ventricles, often (but not always) with a narrow QRS complex; it conventionally excludes atrial flutter and atrial fibrillation. The two most common forms of SVT in children are atrioventricular re-entrant tachycardia (AVRT), including the Wolff-Parkinson-White (WPW) syndrome, and atrioventricular nodal reentrant tachycardia (AVNRT).

Typical ECG findings of SVT include:

- Heart rate that is usually >220/minute in infants, >180/min in children, and has no beat to beat variability
- P waves are absent or abnormal
- PR interval may not be present or short PR interval with ectopic atrial tachycardia
- R-R interval is usually constant
- QRS is usually narrow. Conduction delay along the ventricular system may lead to an appearance of wide complex tachycardia, known as SVT with aberrant conduction.

Ventricular tachycardia: Ventricular tachycardia (VT) originates from the ventricular myocardium or Purkinje cells below the bifurcation of the bundle of His. VT is associated with sudden cardiac death. As a result, patients who develop VT or at risk for developing VT must be identified, evaluated, and treated if necessary. VT may present with or without pulses. Causes of VT include underlying heart disease or cardiac surgery, prolonged QT syndrome, or myocarditis/cardiomyopathy. Other causes include hyperkalemia and toxic ingestions (e.g. tricyclic antidepressants).

Findings of ventricular tachycardia on ECG include:

- Ventricular rate is >120 beats per minute and regular
- P waves are often not identifiable, may have AV dissociation, or may have retrograde depolarization
- QRS is typically wide (>0.09 sec)
- T waves are often opposite in polarity from the QRS complex

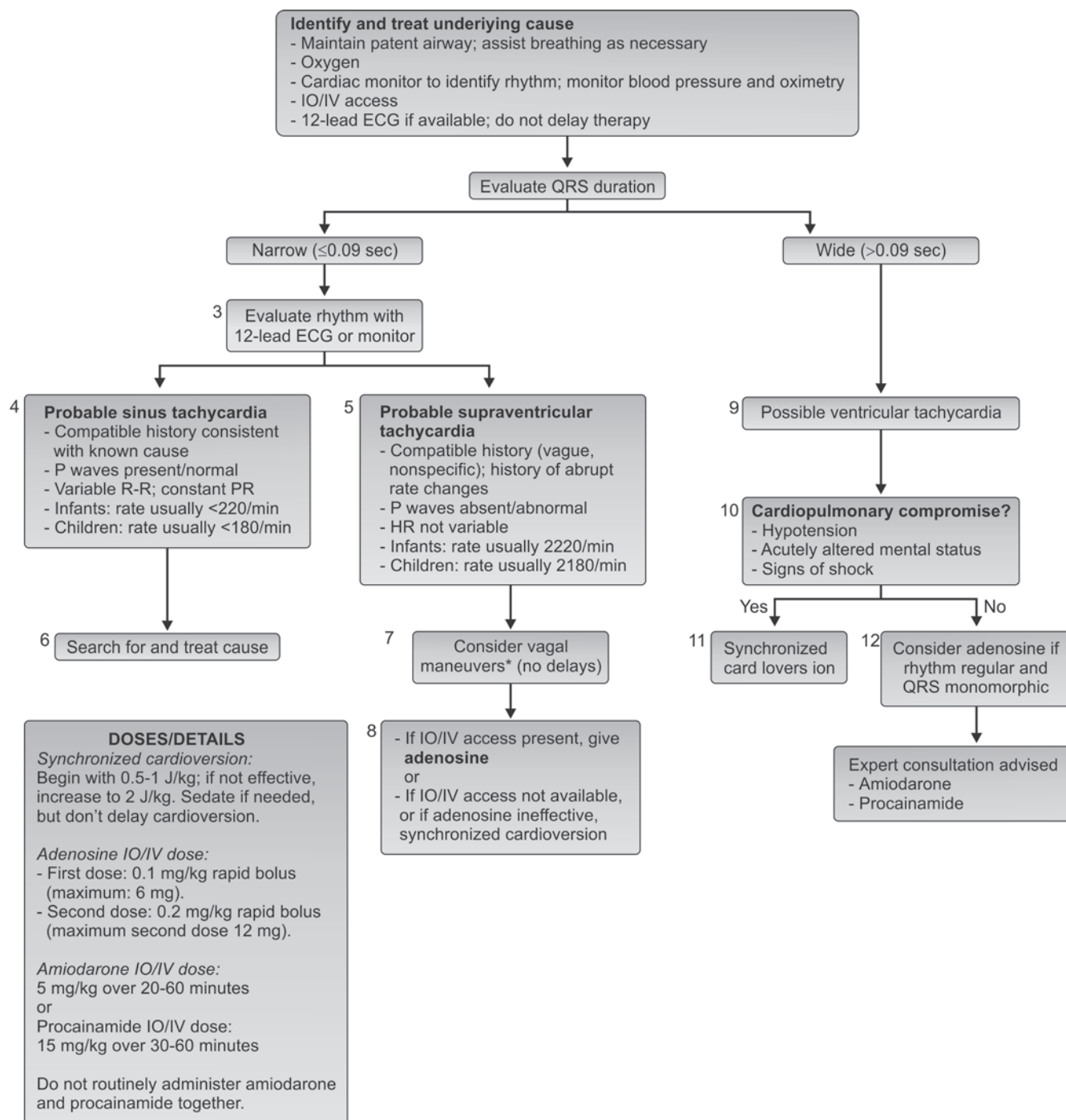
Tachyarrhythmia management: The management of sinus tachycardia focuses on treatment of the underlying physiologic derangement and is largely supportive. The management of tachyarrhythmia that are not sinus in origin is guided by the appearance of the QRS complex, and by the patient's status, whether compensated or uncompensated (Flow chart 3):

- Patients with either narrow or wide complex tachycardia who have significantly impaired consciousness and hypotensive shock should be treated with synchronized cardioversion
- Patients who are relatively stable may receive a trial of anti-arrhythmic therapy, based on whether the arrhythmia is believed to originate from above the AV node (narrow complex, e.g. adenosine; initial dose: 0.1 mg/kg) or below the AV node (wide complex, e.g. amiodarone 5 mg/kg).

Pulseless Arrest

Pulseless arrest refers to cessation of blood circulation caused by absent or ineffective cardiac mechanical activity. Most pediatric cardiac arrests are hypoxic/asphyxial arrests that result from a progression of respiratory distress, respiratory failure, or shock rather than from primary cardiac arrhythmias ("sudden cardiac arrest"). Thus, the presenting rhythm is typically asystole. The pulseless arrest can also be associated with pulseless electrical activity (PEA), ventricular fibrillation (VF), and pulseless ventricular tachycardia (VT). Children with pulseless arrest appear apneic or display a few agonal gasps. They have no palpable pulses, and are unresponsive. Overall survival from pediatric cardiac arrest is poor, and the incidence of neurologic deficits in survivors is high.

Out-of-hospital arrests in children six months to young adulthood often occur at or near home. The most common cause of death is from trauma, leading to respiratory compromise and/ or shock. Massive head injury and severe multiple systems trauma are common in non-survivors. Sudden infant death syndrome (SIDS) is a leading cause of death in infants <6 months. Sudden collapse due to VF/ pulseless VT occurs in up to 18 percent of all pediatric prehospital cardiac arrests, but is less commonly the presenting rhythm in younger children between the ages of one and eight years (7.6%).¹³ Predisposing conditions include hypertrophic cardiomyopathy, anomalous coronary artery (from the pulmonary artery), long QT syndrome, myocarditis, drug intoxication, and commotio cordis (i.e., sharp blow to chest). These patients may have intact survival if defibrillation is performed within minutes of arrest. For in-hospital cardiac arrest, shockable rhythms are present at some point during the resuscitation in 27 percent of children, with 10 percent having VF/ VT as the initial arrest rhythm. Survival is higher if VF or VT is the presenting arrhythmia (35% survival) versus "non- shockable" rhythms, such as asystole (11%).²

Flow chart 3: Pediatric tachycardia algorithm (with a pulse and poor perfusion): 2010 PALS guidelines

PALS: Pediatric advanced life support; IO: Intraosseous; IV: Intravenous; ECG: electrocardiogram.

* Vagal maneuvers: In infants or young children, place a plastic bag filled with ice and cold water over the face for 15 to 30 seconds or stimulate the rectum with a thermometer. In older children, encourage bearing down (Valsalva maneuver) for 15 to 20 seconds. Carotid massage and orbital pressure should not be performed in children. Source: Pediatric Advanced Life Support: 2010. American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. © 2010 American Heart Association, Inc.

- *Asystole*: Children with asystole have cardiac standstill with no discernible electrical activity.
- *Pulseless electrical activity (PEA)*: It consists of any organized electrical activity observed on ECG in a patient with no central palpable pulse. Reversible conditions which may underlie PEA includes H's (Hypovolemia, Hypoxia, Hydrogen ion (acidosis), Hypo-/hyperkalemia Hypoglycemia and Hypothermia) and T's (Toxins, Tamponade cardiac, Tension pneumothorax, Thrombosis-coronary or pulmonary and Trauma)
- *Ventricular fibrillation*: It is characterized by chaotic electrical activity with no organized rhythm and no coordinated contractions.
- *Pulseless VT*: It is a cardiac arrest of ventricular origin characterized by organized, wide QRS complexes. Torsades de pointes or polymorphic VT displays a QRS complex that changes in polarity and amplitude, appearing to rotate around the ECG isoelectric line (translation: "twisting of the points"). This arrhythmia may be associated with markedly prolonged QTc interval from congenital conditions, drug toxicity and electrolyte disturbances (e.g. hypomagnesemia). Ventricular tachycardia, including torsades de pointes, can deteriorate into ventricular fibrillation.

Management: The most important part of management for pulseless arrest is highly effective chest compressions (push hard, push fast, allow complete chest recoil, and minimize interruptions) by a trained person. The compressions should be interrupted only for ventilation, rhythm check, and shock delivery. Once basic cardiopulmonary resuscitation is established, treatment of pulseless arrest requires rapid assessment of rhythm, performance of defibrillation as indicated, and pharmacotherapy aimed at increasing coronary artery circulation and restoration of organized cardiac conduction (Flow chart 4).

Vascular Access

It is a critical step in pediatric resuscitation. During pulseless arrest, intraosseous cannulation and peripheral venous access should be pursued simultaneously. Resuscitation medications given through a peripheral IV should be followed with a 5 mL flush of normal saline to move the drug from the peripheral to the central circulation. Many pediatricians prefer intraosseous cannulation as the initial route of vascular access, especially in young infants with pulseless arrest. Attempts at peripheral and central venous access in the head, neck, and chest should not interrupt chest compressions. Central lines are more secure than peripheral access and provide more rapid onset and higher peak concentration of medications but are not required during initial resuscitation attempts.

Endotracheal Drug Administration

Although lipid soluble drugs, such as lidocaine, epinephrine, atropine, and naloxone ("LEAN"), may be

administered via endotracheal tube (ETT), the intravascular route is always preferred. Optimal drug dosing via endotracheal tube is unknown, with unpredictable drug absorption leading to lower blood levels when compared with the same dose given intravascularly. While using ETT route for drug administration, one should increase the epinephrine dose tenfold and the dose of other medications (atropine, lidocaine, naloxone) two- to threefold. It is important to hold compressions during ETT administration and follow a drug administration with 3 to 5 mL of normal saline and provide five positive pressure ventilations after instilling the drug.

Defibrillation

Defibrillation does not restart the heart; the shock "stuns" the heart by depolarizing all of the myocardial cells, hopefully terminating VF and allowing the heart's natural pacemaker cells to resume an organized rhythm. After delivering a shock, the caregivers should perform five cycles of CPR before checking the rhythm. CPR may be discontinued if a perfusing rhythm has been established. Biphasic defibrillators have a high first shock efficacy rate for ventricular fibrillation (VF) of short duration in adults. This procedure eliminates VF but may not lead to a perfusing rhythm (often the patient will be in asystole or PEA) or myocardial ischemia prevents proper cardiac contractility. After delivering the shock, chest compressions should resume immediately for five cycles. Cardiopulmonary resuscitation is required to maintain blood flow to the heart, coronary circulation, and brain until effective cardiac contractility resumes.

Although manual defibrillators or automated external defibrillators with pediatric attenuating devices are preferred for use in infants and children, automated external defibrillators without pediatric attenuating devices may be used if they are the only option available.

Pharmacologic Therapy

Epinephrine is the most commonly used medication in children with pulseless arrest. It is classified as a catecholamine, vasopressor, and inotrope. For pulseless arrest, the IV/IO dosing is 0.01 mg/kg (0.1 mL/kg of the 1:10,000 concentrations given every three to five minutes; maximum single dose: 1 mg (10 mL)). High dose epinephrine is no longer recommended with the exception of endotracheal dosing. When epinephrine is administered via ET tube, use 0.1 mg/kg (0.1 mL/kg of the 1:1000 concentration by endotracheal tube every three to five minutes). The IV/IO route is always preferred. A brief summary of the resuscitation drugs is given in Table 3.

Early Postresuscitation Management

The early postresuscitation period involves the time soon after return of spontaneous circulation or recovery from

circulatory or respiratory failure. During this time, the clinician must continue to treat the underlying cause for the life threatening event and monitor for common respiratory or circulatory problems that may cause secondary morbidity or death.⁸

Oxygen administration: Once return of spontaneous circulation has been achieved, the clinician should titrate inspired oxygen to maintain arterial oxyhemoglobin saturation ≥ 94 –99 percent while avoiding hyperoxemia.

Intubated patients: All intubated children require continued assessment to ensure proper endotracheal tube positioning, continuous monitoring of oxygenation (pulse oximetry), and ongoing monitoring of ventilation (e.g., continuous end-tidal CO₂ monitoring, if available, and/or intermittent blood gas assessment). Insertion of a gastric tube helps to reduce gastric distension. The causes of sudden decompensation in a child who has been successfully intubated with an artificial airway are described by the mnemonic “DOPE”:

- D: Dislodged or displaced endotracheal tube (right mainstem or esophageal location)
- O: Obstructed endotracheal tube (e.g. mucous plug, kinked endotracheal tube)
- P: Pneumothorax
- E: Equipment failure (e.g. ventilator malfunction, oxygen disconnected or off)

Recurrent shock: After fluid resuscitation in a child, circulatory instability may recur as the result of ongoing fluid loss, decreased cardiac function, and/or harmful alterations in systemic vascular resistance. Goal-directed therapy emphasizes the need to assess clinical findings of perfusion (e.g. capillary refill, urine output), measure central venous pressure, and measure central venous oxygen saturation, to determine the best course of action. If the child is not being treated in a center with pediatric emergency and critical care expertise, the child should be stabilized and rapidly transferred for definitive care at a regional pediatric center. Critically ill or injured children typically

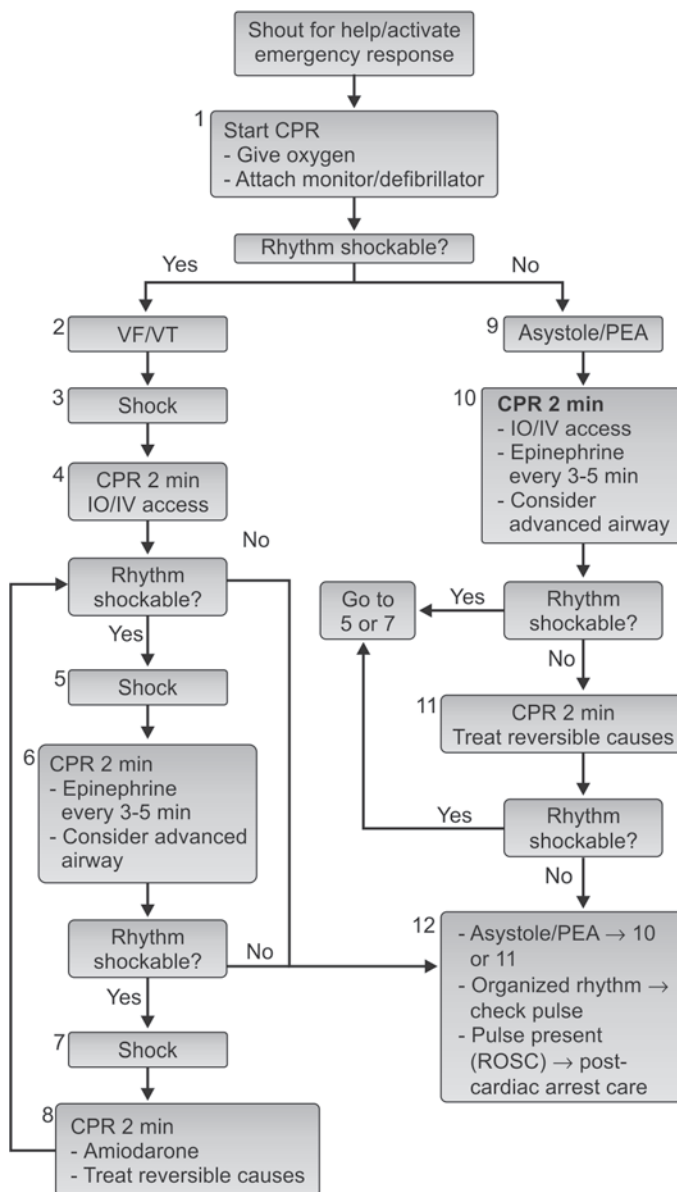
Table 3: Pediatric Resuscitation Pharmacology

Medication	Dose	Remarks
Adenosine	0.1 mg/kg (maximum 6 mg) Second dose: 0.2 mg/kg (maximum 12 mg)	Monitor ECG Rapid IV/IO bolus with flush
Amiodarone	5 mg/kg IV/IO; may repeat twice up to 15 mg/kg Maximum single dose 300 mg	Monitor ECG and blood pressure; adjust administration rate to urgency (IV push during cardiac arrest, more slowly—over 20–60 minutes with perfusing rhythm). Expert consultation strongly recommended prior to use when patient has a perfusing rhythm. Use caution when administering with other drugs that prolong QT (obtain expert consultation)
Atropine	0.02 mg/kg IV/IO 0.04–0.06 mg/kg ET* Repeat once if needed Minimum dose: 0.1 mg Maximum single dose: 0.5 mg	Higher doses may be used with organophosphate poisoning
Calcium chloride (10%)	20 mg/kg IV/IO (0.2 mL/kg) Maximum single dose 2 g	Administer slowly
Epinephrine	0.01 mg/kg (0.1 mL/kg 1:10,000) IV/IO 0.1 mg/kg (0.1 mL/kg 1:1000) ET* Maximum dose 1 mg IV/IO; 2.5 mg ET	May repeat every 3–5 minutes
Glucose	0.5–1 g/kg IV/IO	Newborn: 5–10 mL/kg D ₁₀ W Infants and Children: 2–4 mL/kg D ₂₅ W Adolescents: 1–2 mL/kg D ₅₀ W
Lidocaine	Bolus: 1 mg/kg IV/IO Infusion: 20–50 mcg/kg/minute	
Magnesium sulfate	25–50 mg/kg IV/IO over 10–20 minutes, faster in torsades de pointes Maximum dose 2 g	
Naloxone	Full Reversal: <5 y or ≤ 20 kg: 0.1 mg/kg IV/IO/ET* ≥ 5 y or >20 kg: 2 mg IV/IO/ET*	Use lower doses to reverse respiratory depression associated with therapeutic opioid use (1–5 mcg/kg titrate to effect)
Procainamide	15 mg/kg IV/IO Adult Dose: 20 mg/min IV infusion to total maximum dose of 17 mg/kg	Monitor ECG and blood pressure; Give slowly—over 30–60 minutes. Use caution when administering with other drugs that prolong QT (obtain expert consultation)
Sodium bicarbonate	1 mEq/kg per dose IV/IO slowly	After adequate ventilation

• IV indicates intravenous; IO, intraosseous; and ET, via endotracheal tube.

• * Flush with 5 mL of normal saline and follow with 5 ventilations

Flow chart 4: Pediatric Cardiac Arrest Algorithm: 2010 PALS Guidelines

**Doses/details****CPR quality**

- Push hard ($\geq 1/3$ of anterior-posterior diameter of chest) and fast (at least 100/min) and allow complete chest recoil
- Minimize interruptions in compressions
- Avoid excessive ventilation
- Rotate compressor every 2 minutes
- If no advanced airway, 15:2 compression-ventilation ratio. If advanced airway, 8-10 breaths with continuous chest compressions

Shock energy for defibrillation

First shock 2 J/kg, second shock 4 J/kg, subsequent shocks ≥ 4 J/kg, maximum 10 J/kg or adult dose.

Drug therapy

- Epinephrine IO/IV dose: 0.01 mg/kg (0.1 mL/kg of 1:10,000 concentration). Repeat every 3-5 minutes. If no IO/IV access, may give endotracheal dose: 0.1 mg/kg (0.1 mL/kg of 1:1000 concentration).

- Amiodarone IO/IV dose:

- 5 mg/kg bolus during cardiac arrest. May repeat up to 2 times for refractory VF/pulseless VT.

Advanced airway

- Endotracheal intubation or supraglottic advanced airway
- Waveform capnography or capnometry to confirm and monitor ET tube placement
- Once advanced airway in place give 1 breath every 6-8 seconds (8-10 breaths per minute)

Return of spontaneous circulation (ROSC)

- Pulse and blood pressure
- Spontaneous arterial pressure waves with intra-arterial monitoring

Reversible causes

- Hypovolemia
- Hypoxia
- Hydrogen ion (acidosis)
- Hypoglycemia
- Hypo-/hyperkalemia
- Hypothermia
- Tension pneumothorax
- Tamponade, cardiac
- Toxins
- Thrombosis, pulmonary
- Thrombosis, coronary

PALS: Pediatric advanced life support; VF: Ventricular fibrillation; VT: Ventricular tachycardia; PEA: Pulseless electrical activity; IO: Intraosseous; IV: Intravenous; CPR: Cardiopulmonary resuscitation; ROSC: Return of spontaneous circulation. Source: Pediatric Advanced Life Support: 2010. American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. © 2010 American Heart Association, Inc.

benefit from transport by a team with pediatric expertise and advanced pediatric treatment capability, although in some isolated cases (e.g. expanding epidural hematoma) more rapid transport by an immediately available non-pediatric team may be advantageous.

Prior to transfer the physician responsible for the child's care at the transferring hospital should speak directly to the physician who will be taking charge of the patient at the receiving hospital. All documentation of care (e.g. medical chart, medication administration

record, laboratory results, copies of ancillary studies (radiographs, ECGs)) should be sent with the patient.

Family Presence During Resuscitation

Observational studies indicate that caretakers should be given the option of being present during the in-hospital resuscitation of their child.⁸ Most parents want the opportunity to remain with their child during resuscitation and believe it is their right. Caretakers present during the resuscitation of a family member frequently reported that their presence during the resuscitation was beneficial to the patient. Two-thirds of caretakers present during the resuscitation of a child who died reported that their presence helped with their adjustment to the death and the grieving process. Studies of hospital personnel suggest that the presence of a family member, in most instances, was not stressful to staff and did not negatively impact staff performance. When family members are present during a pediatric resuscitation, a staff member with clinical knowledge, empathy, and strong interpersonal skills should be present with them to provide support and answer questions. In the rare instance that family presence is disruptive to team resuscitation efforts, the family members should be respectfully asked to leave.¹⁴⁻¹⁶

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Section 13

Cardiology

Editor
Manvinder Singh Sachdev

Clinically Useful Classification and an Approach to Acyanotic Congenital Heart Disease

Manvinder Singh Sachdev

INTRODUCTION

Congenital heart defects (CHD) occur due to structural malformation of the heart or great vessels during intrauterine development of the fetus. Although the defects are present from birth the age of presentation can vary from newborn period to adulthood.¹ According to studies from different parts of the world the incidence of congenital heart defects is 7 to 8 per 1000 live-born infants and they cause 3 percent of all infant deaths. The incidence of CHD has remained almost the same over the past few years. About 33 to 50 percent of these defects are critical. A critical CHD can be defined as a congenital heart disease which requires surgery or catheter intervention in the first year of life.² Early detection and appropriate management can significantly improve the morbidity and mortality and the outcome of congenital heart defects.³

CLASSIFICATION OF CONGENITAL HEART DISEASE

Congenital heart defects may be classified into acyanotic and cyanotic heart disease based on the type of defect and presence of cyanosis.¹

Acyanotic Lesions

Acyanotic heart defects can be further categorized as lesions which either increase the volume load of the heart, i.e. those with increased pulmonary blood flow or increase the pressure load on the heart (obstructive) (Table 1). Heart defects which cause left-to-right shunt lesions increase the volume load of the heart whereas increased pressure load is caused due to defects which cause ventricular outflow obstruction or narrowing of any of the great vessels (aorta or pulmonary artery).⁴ In acyanotic cardiac lesions pulmonary blood flow is normally adequate or even excessive, but the systemic blood flow is compromised.

Blood is oxygenated appropriately in the lungs, but it is not delivered efficiently to the tissues.⁴

Cyanotic Lesions

In cyanotic congenital heart defects with reduced pulmonary blood flow, the blood flow to the systemic vasculature is well maintained, but blood flow to the pulmonary vasculature is compromised as the systemic venous blood bypasses the pulmonary circulation and enters the left side of the heart (right to left shunt). Hence,

Table 1: Classification of congenital heart anomalies

Cyanotic heart diseases	
<i>Increased pulmonary blood flow</i>	<i>Examples</i>
	<ul style="list-style-type: none">• Transposition of the great arteries• Total anomalous pulmonary venous return• Tricuspid atresia, without PS• Persistent truncus arteriosus
<i>Decreased pulmonary blood flow</i>	<i>Examples</i>
	<ul style="list-style-type: none">• Tetralogy of Fallot• Pulmonary atresia• Tricuspid atresia, VSD, pulmonary stenosis• DORV, VSD, PS• TGA VSD PS
Acyanotic	
<i>Increased pulmonary blood flow</i>	<i>Examples</i>
	<ul style="list-style-type: none">• Ventricular septal defect• Atrial septal defect• Patent ductus arteriosus• Atrioventricular septal defect
<i>Obstructive</i>	<i>Examples</i>
	<ul style="list-style-type: none">• Pulmonary stenosis• Aortic stenosis• Aortic coarctation

even though blood is delivered to the tissues efficiently, systemic arterial desaturation (cyanosis) occurs as the blood is not adequately oxygenated.⁴ The other type of lesions in cyanotic congenital heart disease is those with increased pulmonary blood flow where cyanosis occurs as a result of mixing of the oxygenated and deoxygenated blood. Cyanosis caused due to intrapulmonary right to left shunting and pulmonary venous desaturation due to congestive heart failure are not included in cyanotic CHD.¹

WHY IS CLASSIFICATION NECESSARY

The physiologic presentations and age of presentation of the various congenital heart anomalies (cyanotic and acyanotic heart diseases) are variable. Congenital cardiac lesions may present as asymptomatic heart murmur, cyanosis (often without a murmur), or catastrophic heart failure and shock.⁵ A good understanding and knowledge about the range of abnormalities and possible presentations of the various cyanotic and acyanotic heart diseases are important for accurate diagnosis and improving outcome of congenital heart anomalies. According to studies timely recognition of hemodynamically significant congenital heart disease can improve outcomes hence it is important to have strategies that can help in timely diagnosis and appropriate treatment.^{5,6}

APPROACH TO ACYANOTIC CONGENITAL HEART DISEASE

A systematic approach while treating a child with possibly acyanotic congenital heart disease is important as it helps to arrive at the provisional diagnosis of the lesion and initiate management accordingly in this subgroup of patients. An effective diagnostic strategy while dealing with patients with possibly acyanotic congenital heart disease, at presentation can expedite diagnosis and management and improve overall prognosis.

The following step-wise approach is usually needed:

Differentiating Cyanotics and Acyanotics

The first step in approaching any patient with congenital heart disease is differentiating cyanotics from acyanotic patients. Cyanosis is caused due to presence of desaturated blood in the capillary beds as deoxygenated hemoglobin is blue. When an infant or child presents with cyanosis it means that at least 3 to 5 mg/dl of deoxyhemoglobin in the blood is present in blood. In presence of any of the following findings the patient is classified as cyanotic congenital heart disease:

- Presence of central cyanosis
- Saturation by pulse oximeter of <94 percent.

All other patients are labeled as acyanotic congenital heart disease. As cyanosis becomes evident to naked eye only when the saturation falls below 85 percent, pulse oximeter is a very important tool in differentiating cyanotic congenital heart disease from acyanotic congenital heart disease.⁷

Identify Patients with Increased Pulmonary Blood Flow

The left-to-right shunt lesions ventricular septal defects, atrial septal defects, patent ductus arteriosus, and endocardial cushion defects comprise about 50 percent of all congenital heart disease. In these lesions blood is shunted from the systemic system into the pulmonary system resulting in increased pulmonary blood flow. The high pulmonary vascular resistance in the neonate period limits the amount of shunt but with decrease in pulmonary vascular resistance after the first few weeks of life increases the pulmonary blood flow and pressures. Clinical manifestation and severity of presentation is directly proportional to the degree of pulmonary vascular blood flow. Higher blood flow causes chamber enlargement and signs of congestive heart failure.⁸ Increase pulmonary blood flow is suspected in presence of one or more of the following features on physical examination:

- Recurrent lower respiratory tract infection (LRTI)
- Feeding difficulty
- Excessive sweating
- Hyperdynamic precordium
- Failure to gain adequate weight or failure to thrive
- Presence of tachypnea, tachycardia and retractions.

Objective assessment of pulmonary blood flow can be made from a chest X-ray (Fig. 1). Features of increased PBF on CXR:

- Cardiomegaly
- Presence of >4 end on vessels in the middle 1/3rd of the lung field
- If >6 vessels can be traced to the lateral 1/3rd.

Small left to right shunts may not show the presence of either the clinical parameters or CXR findings of increased pulmonary blood flow.

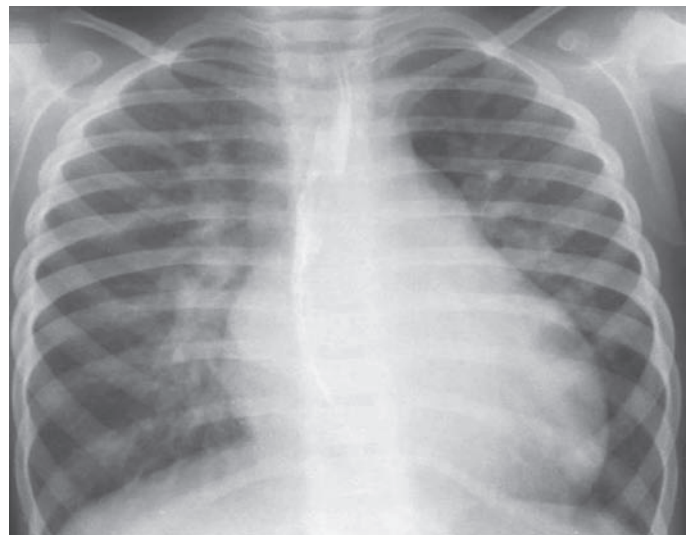


Fig. 1: CXR showing cardiomegaly with increased pulmonary blood flow

Presenting Features and Age of Presentation

Clinical presentation and age of presentation is different for the various acyanotic congenital heart diseases.

Ventricular Septal Defect (VSD)

Patients with large or a moderate sized VSD usually present with history of recurrent LRTI, feeding difficulty and failure to gain weight. These children usually present in early infancy and are quite symptomatic.

Atrial Septal Defect (ASD)

These patients usually present beyond infancy and are usually picked up as a result of a gracile built. They do not present with features of increased blood flow. <10 Percent of patients with ASD present with congestive heart failure.

Patent Ductus Arteriosus (PDA)

Presenting features and age of presentation is almost same as that of patient with VSD.

Obstructive Lesions

These patients are usually asymptomatic except in presence of critical lesions. Symptoms include dyspnea on exertion, chest pain and palpitation.

Clinical Examination

Pulse and Blood Pressure

Examination of pulse and measurement of blood pressure (BP) in all the four limbs helps to diagnose patient with coarctation of the aorta.

- In coarctation lower limb pulses may be feeble or absent. Four limb BP measurements may show evidence of upper limb hypertension.
- Bounding pulses may be present in a child with PDA.

Precordial Activity

- In a large VSD or PDA precordium is usually hyperdynamic
- Hyperkinetic LV apex is usually observed in patients with moderate to large VSD and PDA
- Forceful LV type apex is noted in left side obstructive lesions like AS/coarctation of aorta
- RV heave is a common finding in patient with moderate to severe pulmonary stenosis.

Second Heart Sound

- Accurate auscultation of 2nd heart sound helps to arrive at a workable diagnosis of congenital heart disease
- Wide and fixed split S2 is usually present in patient with ASD

- Closely split S2 with loud P2 is heard in presence of large VSD
- Wide and variable split S2 with normal intensity of P2 is usually found in cases of moderate VSD
- Second heart sound may be normal in patients with small VSD, mild to moderate PS and in patients with congenital aortic stenosis of any severity
- Wide and variable split second heart sound with soft pulmonary component is found in patients with moderate to severe pulmonary stenosis.

Murmur

Pansystolic murmur: Presence of pansystolic murmur in patients of acyanotic congenital heart disease indicates:

- *Moderate VSD:* Murmur at left parasternal area.
- *Tricuspid regurgitation:* Murmur heard at left parasternal area increasing on inspiration
- *Mitral regurgitation:* Murmur best heard at the apex and radiating to the axilla.

Systolic ejection murmur:

- *Aortic stenosis:* Systolic ejection murmur of AS is best heard in the right and left upper parasternal area and radiating to the carotids.
- *Pulmonary stenosis:* Murmur is best heard in the pulmonary area and radiates to the lung fields. The murmur is usually of harsh quality.
- *Large VSD:* Systolic ejection murmur of a large VSD is best heard in left upper parasternal area and is usually of a short duration. The intensity of the murmur is usually grade 2.

Continuous murmur: Continuous murmur heard in the left infraclavicular area is usually due to a small to moderate patent ductus arteriosus.

Chest X-ray (CXR)

ASD (Fig. 2)

- Cardiomegaly
- Right atrial enlargement
- Dilated main pulmonary artery
- Increased pulmonary vascular markings.

VSD (Fig. 3)

- Cardiomegaly
- Left ventricular enlargement
- Increased pulmonary vascular markings.

PDA (Fig. 4)

- Cardiomegaly
- Left ventricular enlargement
- Increased pulmonary vascular markings
- Prominent aorta.



Fig. 2: CXR showing cardiomegaly with right atrial enlargement with increased pulmonary blood flow



Fig. 3: CXR shows cardiomegaly with left ventricular enlargement with increased pulmonary blood flow

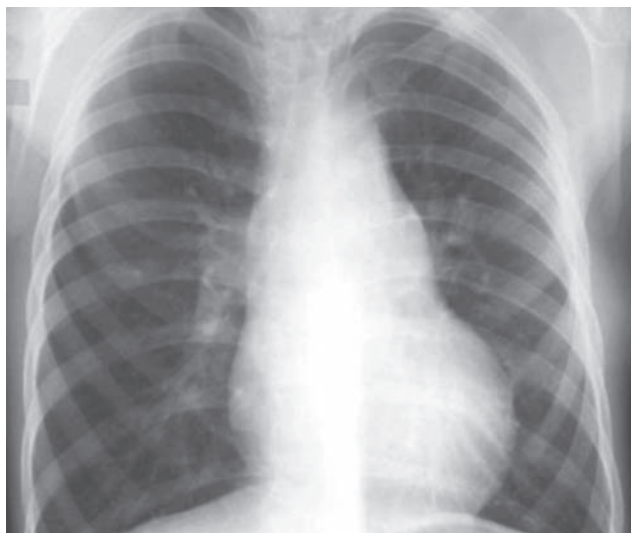


Fig. 4: CXR showing mild cardiac enlargement with left ventricular type apex with prominence of aortic Knuckle and normal pulmonary blood flow (CXR of small PDA)



Fig. 5: CXR showing normal cardiac silhouette with normal pulmonary vascular markings with prominent main pulmonary artery (poststenotic dilatation) in a case of severe valvular pulmonary stenosis

CXR of PS (Fig. 5)

- Normal size heart
- Dilated main pulmonary artery (MPA) and left pulmonary artery (LPA)
- Normal pulmonary vascular markings.

CXR of AV Canal Defect (Fig. 6)

- Cardiomegaly
- Left atrial and left ventricular enlargement
- Increased pulmonary blood flow.

ECG**ASD (Fig. 7)**

- Right axis deviation
- Right atrial enlargement
- Rsr' in V1

VSD/PDA (Fig. 8)

- Normal axis, right axis deviation seen in presence of pulmonary hypertension
- LVH (volume overload type)
- Biventricular hypertrophy seen in patients with Large VSD.

AV Canal Defect (Fig. 9)

- Superior axis
- Biventricular hypertrophy.

AS/COA (Fig. 10)

- Normal or left axis
- Left ventricular hypertrophy.

PS (Fig. 11)

- Right axis deviation
- Right ventricular hypertrophy.



Fig. 6: CXR showing cardiomegaly with increased pulmonary blood flow

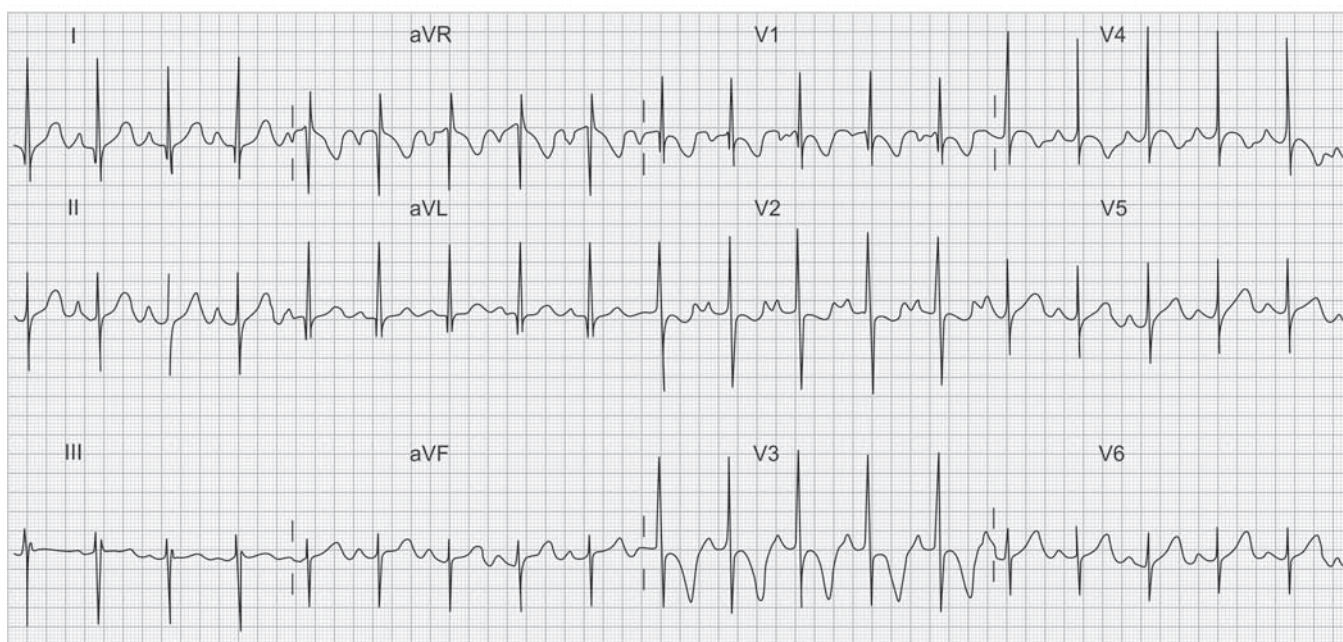


Fig. 7: ECG of a child with secundum ASD showing RSR' pattern in lead V1

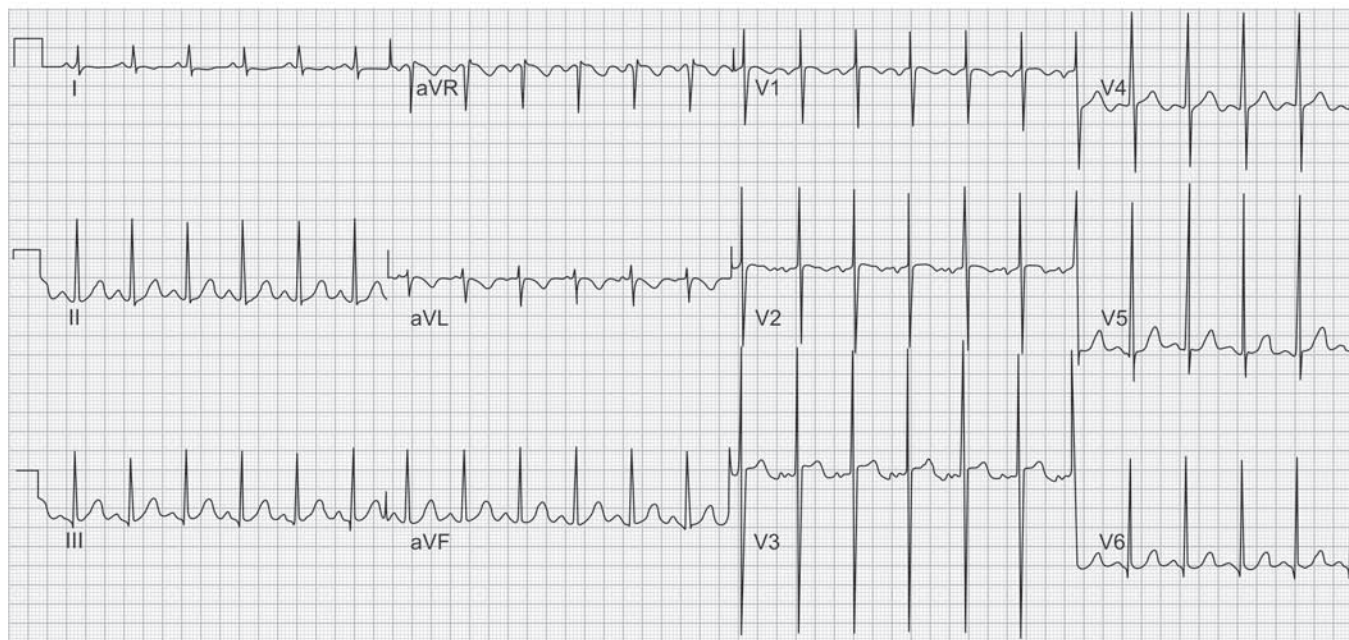


Fig. 8: ECG of a child with moderate ventricular septal defect showing normal axis with evidence of left ventricular volume overload

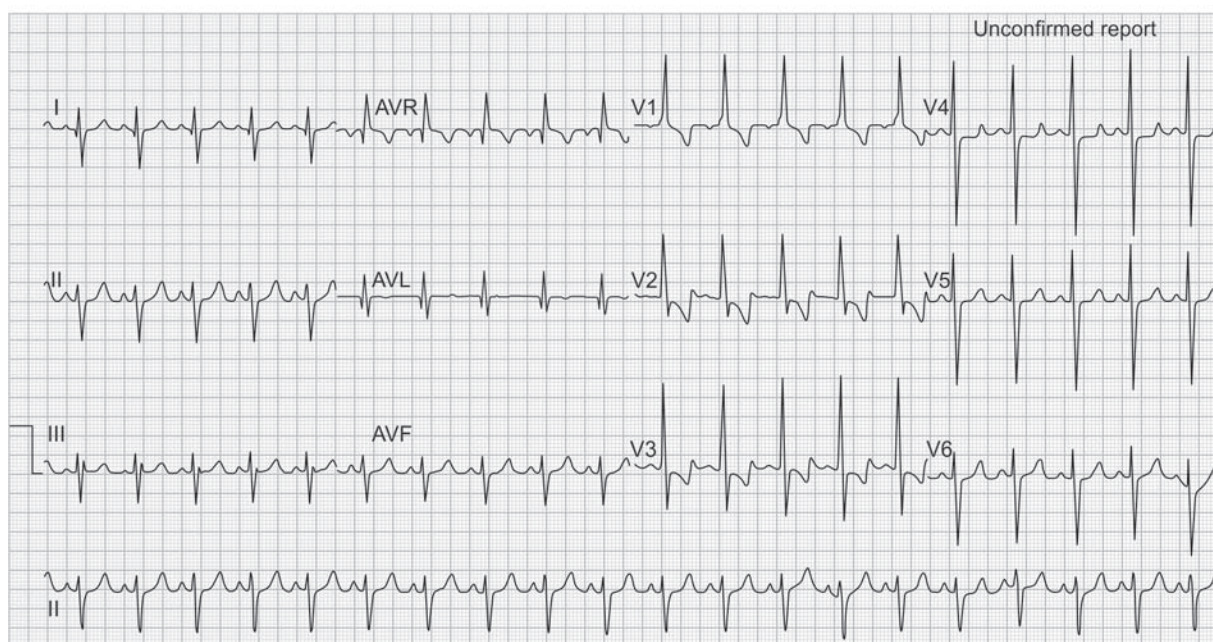


Fig. 9: ECG of a patient with complete AV canal defect showing northwest axis with right ventricular hypertrophy

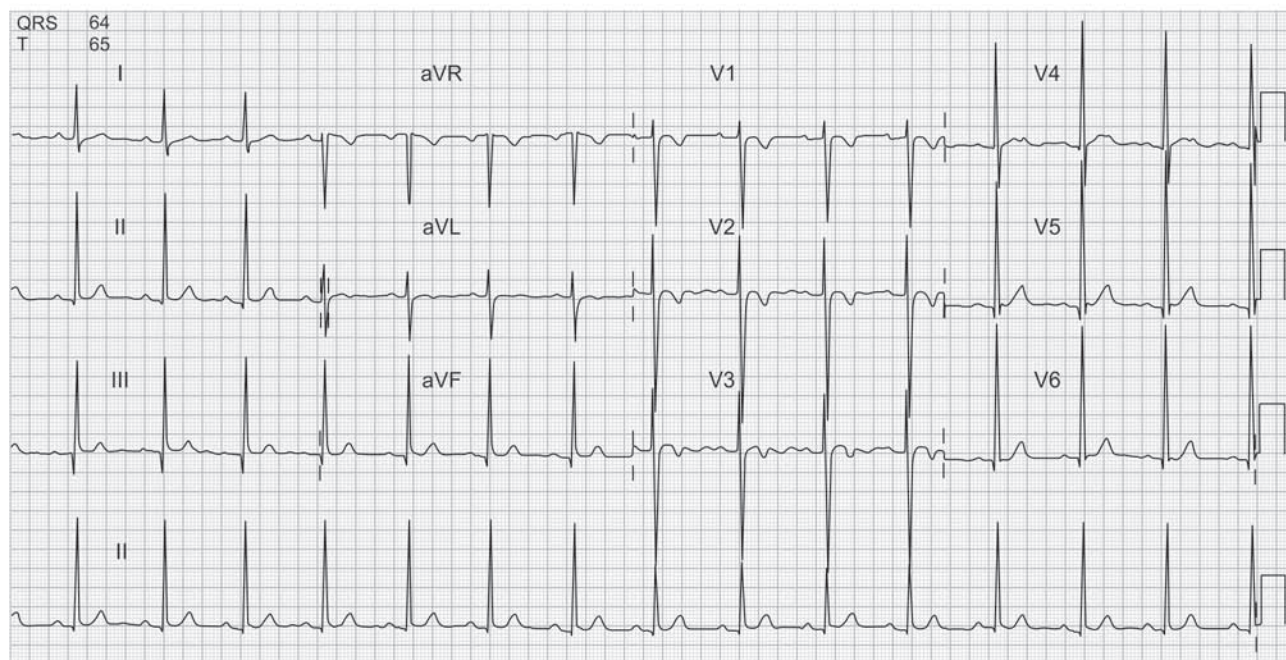


Fig. 10: ECG of a patient with severe coarctation of aorta showing normal axis with left ventricular hypertrophy

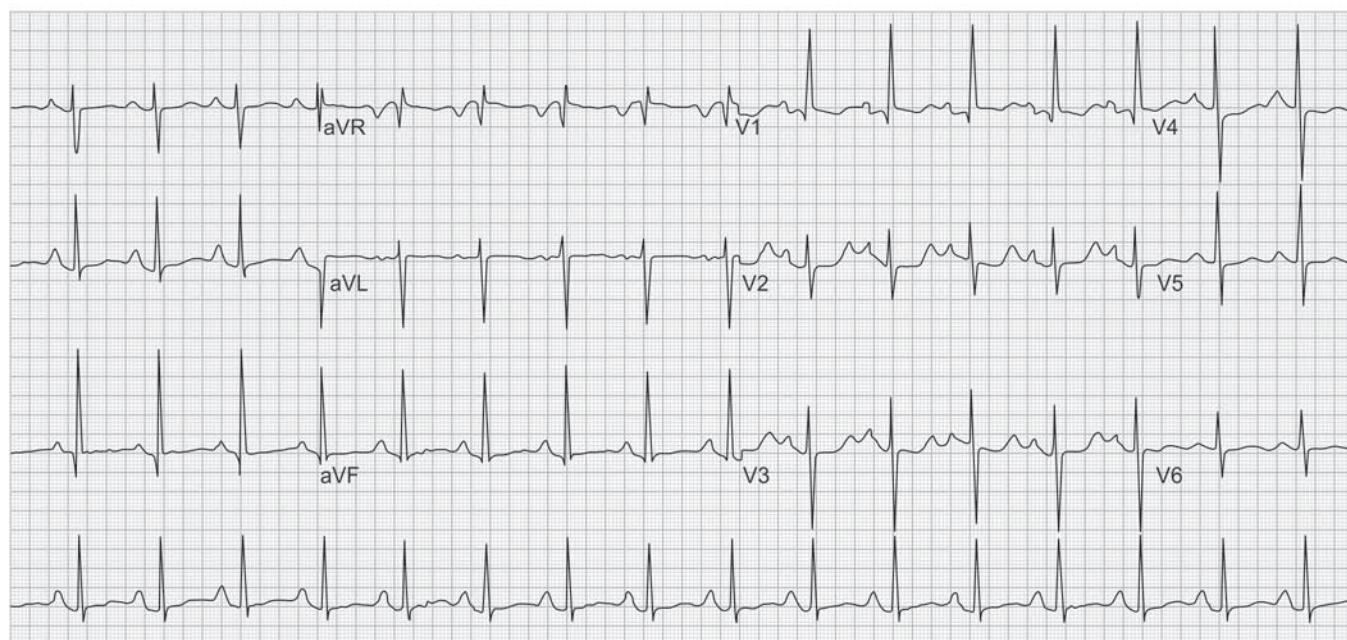


Fig. 11: ECG showing right axis deviation with monophasic R wave in V1 suggestive of right ventricular hypertrophy

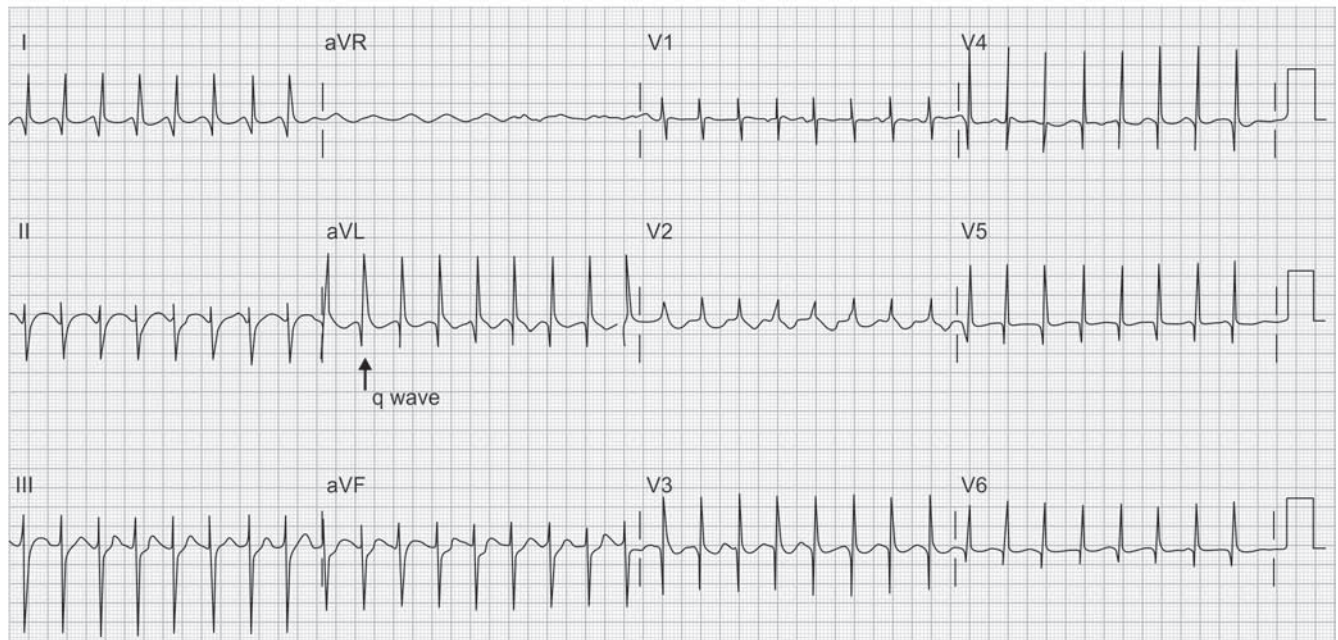


Fig. 12: ECG of a child with anomalous origin of the left coronary artery from pulmonary artery showing prominent q waves with lead I and aVL

ALCAPA (Fig. 12)

- Q in lead I and aVL.

CONCLUSION

To summarize it is very essential to classify congenital heart disease as this classification forms the basis of approach to these patients. Clinical approach supplemented with chest X-ray and ECG can help to arrive at a working diagnosis of the lesions. This can assist to initiate management in these patients before they are referred for further evaluation and management.

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Cyanotic Congenital Heart Disease: A Diagnostic Approach

Neeraj Agarwal

INTRODUCTION TO CYANOSIS

Congenital heart defects are classified into two groups namely acyanotic congenital heart disease and cyanotic congenital heart disease (CCHD).¹ Cyanosis (Greek word meaning dark blue) can be central or peripheral, where central cyanosis is characterized by blue discoloration of nails and mucous membranes. It must be remembered that mild degree of desaturation may not be visible to naked eyes and can only be picked up by pulse oximetry.

Cyanosis is a serious sign (Table 1) and needs to be picked up as early as possible. There are different confounding factors (Table 2) which can mask the diagnosis or may lead to erroneous diagnosis of cyanosis. Naked eyes

Table 1: Principal causes of cyanosis

- *Peripheral cyanosis*
Cold, hypovolemia, low cardiac output, and autonomic vasomotor instability in newborn
- *Central cyanosis*
 - Respiratory disorders
Respiratory distress syndrome (hyaline membrane disease), pneumonia, bronchiolitis, asthma, pneumothorax, airway obstruction and bronchopulmonary dysplasia, pulmonary malformations, cystic fibrosis and various other congenital lesions in the newborn compromising the airways (e.g. diaphragmatic hernia, tracheo-oesophageal fistula, Choanal atresia and others).
 - Cardiovascular disorders
 1. Congenital heart disease with decreased pulmonary blood flow.
 2. Congenital heart disease with normal or increased pulmonary blood flow.
 3. Persistent pulmonary artery hypertension of the newborn.
 4. Pulmonary vascular disease (Eisenmenger physiology).
 5. Pulmonary arteriovenous malformation.
 - Neurological disorders including central apnea/drug induced apnoea and respiratory neuromuscular dysfunction like spinal muscular atrophy.
 - Abnormal hemoglobin: Methemoglobinemia

Table 2: Difficulty in diagnosis of cyanosis

Over diagnosis of CCHD

- Peripheral cyanosis
- Respiratory disease mimicking cyanotic heart disease
- Pulmonary congestion due to left to right shunts
- Cold extremities or shock with falsely low readings

Missed diagnosis of CCHD

- Mild cyanosis (frequently CCHD with high pulmonary flow)
- Anemia (at least 3 gm % of desaturated hemoglobin needed to manifest as cyanosis)
- Dark skin (naked eyes may miss cyanosis)

can usually pick up the cyanosis when saturation is less than 85 percent with a hemoglobin level of 12 to 13 gm percent. But there are various factors which will determine the visibility of cyanosis in a particular subject. Cyanosis is dependent on absolute concentration of deoxygenated hemoglobin (Hb) and not on the ratio of deoxygenated to oxygenated hemoglobin. Cyanosis will be visible to eyes if absolute deoxygenated hemoglobin is at least 3 gm percent in arterial blood (approximate equivalent of 5 gm percent in capillary blood). So if patient is anemic where total Hb level is low, the visibility of cyanosis will also be less or in other words, amount of desaturation has to be less to be visible to naked eyes in an anemic patient compared to a patient with normal Hb. Similarly, polycythemia patient may exhibit visible cyanosis even at 90 percent saturations (provided total deoxygenated Hb level is at least 3 gm%).

PERIPHERAL CYANOSIS

When peripheral vasoconstriction results in decreased peripheral perfusion, more oxygen is extracted from peripheral blood. Decrease in oxygen content of venous blood produces bluish discoloration. Patients with peripheral cyanosis have normal systemic arterial oxygen saturation.

Causes of peripheral cyanosis include vasomotor instability as seen in neonates, vasoconstriction caused by exposure to cold or hypovolemia, elevated venous pressure as in congestive heart failure (CHF), polycythemia, and low cardiac output. Polycythemia leads to increase in blood viscosity which impairs capillary blood flow producing excessive amount of reduced Hb. The increased extraction of oxygen results from sluggish movement of blood through the capillary circulation. To obviate the influence of cold temperature, infants should be examined for assessment of cyanosis while quiet in a neutral thermal environment. Although peripheral cyanosis is seen in conditions in which the infant is exposed to a cold environment, it could also be the presenting sign of serious conditions such as sepsis, hypoglycemia, or low cardiac output; hence peripheral cyanosis should not be ignored unless other conditions have been ruled out.

DIFFERENTIAL CYANOSIS

In this scenario, lower part of body is cyanotic and upper part of body is pink. This is seen in conditions in which there is right to left shunt from the pulmonary artery to the descending aorta through the patent ductus arteriosus (PDA). Any condition that gives rise to right-to-left shunt through the PDA is likely to give rise to differential cyanosis. Common examples include interrupted aortic arch with PDA and persistent pulmonary hypertension of newborn (PPHN). In reverse differential cyanosis, the upper part of the body remains cyanotic while the lower part of the body remains pink. Examples include transposition of the great arteries (TGA) with pulmonary hypertension and shunt through PDA, and also TGA with left ventricular outflow obstruction.

CLASSIFICATION OF CYANOTIC CONGENITAL HEART DISEASE (CCHD)

In cyanotic congenital heart disease, deoxygenated blood bypasses the pulmonary circulation and enters into the systemic circulation causing systemic deoxygenation. That means there should be a right to left shunt either at atrial level, ventricular level or great arteries level to cause cyanosis. CCHD does not include pulmonary right to left shunt (e.g. pulmonary arteriovenous malformations) and other noncardiac causes of cyanosis. Figure 1 illustrates an example of noncardiac cause of cyanosis.

There is an endless list for cyanotic congenital heart defects with various combinations and thus various classifications. Physiology is a practical classification system because physiology is what is dealt with clinically and CCHD patients can be grouped physiologically mainly into two groups—CCHD with low pulmonary blood flow, CCHD with high pulmonary blood flow.²⁻⁴ Admixture lesions are also a group in the classification system where cyanosis

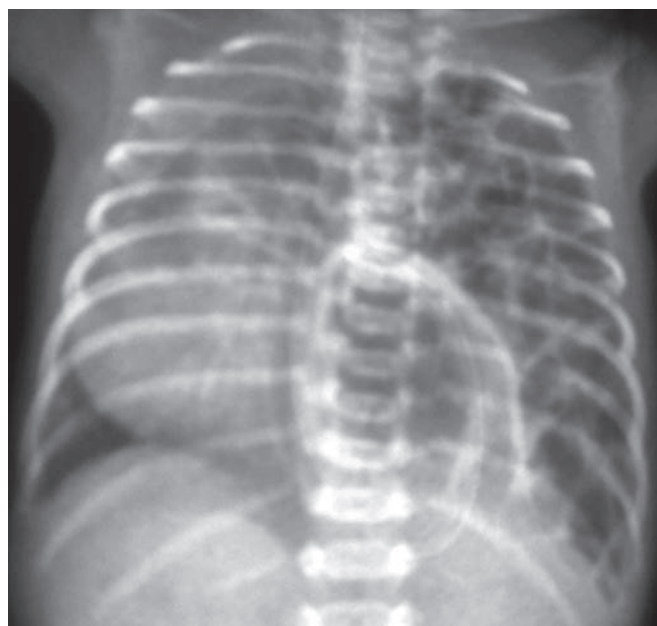


Fig. 1: This newborn presented with respiratory distress and desaturation at birth. Chest X-ray showed left diaphragmatic hernia with mediastinal shift

results from obligatory mixing of desaturated blood with oxygenated blood.⁵ This can occur at venous level {(total anomalous pulmonary venous connection (TAPVC))}, atrial level (common atrium), ventricular level (single ventricle) or great arterial level (Truncus arteriosus) or TGA where partial mixing can occur at the level of atrial septal defect (ASD), ventricular septal defect (VSD) or PDA.

Although some combinations may have a balanced physiology and normal pulmonary blood flow for some time, they usually end up in either of these two subgroups. For example, a case of VSD and moderate pulmonary stenosis may be balanced enough to be asymptomatic or mildly cyanotic for a long time and as the severity of pulmonary stenosis increases over time, pulmonary blood flow will decrease and child will become more cyanotic. Similarly, a case of high pulmonary blood flow if left unoperated and pulmonary vascular resistance increases, then Eisenmenger physiology will develop where pulmonary blood flow is low.

There are few other groups in this classification system that cover lesions which are not commonly encountered. One of them is cyanotic heart disease without PS but normal pulmonary blood flow like SVC entering the left atrium. Pulmonary AVM is not a CCHD but this also presents with cyanosis and normal pulmonary blood flow. The other notable group is neonates presenting with features of pulmonary venous congestion like obstructed TAPVC/hypoplastic left heart syndrome (HLHS) with restrictive PFO (these lesions are separately covered in neonatal cardiac chapters).

Table 3: Cyanotic congenital heart defects—5 Ts to remember

Tetralogy of Fallot (TOF)
Tricuspid valve abnormalities—tricuspid atresia, tricuspid stenosis, tricuspid valve displacement (Ebstein anomaly and other Ebstein like malformations)
Truncus arteriosus
Total anomalous pulmonary venous connection
Transposition of great arteries

Famous 5T's can be remembered as the most commonly encountered cyanotic congenital heart defects. (Table 3)

ASSESSMENT OF PULMONARY BLOOD FLOW (QP)

As already described, cyanotic congenital heart disease is practically classified into two physiological groups based on pulmonary blood flow. The next critical question is how to assess pulmonary blood flow (Qp) in various clinical scenarios. There are few signs and symptoms which can help us in deciding the pulmonary blood flow and objective assessment of pulmonary blood flow can be done accurately with the help of Chest X-ray (CXR).^{3,4}

The features of high pulmonary blood flow are recurrent chest infections, failure to thrive, excessive sweating on feeding/activity, feeding difficulty with suck rest suck cycle and subcostal chest in drawing. On examination, they have hyperactive precordium with cardiomegaly and flow murmurs across pulmonary valve due to excessive blood flow. They may have tachypnea, tachycardia and other signs of CHF. One more clue in examination is presence of Harrison's sulcus which indicates the presence of high pulmonary blood flow since long time.

The features of low pulmonary blood flow in cyanotic heart lesions are mainly dyspnea on exertion, squatting episodes and hypercyanotic spell. On examination, they will have quiet precordium, no or minimal cardiomegaly and ejection systolic murmur of right ventricular outflow tract obstruction (although all cases will not have murmur like in pulmonary atresia there is no outflow tract obstruction murmur). Typically, they don't have predisposition to recurrent chest infections and other features of CHF (Unless there is secondary cause for CHF like anemia) due to protective effects of right ventricular outflow tract obstruction.

Objective assessment of pulmonary blood flow is by chest X-ray (Fig. 2). Signs of high pulmonary blood flow on chest X-ray will be cardiomegaly and increased pulmonary vascularity evidenced by more than 4 end vessels in the middle third of lung fields or more than 6 vessels traceable to lateral third of lung fields.

Assessment of pulmonary blood flow is very useful clinical assessment and management of most of the cyanotic heart lesions can be started after assessing the

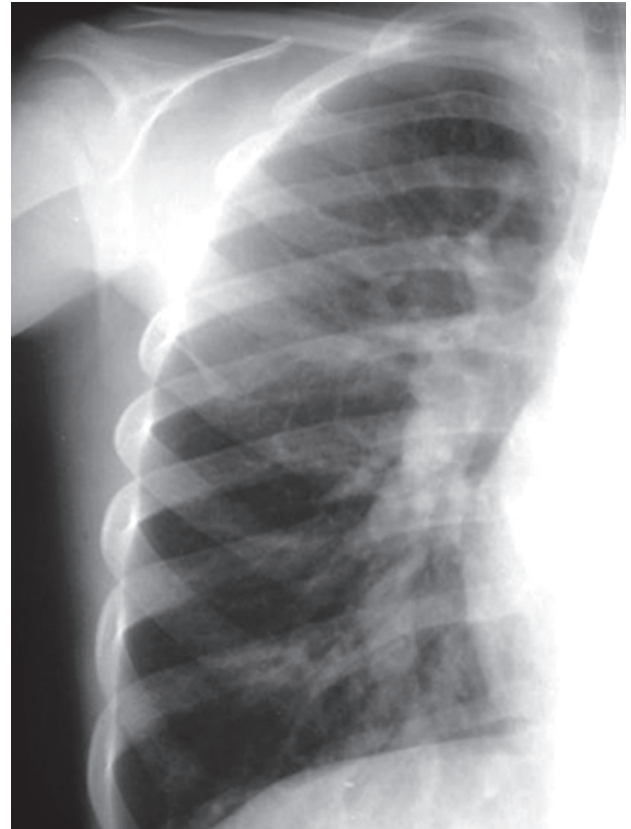


Fig. 2: Chest X-ray showing high pulmonary blood flow. Note the proximal dilated pulmonary arteries and pulmonary vasculature extending up to distal third of lungs. Also seen are dilated end on vessels in middle-third of lungs

pulmonary blood flow. Medical management of CCHD with low pulmonary blood flow is mainly on the lines of TOF physiology. They are given β -blockers, plenty of fluids and measures to prevent iron deficiency anemia. The lesions which present with high pulmonary blood flow are managed with diuretics and digoxin till the surgical plan is formulated.

CCHD WITH LOW PULMONARY BLOOD FLOW (TABLE 4)

This group is characterized by tetralogy of Fallot (TOF) and various other defects presenting as TOF physiology namely tricuspid atresia, VSD and pulmonary stenosis (PS), DORV VSD PS, TGA VSD PS, corrected TGA VSD PS, pulmonary atresia with or without VSD and various other single ventricular anomalies with PS (Figs 3 and 4). Ebstein anomaly also behaves as CCHD with low pulmonary flow; due to lack of forward flow across right ventricular outflow tract and intracardiac right to left shunt across ASD/ PFO (Fig. 5). Similarly critical pulmonary stenosis also has low pulmonary blood flow and right to left shunt across interatrial communication (as ASD or

Table 4: CCHD with low pulmonary blood flow

- Tetralogy of Fallot
- Tricuspid atresia, VSD and PS
- DORV, VSD and PS
- TGA, VSD and PS
- VSD with PS
- AV canal defect with PS
- Pulmonary atresia with/without VSD
- Pulmonary atresia with various other malformations (Univentricular or biventricular)
- CTGA, VSD, PS
- Ebstein's anomaly
- Univentricular heart with pulmonary stenosis
- Miscellaneous complex malformations with obstruction to pulmonary blood flow

DORV=Double outlet right ventricle; TGA=Transposition of great arteries; CTGA=Corrected transposition of great arteries; PS=pulmonary stenosis.

PFO) causing cyanosis but this is grouped as Acyanotic congenital heart disease.

Typical features of TOF physiology are history of dyspnea on exertion, squatting episodes or cyanotic spells. As pulmonary blood flow is reduced in this subgroup, there is no propensity for recurrent chest infections, sweating or other manifestations of congestive heart failure. Examination in TOF physiology reveals quiet precordium, no cardiomegaly and ejection systolic murmur of right ventricular outflow obstruction. Second heart sound is usually single in TOF physiology (either due to absent P2 in pulmonary atresia, not heard due to posterior pulmonary valve as in TGA or DORV, delayed and soft P2 with dextroposed aorta in TOF with virtually single S2). In TOF physiology, if cyanosis is out of proportion to murmur or apex is left ventricular type, then lesions other than TOF must be given consideration. In case of TOF, longer the ejection systolic murmur (ESM) of outflow tract obstruction

better is the saturation and if patient has long ESM with lower saturations then lesions other than TOF should be considered. Multiple heart sounds and clicks with low pressure pansystolic murmur of TR should raise possibility of Ebstein's anomaly of tricuspid valve.

Chest X-ray in TOF physiology will show no cardiomegaly and diminished pulmonary vascular markings. Figure 3 shows a classical boot shaped heart with upturned right ventricular apex and low QP. Chest X-ray will also help in determination of type of apex. Right ventricular apex with oligemic lung fields will include the possibility of TOF, DORV, VSD with PS or pulmonary atresia with VSD (Remember pulmonary atresia patient will not have

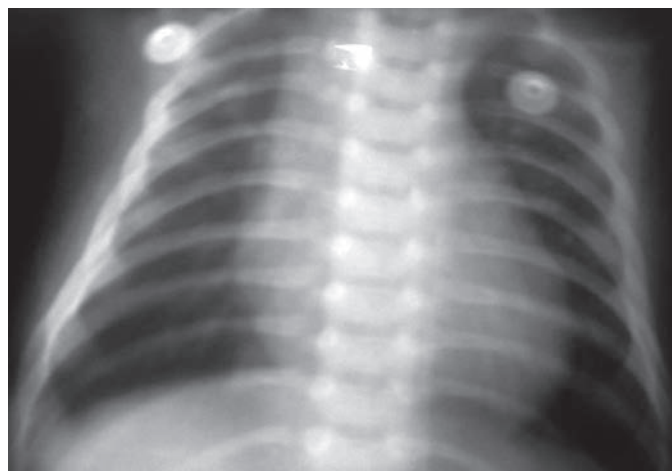


Fig. 4: Chest X-ray showing left ventricular type of apex with pulmonary oligemia. There is no cardiac enlargement. Echo showed tricuspid atresia, VSD and pulmonary stenosis. This three-month-old child presented with resistant cyanotic spells and underwent immediate BT shunt surgery

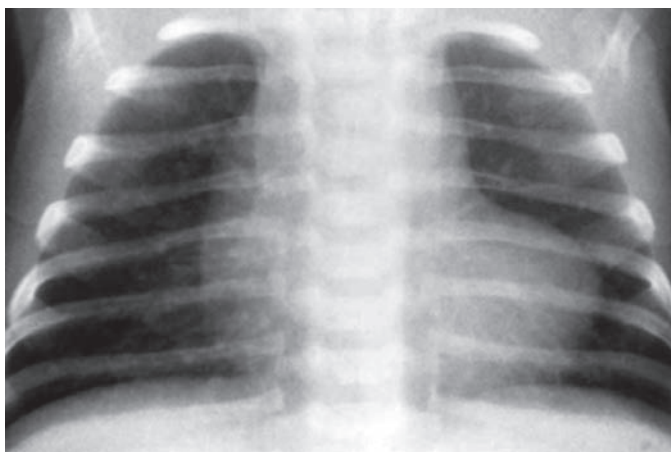


Fig. 3: Classical chest X-ray of tetralogy of Fallot showing boot shaped heart (right ventricular type of upturned apex) with small hila and reduced pulmonary blood flow

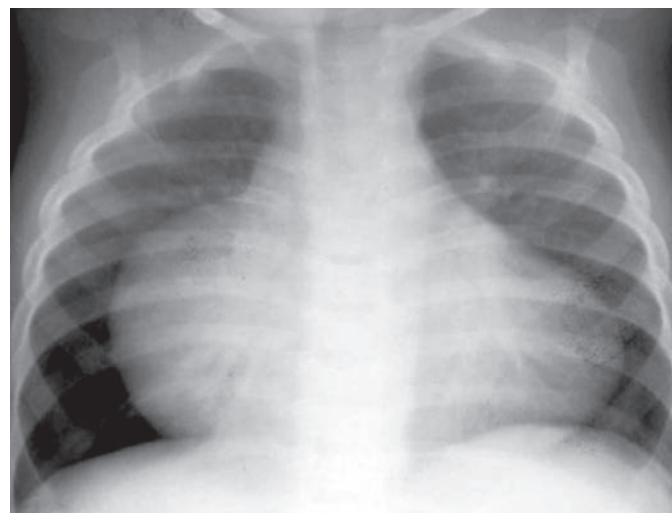


Fig. 5: Chest X-ray showing cardiomegaly and typical box shaped heart seen in Ebstein anomaly. Pulmonary blood flow is oligemic. This neonate presented at day 3 of life with cyanosis when PDA got smaller and was started on prostaglandin E1 infusion to open PDA for improving saturations

ESM of right ventricular outflow tract obstruction). Left ventricular apex should point towards tricuspid atresia or pulmonary atresia with intact ventricular septum. Ebstein anomaly will have a box like configuration with enlarged right atrium, narrow upper mediastinum and enlarged leftward convexity of enlarged infundibulum (Fig. 5).

ECG has a tremendous value in the differential diagnosis of various lesions in TOF physiology. Right axis deviation (RAD), right ventricular hypertrophy (RVH) and early transition from V1 to V2 will point towards diagnosis of TOF (tall monophasic R wave in lead V1 and then abrupt change to rS pattern in lead V2 as in Figure 6) where as right axis deviation with counter clock loop and prolonged PR interval will favor diagnosis of DORV. Left axis deviation with counterclockwise depolarization (Q waves in lead I and aVL) will be seen in TOF with atrioventricular septal defect (AVSD). Left axis deviation with counter clock depolarization along with left ventricular hypertrophy (LVH) is a feature of tricuspid atresia (Fig. 7) where as normal/rightward QRS axis and clockwise depolarization with left ventricular hypertrophy is seen in pulmonary atresia with intact ventricular septum. Biventricular hypertrophy (BVH) will be a feature of TGA, VSD PS, DORV VSD PS and Eisenmenger. Typical ECG changes in Ebstein anomaly are Himalayan tall peaked P waves, prolonged PR interval, bizarre second QRS attached to preceding normal QRS (Fig. 8). Some of these Ebstein patients may have Wolff-Parkinson-White pre-excitation or supraventricular tachycardia. Atrioventricular conduction

disturbances varying from first degree heart block to complete heart block along with presence of Q waves in right precordial leads and absent Q waves in left precordial leads may suggest CTGA. Single ventricular anatomy may be manifested by stereotyped QRS patterns.

CCHD WITH HIGH PULMONARY BLOOD FLOW (TABLE 5)

This group of disorders encompasses complex cyanotic heart defects which has torrential pulmonary blood flow and present in early infancy with features of congestive heart failure (when neonatal pulmonary vascular resistance drops). This group of disorders is predisposed to early congestive heart failure and 90 percent of these patients, if untreated don't survive beyond their first birthday. Compared to their counterparts of acyanotic congenital heart disease with high pulmonary flow, they tend to present earlier at around 2 to 3 weeks of age with feeding difficulty where infant takes feed for a while, gets tired and leaves the breast and then again starts taking feed (suck rest suck cycle). Parents may notice sweating while feeds and subcostal chest in-drawing. They have difficulty in taking feeds, high energy expenditure due to increased work of breathing and repeated chest infections leading to failure to thrive. Some may have an episode of lower respiratory tract infection needing hospitalization as first presentation.³

Examination in such cases reveals minimal cyanosis (saturation in the range of high 80s and in some cases

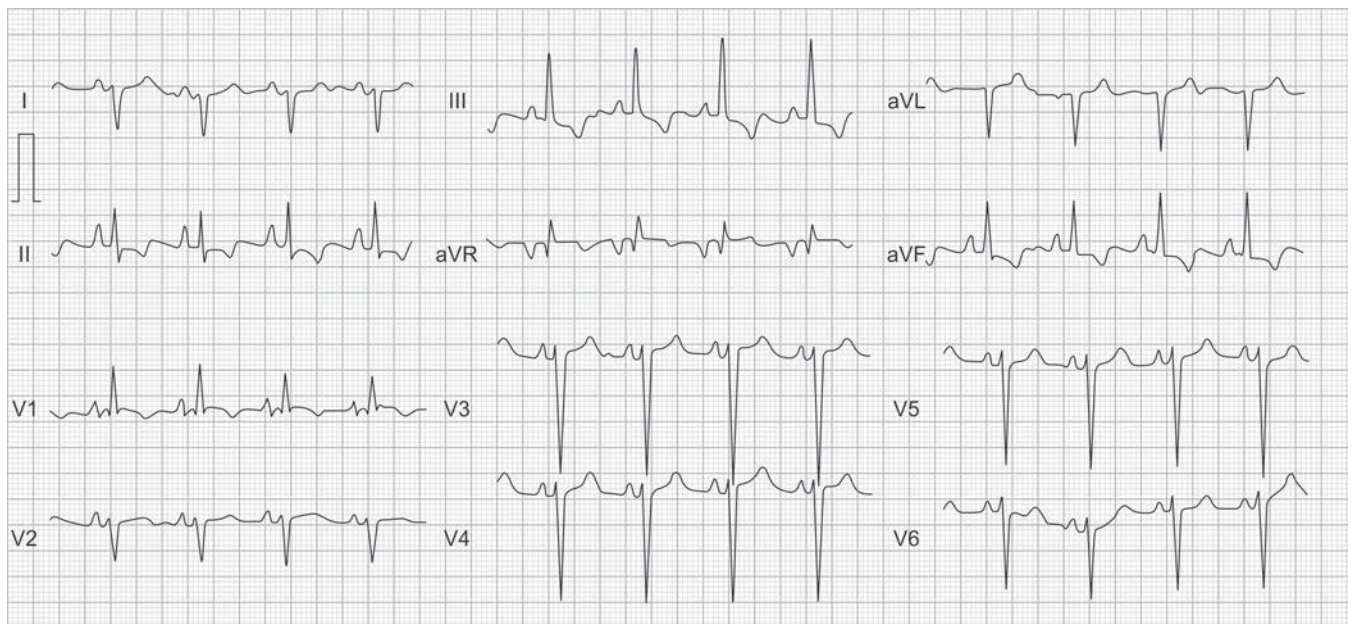


Fig. 6: This patient presented with features of TOF physiology. ECG showing right axis deviation with right ventricular hypertrophy. Note the upright R wave in V1 and predominant S wave in V6 suggestive of right ventricular hypertrophy. Sudden transition of R wave in V1 to S wave in V2 is highly suggestive of TOF

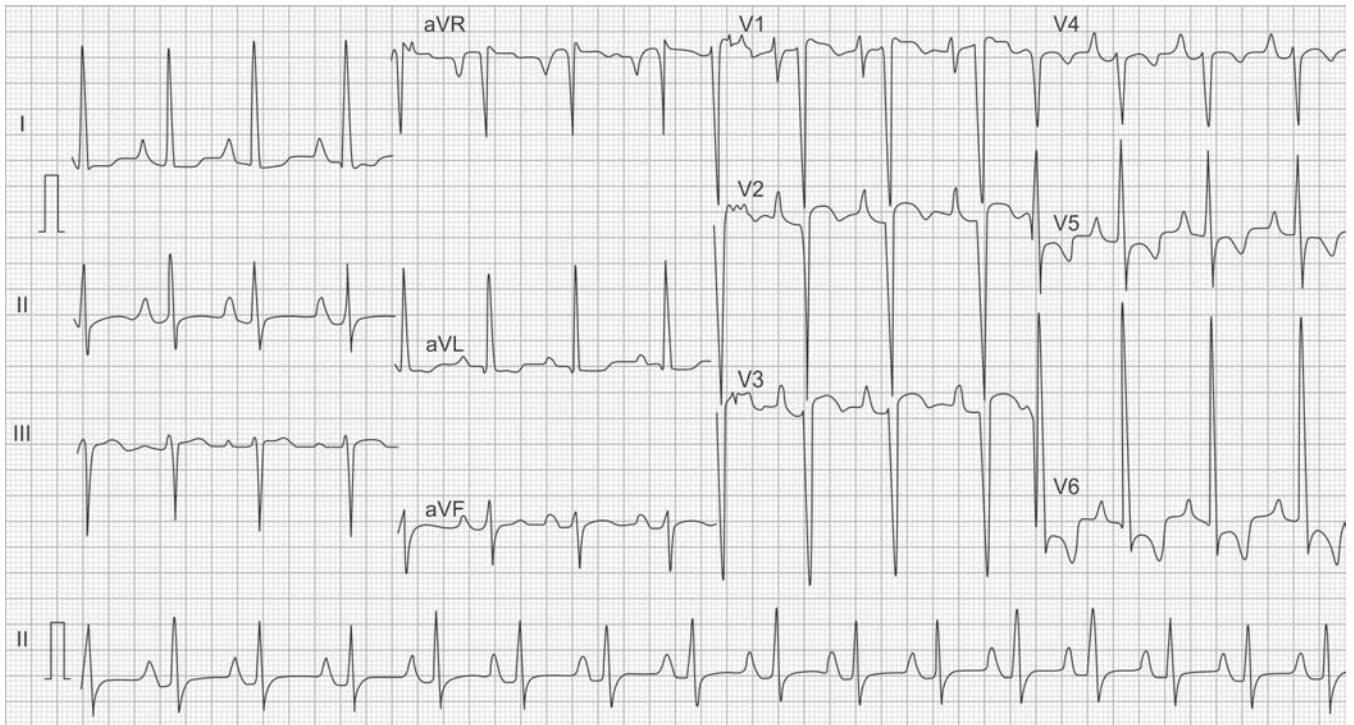


Fig. 7: 12-lead electrocardiogram in a patient of tricuspid atresia demonstrating left axis deviation. Also note deep S waves in right chest leads and tall R waves in left chest leads indicative of left ventricular hypertrophy and very little right ventricular forces suggestive of small right ventricle. Also note tall P waves suggestive of right atrial enlargement, all typical features of tricuspid atresia

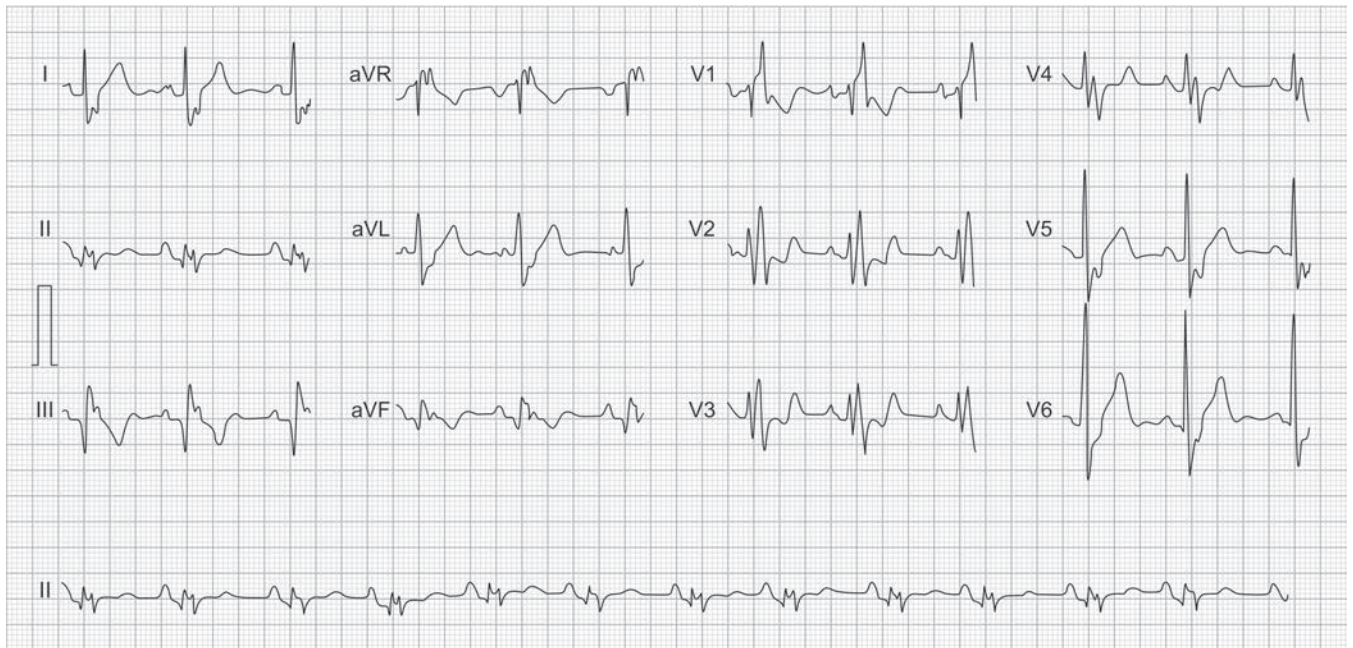


Fig. 8: ECG in Ebstein's anomaly of tricuspid valve showing right bundle branch block pattern with polyphasic and splintered QRS. The QRS is wide and lead V2 shows rS pattern mimicking right bundle branch block. Lead II shows multiple small deflections (splintered QRS)

above 90) which may be picked up by pulse oximeter only. Lower degree of saturation is due to high pulmonary blood flow going to lungs for oxygenation. Most of these patients will have signs of flow murmur in mitral/tricuspid valve and semilunar valves. Wide fixed S2 split along with signs of high pulmonary blood flow is seen in TAPVC, although in obstructed TAPVC features are mainly of pulmonary hypertension rather than increased pulmonary blood flow. TOF with absent pulmonary valve will have a “to and fro murmur” along with single soft S2 (only soft A2 heard due to dilated pulmonary trunk and P2 is absent due to absent pulmonary valve) giving an impression of sawing wood. Bounding pulses, single loud S2 with harsh ejection systolic murmur in left 3/4th intercostal space, radiating up and to right along with early diastolic murmur and ejection click is specific feature of truncus arteriosus.

Chest X-ray will confirm the high pulmonary vascularity and cardiomegaly. Absence of thymic shadow is commonly seen in CCHD high QP. Characteristic X-ray features can be seen in some cases. Few examples include dilated RA and RV in TAPVC (characteristic Snowman appearance seen only in supracardiac TAPVC as in Figure 9), dilated RA and RV along with massive dilatation of pulmonary trunk and proximal PA branches in TOF with absent pulmonary valve, egg on side appearance in TGA and high take off of pulmonary arteries in truncus arteriosus (Fig. 10).

ECG can be helpful in narrowing down the diagnosis. TAPVC has an rsR' pattern as seen in ASD. LAD with RVH/BVH in DORV Subaortic VSD with high pulmonary flow where as LAD with LVH is seen in tricuspid atresia. RVH is present in TGA, TAPVC, DORV and BVH is seen in truncus and TGA with VSD.

Table 5: Cyanotic congenital heart lesions with increased pulmonary blood flow

1. Tricuspid atresia with nonrestrictive ventricular septal defect
2. Transposition of the great arteries with patent ductus arteriosus or ventricular septal defect or both
3. Double-outlet right ventricle with VSD and without pulmonary stenosis
4. Truncus arteriosus
5. TOF with absent pulmonary valve
6. Univentricular heart with nonrestrictive pulmonary blood flow
7. Total anomalous pulmonary venous connection
8. Miscellaneous complex malformations without obstruction to pulmonary blood flow

CYANOTIC CHD: THE DIAGNOSTIC PATHWAY (TABLE 6)

The most important assessment is done by detailed medical history including antenatal drug intake by mother and perinatal events. Special emphasis should be to determine

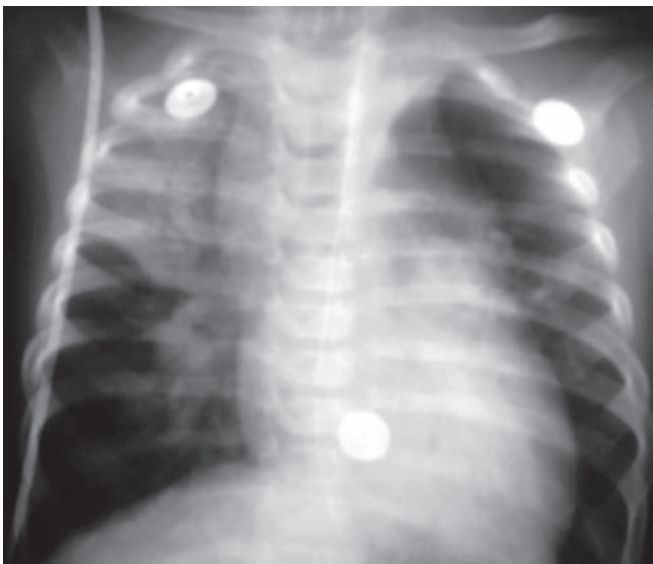


Fig. 9: This is a six-month-old child who presented with right upper zone bronchopneumonia. Examination revealed wide fixed S2 split and saturation of 85 percent. Chest X-ray showing minimal cardiomegaly and wide upper mediastinum and increased pulmonary blood flow. Echo showed supracardiac type of TAPVC. Patient underwent surgical repair after treatment of bronchopneumonia

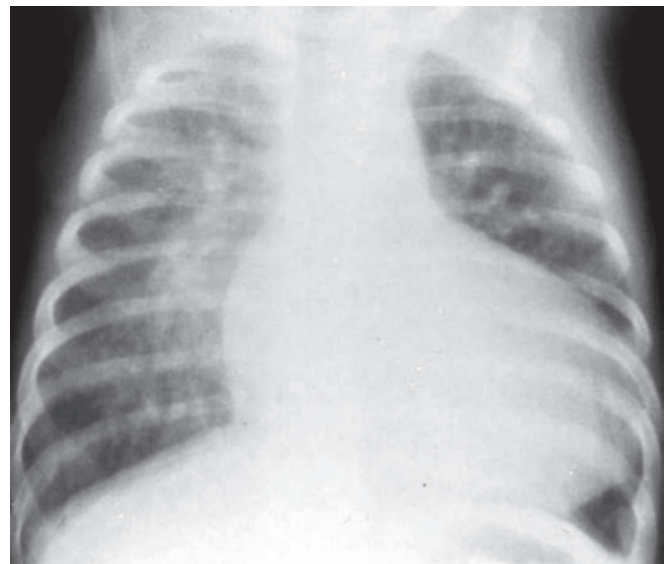


Fig. 10: Chest X-ray showing cardiomegaly with high pulmonary blood flow and narrow upper border of mediastinum. Note the proximal dilated pulmonary arteries and pulmonary vasculature extending up to distal-third of lungs. Also seen are dilated end on vessels in middle-third of lungs. This newborn presented with signs of congestive heart failure at 1 month of age and echo showed truncus arteriosus

Table 6: Cyanotic heart disease evaluation: specific points to remember

History (including prenatal, perinatal events)	Features of low pulmonary blood flow as cyanotic spell, squatting, dyspnea on exertion OR Features of high pulmonary blood flow as recurrent chest infections, failure to thrive, sweating while feeding and feeding difficulty.
Physical examination	Including degree of cyanosis, dysmorphism, femoral pulse palpation, determination of viscero-cardiac situs and detailed cardiac evaluation. Signs of high pulmonary blood flow as hyperactive precordium, cardiomegaly, hepatomegaly and flow murmur across pulmonary valve.
Chest X-ray	Look for situs, signs of high/low pulmonary blood flow, cardiomegaly and distinctive features of certain disorders like snowman appearance in supracardiac TAPVC, boot shaped heart in TOF, and egg on side appearance in TGA.
ECG	Mainly QRS axis and ventricular hypertrophy patterns. Also look for characteristic findings of ECG like Himalayan P waves in Ebstein anomaly, left axis deviation with absence of right ventricular forces in tricuspid atresia.
CT scan/ Angiographic studies	May be needed in some complex cases to delineate specific anatomy like pulmonary artery size or determination of preoperative hemodynamics as in single ventricular palliative procedures.

the onset of cyanosis and to determine features of high versus low pulmonary blood flow based on features described above. Examination should include assessment of cyanosis by pulse oximetry and determination of cardio visceral situs including detailed cardiac assessment with special emphasis on second heart sound (Table 7). Chest X-ray can help in the assessment of pulmonary vascularity, cardiomegaly and situs determination along with exclusion of pulmonary lesions. Look for classical X-ray and ECG features of specific diseases. ECG along with Chest X-ray can help in narrowing down the diagnosis in CCHD⁶ (Flow chart 1 to 3). For example, in a patient with right axis deviation with right ventricular hypertrophy, the most common lesions are TOF, DORV, pulmonary atresia, TAPVC and TGA. Chest X-ray in such cases will narrow down the subgroup with pulmonary plethora (TAPVC, TGA, DORV without PS) or pulmonary oligemia (TOF, pulmonary atresia, DORV VSD PS). Further differential can be made on the basis of predominant ventricular apex and knowledge of ECG and X-ray findings in a specific disease.⁶⁻⁸ This is important to note that neonatal cyanotic heart lesions have a different spectrum and hyperoxia test along with other methods to differentiate cardiac versus

Table 7: Characteristics of second heart sound (S2) in CCHD

Tetralogy of Fallot (TOF)	Single S2 noted. Only A2 heard on bedside despite being soft P2 also. Dilated and dextroposed aorta gives loud A2, severe PS leads to soft delayed P2
TOF with absent pulmonary valve	Single S2 (only A2 heard) due to absent pulmonary valve. A2 is soft due to dilated pulmonary trunk.
Pulmonary atresia	Single S2 (P2 absent and only A2 present)
TGA, CTGA, DORV and other malposed great arteries	Single S2 heard due to malposed great arteries (mainly posterior placed pulmonary artery)
Truncus arteriosus	Single S2 as only one truncal valve present
TAPVC	Wide fixed S2 split
Tricuspid atresia	Many combinations of tricuspid atresia seen. S2 usually single. Associated with pulmonary atresia (only A2), severe PS (soft delayed P2 may not be heard) or associated with malposed great arteries (where only one A2 heard due to posterior placed pulmonary artery)

Table 8: Common causes of cyanosis in neonates*Duct dependent pulmonary circulation*

- Pulmonary atresia, intact ventricular septum
- Pulmonary atresia, VSD and PDA
- Single ventricle with pulmonary atresia
- Severe forms of Ebsteins anomaly

Critical right ventricular outflow tract obstruction with intracardiac shunt

- Critical pulmonary stenosis with interatrial communication
- Tetralogy of Fallot with critical pulmonary stenosis
- Double outlet right ventricle, VSD with pulmonary stenosis

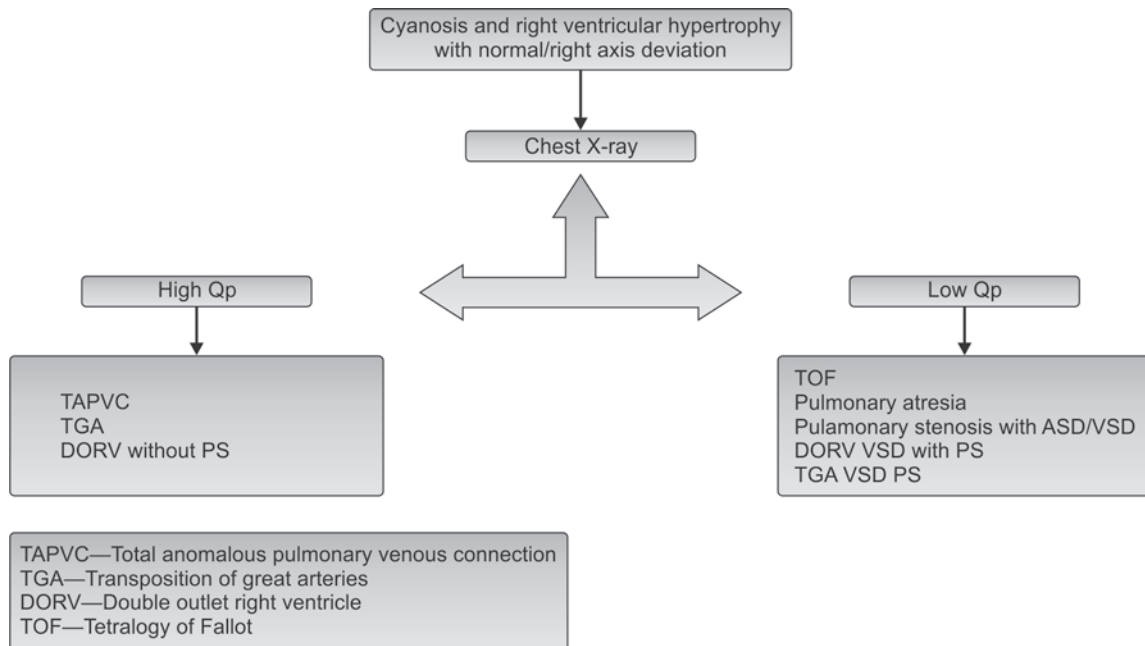
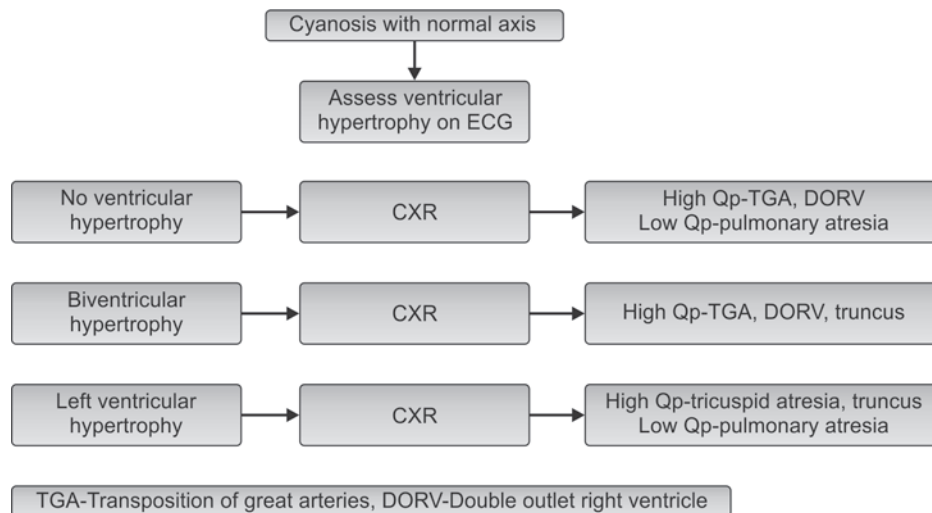
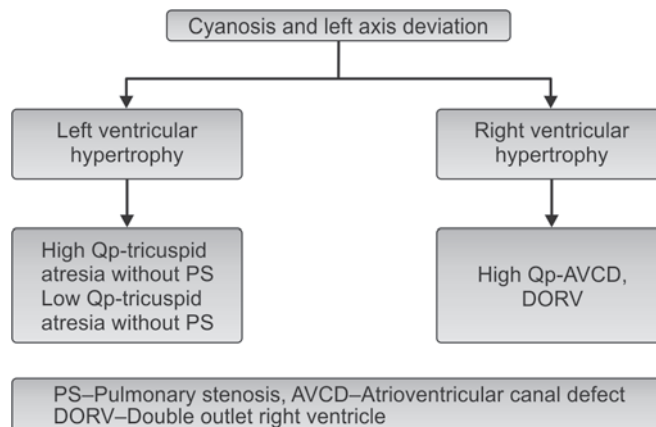
Admixture lesions

- Transposition of great arteries, intact interventricular septum
- Total anomalous pulmonary venous connection
- Truncus arteriosus
- Double outlet right ventricle with VSD
- Single ventricle anomalies with or without pulmonary stenosis

other causes of cyanosis are discussed in other chapters in this book which are dealing exclusively with neonatal cardiac diseases (Table 8).

SUMMARY

Cyanotic congenital heart disease (CCHD) is one of the most complex lesions in cardiology but a mathematical approach can be used to reach a diagnosis. There is no doubt that surprises will happen even with the most

Flow chart 1: A child with cyanosis and right ventricular hypertrophy on ECG**Flow chart 2:** A child with cyanosis and normal axis on ECG**Flow chart 3:** A child with cyanotic heart disease and left axis deviation

experienced clinician in this field, a thorough approach combined with Chest X-ray and ECG should be able to provide a working clinical diagnosis and management can be started before access to echocardiography.

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Evaluation and Management of Arrhythmias in Children

Kiran Viralam

INTRODUCTION

“Cardiac Arrhythmia” refers to the absence of normal sinus rhythm in the heart. Pediatric arrhythmias pose a real diagnostic and therapeutic challenge. The management should be based on an accurate diagnosis obtained from firm foundation of clinical skill and judgment, with judicious use of latest diagnostic modalities. For the diagnosis, management and follow-up of pediatric arrhythmias use of technology is a must, it should optimize the treatment options and monitor the progress. As far as possible, treatment should not be started for a suspected arrhythmia without a baseline electrocardiograph (ECG), preferably a rhythm strip taken for at least 15 seconds duration.

Any treatment given for a potential arrhythmia can subsequently change the ECG tracing. It is virtually impossible to make a rhythm diagnosis on the basis of history and physical findings alone. Any wrong choice in pharmacological therapy initiated prior to diagnosis may have grave consequences on the overall health. However, short half-life drugs like adenosine or DC shock for hemodynamic impairment associated with arrhythmia are exceptions.

Interpretation of ECGs and management of arrhythmias form only a very small part of pediatric practice. Due to this, it is particularly hard to remain familiar with the nuances. Yet the stakes of mistakes are high. Failure to recognize that a syncope, seizure or cardiac failure is secondary to a cardiac arrhythmia may result in inappropriate treatment and a potentially preventable death.

ASSESSMENT

It is important to recognize that arrhythmias can be dangerous when:

- Heart rate is too fast or too slow to sustain cardiac output,
- Arrhythmia is incessant and unrecognized, or
- Arrhythmia is managed badly.

Coexisting structural heart diseases in children causing compromised cardiac function are particularly vulnerable to arrhythmias.

WHAT QUESTIONS TO ASK, WHAT ANSWERS TO SEEK?

During the initial triage, if the child is found hemodynamically compromised with ECG tracing showing arrhythmias, one should immediately proceed towards immediate rescue measures than spending time on detailed history. A tachyarrhythmic patient with hemodynamic instability may require DC shock and one with bradycardia and hemodynamic compromise may require temporary pacemaker insertion. Detailed history can follow once the hemodynamic stability of the patient is ensured.

Children can describe symptoms depending on their age and vocabulary. Older children can describe symptoms like palpitations, chest pain, dizziness, syncope, breathing difficulties or abdominal pain. It would not be inappropriate to ask objective leading questions, if the child finds it difficult to describe the problem, more so when the problem appears genuine.

Few questions that can help in the initial assessment of arrhythmias would be:¹

- How does an episode start and end?
- What precipitates such episodes?
- How frequently do they occur?
- How long does it last?
- How does the child react during such an episode?
- Has the child found or been taught some maneuvers to terminate the episodes?
- Have the parents found any associations with food or medications in the onset of such episodes?
- Is there a family history of arrhythmia, fits, syncope or premature sudden death?

In cases of younger children, especially infants, not much information can be found in history. Parental account of the problem would remain the source of vital clues. History of irritability and poor feeding of sudden onset without any apparent reason can make one suspect arrhythmias as a cause. Congestive heart failure (CHF) may result due to long standing untreated arrhythmias. Infants with features of CHF (sweating during feeds, tachypnea, easy fatigability, lethargy) in the absence of other explanations should draw attention towards a long standing untreated arrhythmia.

Clinical examination should be directed towards assessment of hemodynamic stability. It is usually normal in between attacks. Attention should not only be directed to the cardiovascular system to exclude structural heart disease but also to general examination to detect systemic disorders. Paroxysmal recurrent arrhythmias may have precipitating factors like fever, anemia, hyperthyroidism or structural cardiac diseases like Ebstein's anomaly or infectious causes like viral myocarditis. A careful clinical examination is helpful in determining these causes.

WHAT INVESTIGATIONS ARE REQUIRED?

The most important tool in the diagnosis of arrhythmia is a 12-lead ECG. Even if the child has already reverted to sinus rhythm, ECG would still be helpful in documenting baseline rhythm, axis, hypertrophy patterns, and abnormal configurations like delta wave. Evaluation of repolarization intervals like prolonged corrected QT interval (QTc) and short PR can be made on the baseline ECG.

HOW TO MEASURE QTc²

It is essential to measure the QTc. This is the value of QT corrected to the heart rate. Lead II and lead V5 are the leads to be used for measuring the QTc and the longer of these two should be reported as QTc. It should be remembered that all the measurements should be in seconds and not in milliseconds or number of small squares or big squares in the ECG. The TP segment forms the baseline of ECG. Measurement should begin at the onset of Q wave to the end of T wave, as defined by the point where the steep down slope of the T wave crosses the baseline. This value in seconds gives QT interval. The preceding RR interval is chosen and measured in seconds. The square root of this value should be measured. On dividing QT interval in seconds by the square root of preceding RR interval in seconds will give the value of QTc. A QTc more than 0.45 seconds in males and 0.46 seconds in females is suspicious and requires expert review.

The ECG recorded during the episode of arrhythmia is an invaluable tool for the diagnosis. If the arrhythmias are sporadic, wherein the arrhythmia ceases by the time an ECG is taken, 24-hour ambulatory Holter monitoring can

be very useful. However, when an episode of arrhythmia is much less frequent, an external event recording is handy tool. These recorders can either record continuous ECG tracings for a month or can be triggered to record an event of arrhythmia during symptoms.

If these modalities fail to give any conclusive evidence due to erratic and uncommon symptoms, one newly developed implantable loop recorder may be useful. These loop recorders are implanted in the pectoral region in a subcutaneous or subpectoral pocket and are active for 14 months. The monitor records a single-lead ECG after activation by the patient or parent or automatically, if a preset heart rate algorithm is triggered.³

HOW TO DIAGNOSE ARRHYTHMIA USING THE EVENT ECG?

A well defined algorithmic approach is utilized to diagnose the type of arrhythmia and to plan a treatment protocol. This approach can be used both for tachyarrhythmias (fast heart rate) and bradyarrhythmias (slow heart rate).

TACHYARRHYTHMIAS (Flow chart 1)⁴

Q1: *Narrow QRS complex or wide QRS complex?*

Narrow QRS complex arrhythmia implies normal conduction via AV node and Bundle of His. The QRS measures less than 0.1 seconds. Hence, they are also termed "Supraventricular." They are the most common arrhythmias encountered in children (Fig. 1).

In contrast, wide QRS complex arrhythmias originate usually below the His bundle often in the ventricles. The QRS measures more than 0.1 seconds. However, supraventricular tachycardias with preexisting bundle branch block or conduction aberrancy are exceptions, which occur proximal to AV node and His bundle, but still have wide QRS (Fig. 2).

The algorithm bifurcates here. The narrow complex tachycardia would be dealt first.

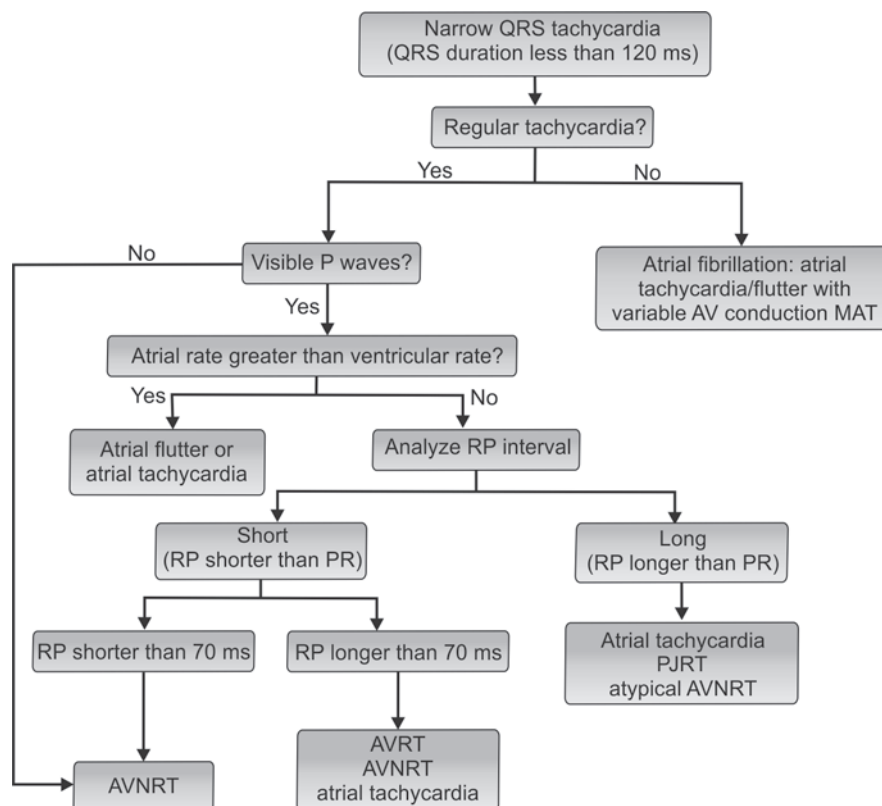
Q2: *Are the RR intervals regular?*

Irregular RR intervals occur either in atrial fibrillations or multifocal atrial tachycardia or atrial tachycardia with variable conduction. However, regular RR intervals need further assessment.

Q3: *Are the P waves visible?*

Analysis of P waves carries an important value. Hence, when the P waves are not visible on a superficial note, one should use few maneuvers to bring out the P waves. Some of these measures are:

- Increasing the speed of ECG tracing from a normal of 25 mm/sec to 50 mm/sec.
- Transesophageal recording with placement of an ECG electrode into the esophagus via the nasopharyngeal

Flow chart 1: Approach to diagnosis of Supraventricular tachycardia⁴**Fig. 1:** ECG tracing of a child with narrow complex tachycardia. Note that the QRS rate is around 250/minute and the width of QRS is less than 0.1 seconds

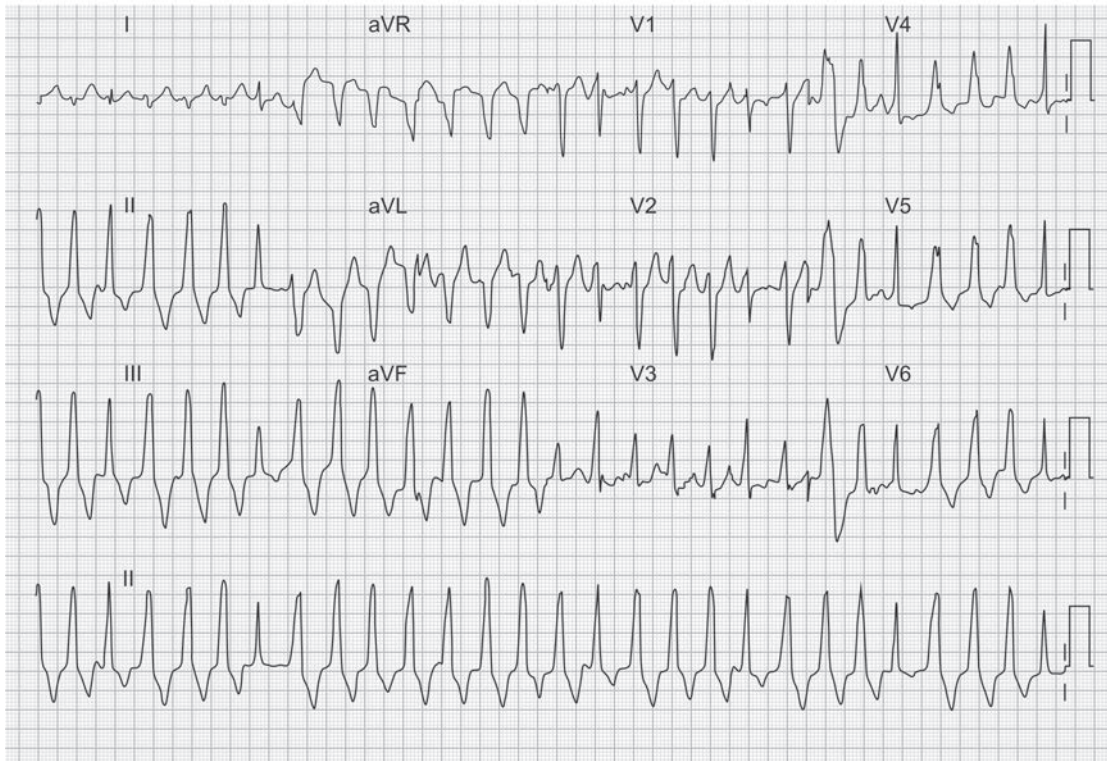


Fig. 2: Wide Complex Tachycardia. QRS duration is more than 0.1 seconds. Also note the fusion beats suggestive of ventricular tachycardia

approach. This probe will receive signals from the left atrium, which can then be compared with a simultaneous surface ECG.

If the P waves are not visible even after using the additional maneuvers, it signifies AV nodal re-entrant tachycardias (AVNRT), in which the P waves may get merged with the QRS. In this context, intravenous adenosine can help both in diagnosis and therapeutics. Intravenous administration of adenosine as a rapid bolus can be used to block the AV conduction. If the tachycardia breaks with adenosine, then it signifies AVNRT (Fig. 3).

Q4: What is P/ QRS ratio?

If P waves are seen, then the ratio of number of P waves to number of QRS complexes (P/QRS) should be assessed. P/ QRS of >1 (atrial rate more than ventricular rate) indicate atrial tachycardia or atrial flutter.



Fig. 3: Effect of intravenous adenosine on AVNRT. Continuous rhythm strip showing how AVNRT breaks into normal sinus rhythm with intravenous adenosine

However, if P/ QRS is less than or equal to 1 (atrial rate same or less than that of ventricle) then RP interval and PR interval should be measured. If the RP interval is longer than PR interval, it suggests atrial tachycardia, paroxysmal re-entrant tachycardia or atypical AVNRT.

If the RP interval is shorter than PR interval, it indicates short RP interval subgroup. In such cases, the actual RP interval should be measured. If the RP interval is less than 0.07 seconds, it usually signifies AVNRT. However, RP interval of more than 0.07 seconds is seen in AV re-entrant tachycardia or atrial tachycardia and in some occasions, AVNRT.

Q5. What if the QRS complex is wide (more than 0.1 second)?

Any tachycardia with wide QRS complex is considered ventricular in origin, unless otherwise proved. They originate distal to the bundle of His. The incidence of ventricular tachyarrhythmias is less than 5 percent of all arrhythmias in children amongst the general population. However, their incidence is high after cardiac surgery for congenital heart diseases and is linked to the mortality and morbidity. They can also occur with metabolic derangements, drug toxicity and myocarditis.



Fig. 4: ECG in Wolff-Parkinson-White Syndrome.⁵ Note the delta waves at the onset of QRS complex after the SVT got converted to Sinus rhythm. This indicates WPW syndrome



Fig. 5: ECG strip showing congenital complete heart block in a newborn. Note that there is no relationship between P waves and QRS complexes. Atrial rate is more than ventricular rate (P/ QRS more than 1). Also note that the QRS complexes are narrow, unlike in acquired complete heart block where QRS complexes are likely to be wide

Q6. Is there any relationship between P and QRS?

In classical ventricular tachycardia, there is no relationship between P and QRS. If the P/ QRS ratio is 1:1, then the possibilities would be SVT with aberrancy, SVT with bundle branch block, antidromic reciprocating tachycardia in Wolff-Parkinson-White (WPW) syndrome or rarely ventricular tachycardia with retrograde atrial conduction.

Q7. What are fusion beats and capture beats?

If a ventricular beat fuses with a sinus beat, the resultant beat is an intermediate complex and is termed a fusion beat. In capture beat, an atrial impulse passes through the AV node and stimulates the ventricle. The resultant beat is again an interpolated narrow complex. Fusion beat and capture beats are diagnostic of ventricular tachycardia.

Wolff-Parkinson-White (WPW) syndrome: This non-inherited condition needs special mention. Children with this condition have an accessory pathway capable of conducting forwards or backwards between the atrium and the ventricle. The result is an AV re-entrant tachycardia, with a higher risk for developing atrial fibrillation. The classical ECG finding is a delta wave, an upward wave at the onset of QRS complex. This results in short PR interval. Any symptomatic WPW should be referred at the earliest. Irrespective of symptoms, all children with a delta wave persisting after the fourth year of life should be seen by a pediatric electrophysiologist for opinion on electrophysiology study and subsequent decision on ablation (Fig. 4).

BRADYARRHYTHMIAS

Only a few causes of bradyarrhythmias are found in children.

Complete heart block (CHB): The ECG will show AV dissociation, with atrial rates faster than ventricular. The QRS complexes can be narrow as in congenital CHB or can be wide QRS complexes as in acquired CHB (Fig. 5).

Sinus node dysfunction: This entity presents with Adams-Stokes syncopal attacks. The ECG will show sinus bradycardia, inability to increase the heart rate during exercise and sinus pauses. It may occur after surgery for congenital heart diseases.

Bradycardia due to medications or poisoning is an important cause in children. Digoxin, beta-blockers, sedative-hypnotics, calcium-channel blockers, tricyclic antidepressants and organophosphorous pesticides can cause bradycardia.

Hence, in cases of unexplained bradycardia of recent onset, a toxicology screen is mandated.

MISCELLANEOUS ARRHYTHMIAS

Sinus Arrhythmia

The heart rate normally increases during inspiration and decreases during expiration. However, this process gets exacerbated in young children and adolescents. Sinus arrhythmia is a normal rhythm for age and does not require any work-up or therapy.

Premature atrial contractions (PAC): They are usually seen in infants and toddlers. If the cardiovascular examination is normal and electrolyte levels are maintained, PAC would be benign. Therapy is considered in infants only if associated with hemodynamic compromise.

Premature ventricular contractions (PVC): They are also seen in infants and adolescents. They are usually monomorphic. Their presence requires thorough cardiovascular examination, estimation of serum electrolytes, 24-hour Holter monitoring and echocardiography to rule out structural heart disease. If no cause is identified even with meticulous investigation, only they should be considered idiopathic. Such idiopathic PVC are benign, self-limited and are easily suppressed with exercise. Treatment is rarely required.

RARE BUT IMPORTANT ARRHYTHMIAS

High incidences of sudden cardiac death make few arrhythmias important, although their individual incidence is not high. Most of them would have molecular genetic basis. They are not amenable to radiofrequency ablation and would mandate the use of implantable cardiac defibrillator. Some of these arrhythmias are as follows:

Long QT Syndrome (LQTS)⁶

Prolonged QT syndrome is a congenital disorder of ventricular repolarisation characterized by prolongation of the

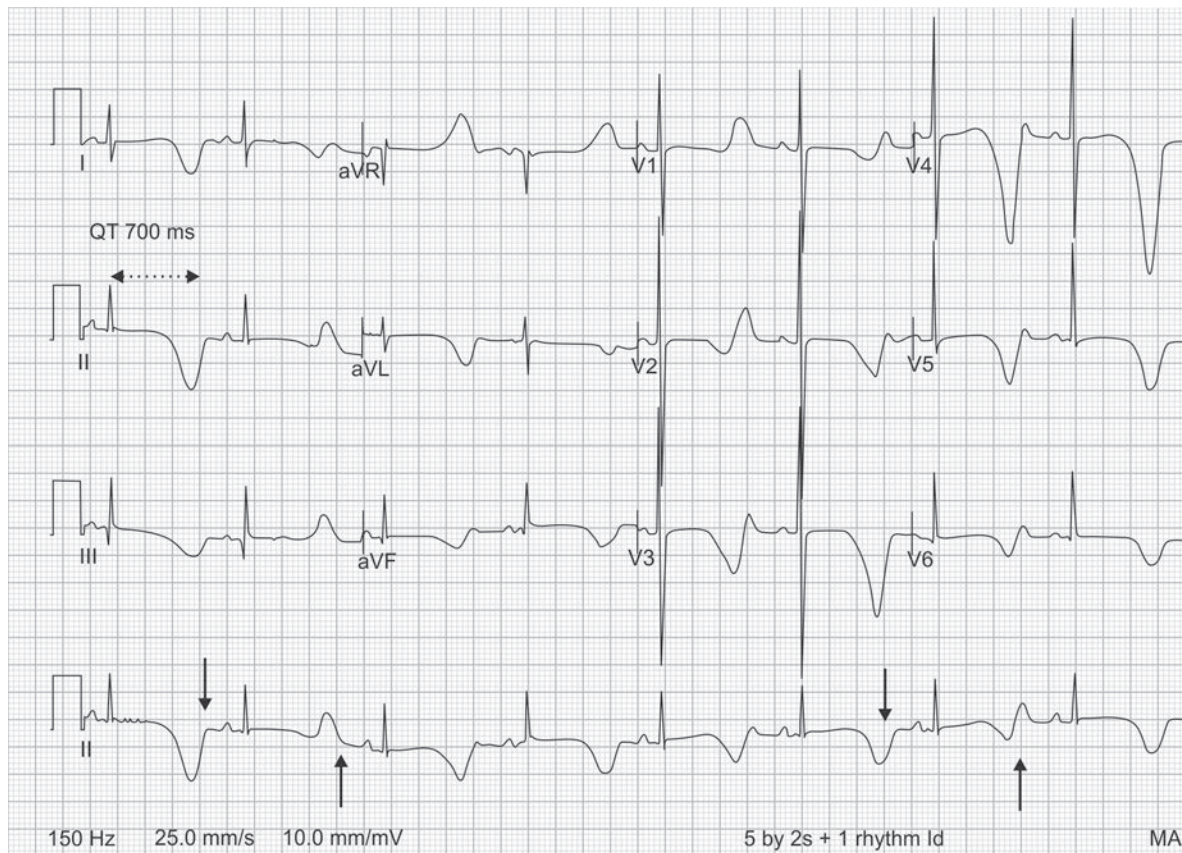


Fig. 6: Long QT syndrome². A rare example of an ECG showing gross prolongation of QT interval. Note the T wave alternans (thick arrows). This finding is said to precede Torsades de Pointes

QT interval on surface ECG. More common among them is Romano-Ward syndrome, a variant of LQTS with autosomal dominant inheritance. The Jervell-Lange-Nielsen syndrome having an autosomal recessive inheritance, is associated with congenital deafness and carries poor prognosis.

LQTS has underlying ion channelopathy affecting ventricular repolarisation, causing a polymorphic ventricular tachycardia called Torsades de Pointes, which can degenerate into ventricular fibrillation causing sudden cardiac death even in an apparently normal child. The usual symptom of LQTS is syncope precipitated by exercise or emotions. Hypoxic seizures are not uncommon and add up to the confusion in diagnosis. A total of 14 mutations have been recognized hitherto for LQTS.

Mortality is considerably reduced by use of beta-blockers. Long acting agents like nadolol is preferred. If the symptoms persist despite beta-blockade, an automated implantable cardiac defibrillator (ICD) should be considered. Small sized ICD units for pediatric population are now available, but would still require repeated revisions of electrodes as the child grows. A 'leadless' ICD which is being developed would eventually resolve this concern.

Beta-blockades should be continued even after ICD. (Fig. 6).

Catecholaminergic Polymorphic Ventricular Tachycardia⁷

This rare autosomal dominant condition affecting intracellular calcium transportation was described by Coumel et al. Children affected by this condition had syncope precipitated usually by exercise. Surface ECG in this condition shows a bidirectional ventricular tachycardia, which can deteriorate rapidly into a polymorphic ventricular tachycardia and sudden cardiac death. Beta-blockade would help, but persisting symptoms would indicate ICD implantation. (Fig. 7).

Arrhythmogenic Right Ventricular Dysplasia (ARVD)⁸

In this rare condition, the right ventricular myocardium is replaced by fibrofatty tissue. The surface ECG tracing shows T wave inversion in the right precordial leads with ventricular tachycardia of left bundle branch block morphology. ARVD has autosomal dominant transmission and is one of the causes of juvenile sudden cardiac death.



Fig. 7: Catecholaminergic polymorphic ventricular tachycardia.² ECG strip of an 8-year old boy with catecholaminergic polymorphic Ventricular Tachycardia during exercise. Note the normal QT interval, but multiple ectopics shown by asterisk mark and a short run of Ventricular Tachycardia shown by the arrow

Brugada Syndrome⁹

Much has been researched on this rare genetic arrhythmia. Syncope caused due to idiopathic ventricular fibrillation characterizes this condition. The typical ECG changes include right bundle branch block and variable ST segment elevation resembling coved or 'saddle type' in the right precordial leads. Brugada syndrome is a disease of young adults. Symptomatic events are commonly associated with febrile illnesses in the young and are usually nocturnal. Administration of sodium channel blocking drugs, such as mexilitine or flecainide sometimes bring about the ECG changes and is used as a diagnostic test too. There is no specific pharmacologic therapy for Brugada syndrome. Prevention and aggressive treatment of febrile illness and use of ICD for symptomatic children forms the treatment plan (Fig. 8).

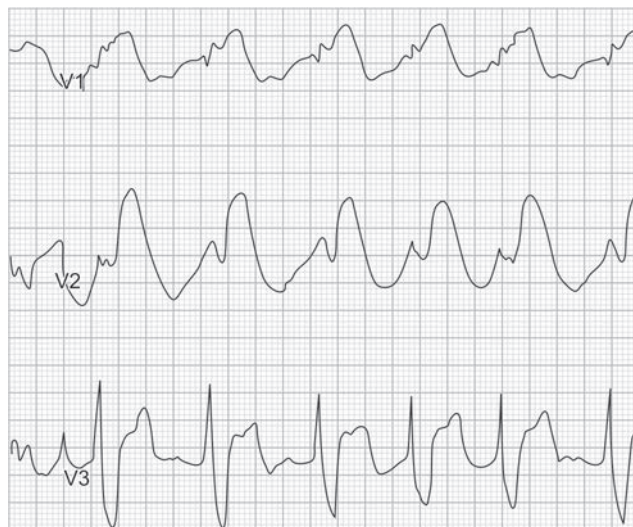


Fig. 8: Brugada syndrome²

MANAGEMENT OF COMMON TACHYARRHYTHMIAS (Flow chart 2)¹⁰

Acute Management:

The purpose of acute management is to interrupt the arrhythmia or to slow down the response rate of ventricle. During an emergency, when the patient presents with hemodynamic compromise, the "ABCs" of resuscitation must be followed. Direct current cardioversion (0.5 to 1 J/kg, up to 2 J/kg) is considered in such situations, without wasting time on dissecting the nature of arrhythmia. If the

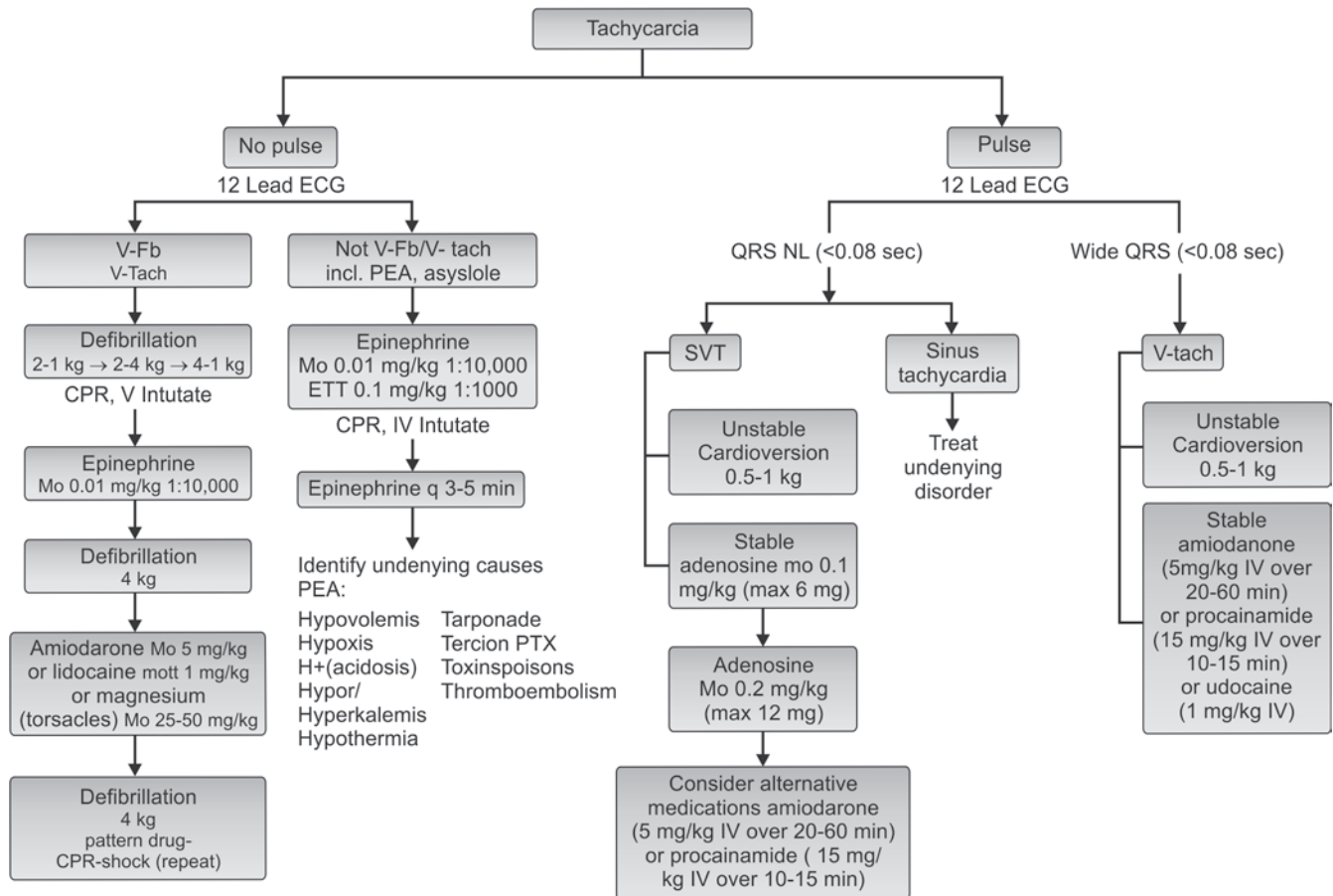
vitals are stable during the arrhythmia, the rhythm can be first evaluated by algorithmic approach explained previously and then treated.

The following are commonly used first-line measures:¹¹

Vagal Maneuvers

They are known to effectively terminate the SVT. In infants, keeping a bag of ice to the center of the face induces the diving reflex and is often helpful in terminating the SVT.

Flow chart 2: Management of tachycardia (PEA: pulseless electrical activity; SVT: supraventricular tachycardia; V-Fib: ventricular fibrillation; V-Tach: ventricular tachycardia).¹⁰ ECG strip of an 8-month old child with Brugada syndrome during fever. Note the right bundle branch block pattern and variable elevation of ST segment in V1 to V3 leads



- For aniodarone administration: repeat doses of 1-5 mg/kg (max amount 5 mg/kg) may be required depending upon patient stability and clinical scenario.
- For lidoozing administration: repeat every 5-10 minutes after initial doses, total dose 3 mg/kg after return of pertusion follow with acntinuous infusion 20-50 mg/kg/min.

In adolescents and older children Valsalva maneuver can be taught to derive similar effect.

Adenosine is the usual first-line medication. Due to its extremely short half-life, it is to be given as a rapid intravenous bolus into a vein close to heart. It interrupts the conduction through the AV node. The dose usually starts with 100 $\mu\text{g}/\text{kg}$ in children and 200 $\mu\text{g}/\text{kg}$ in infants to a maximum of 300 to 500 $\mu\text{g}/\text{kg}$.

Adenosine can also be used as an important diagnostic tool. It does not have any effect on the rate of ventricular tachycardia. However, it may slow the atrial rate and reveal AV dissociation. This will confirm the diagnosis. Adenosine does not produce any hemodynamic deterioration in VT and hence, can be used as a diagnostic tool when there is a strong suspicion of dissociation.

Adenosine can also be used to differentiate the mechanism of SVT. It unmasks pre-excitation by blocking the AV node and thereby increases conduction down an accessory connection. This is useful when accessory connections were previously not apparent. Alternatively adenosine may unmask changes in PR interval, which favours a diagnosis

of dual AV nodal pathway. In few instances of atrial tachycardias and atrial flutter with rapid ventricular response, diagnosis may not be obvious. In such cases, increased AV block and slowed ventricular rate after adenosine help in revealing the underlying atrial rhythm.

Other intravenous drugs used are esmolol, amiodarone, and procainamide. Intravenous calcium channel blockers are contraindicated in infants, as hypotension and sudden death are reported with IV verapamil. However, they can be used in older children and adolescents.

CHRONIC MAINTENANCE THERAPY^{11,12} (TABLE 1)¹¹

Long-term therapy is meant to prevent recurrences. The choice of therapeutic measure is decided by the type of arrhythmia and mechanism, which causes it. For example, re-entrant SVT in which the AV node is a part of the circuit should use therapies that block conduction through the AV node. Hence, situations where tachycardias have responded to adenosine it would be logical to start a drug which acts on AV node for long-term treatment.

Table 1: Commonly used antiarrhythmic agents in the pediatric population¹¹

<i>Antiarrhythmic agents</i>	<i>Doses</i>	<i>Side effects</i>
<i>Class 1</i>		
• Procainamide	<i>Oral:</i> 30–100 mg/kg/d every 6 hours	Nausea, vomiting, lupus like syndrome, pancytopenia, agranulocytosis, confusion
• Lidocaine	<i>Intravenous:</i> 1 mg/kg	Seizure, central nervous system symptoms, arrhythmias, respiratory distress, hypotension
• Mexiletine	<i>Oral:</i> 5–15 mg/ kg/ d every 8 hours	Nausea, vomiting, headache, tremor, dizziness, paresthesia, rash
• Phenytoin	<i>Oral:</i> 2–5 mg/ kg/ d every 12 hours after a loading dose of 10–15 mg/ kg	Rash, Stevens-Johnson syndrome, neuropathy, gingival hypertrophy
• Flecainide	<i>Oral:</i> 2–6 mg/ kg/ d every 8 hours	Arrhythmia, conduction disturbances, dizziness, blurred vision, headache
<i>Class 2</i>		
• Propranolol	<i>Oral:</i> 2–4 mg/ kg/ d every 6 hours	Hypotension, bronchospasm, hypoglycemia (in neonates), lethargy, depression
• Atenolol	<i>Oral:</i> 1–2 mg/ kg/ d every 12 hours	Lethargy, depression, bradycardia, postural hypotension, agranulocytosis
<i>Class 3</i>		
• Amiodarone	<i>Oral:</i> load of 10 mg/ kg every 12 hours for 5–14 days followed by maintenance of 5–7 mg/ kg/ day	Arrhythmias, prolonged QTc interval, hepatotoxicity, hypo- and hyperthyroidism, corneal microdeposits, photosensitivity, pulmonary fibrosis
• Sotalol	<i>Oral:</i> 80–160 mg/ m ² / d every 8 hours for infants or every 12 hours for older children	Arrhythmia, prolonged QTc interval, bradycardia, fatigue, dyspnea
<i>Class 4</i>		
• Verapamil	<i>Oral:</i> 4–8 mg/ kg/ d every 8 hours or every day SR form	Hypotension, bradycardia, cardiac decompensation (esp. in infants). Not used in infants.
<i>Miscellaneous</i>		
• Adenosine	<i>Intravenous:</i> 0.1 mg/ kg rapid bolus	Transient bradycardia and tachycardia, transient AV block
• Digoxin	<i>Oral:</i> Load of 30–40 mcg/ kg (depending on age) over 1st day followed by maintenance of 5–10 mg/ kg/ day every day or divided every 12 hours	AV block, arrhythmias, nausea, vomiting

Digoxin and beta-blockers are used as first-line oral therapy for SVT in children. In Wolff-Parkinson-White syndrome, digoxin and calcium-channel blockers are contraindicated as they enhance ante-grade conduction in the accessory pathway allowing a more rapid ventricular response during atrial flutter or fibrillation, precipitating ventricular fibrillation.

If the first-line therapy is ineffective in controlling SVT, then flecainide, procainamide, sotalol, amiodarone or verapamil (a class IV agent) can be tried.

For primary atrial tachycardias, digoxin or calcium channel blockers are used to slow the AV conduction to decrease the ventricular response rate. Beta-blockers, procainamide, flecainide, propafenone, amiodarone and sotalol are commonly

used to alter the electrophysiology of the atrial substrate to control such arrhythmias.

Radiofrequency catheter ablation has the advantage of being curative therapy, especially in older children and adolescents, if the arrhythmia substrate can be defined (such as accessory pathway, ectopic focus, AV nodal slow pathway etc). After 1990s, ablation has been more widely applied in children also. In infancy, ablation is reserved for refractory and life-threatening arrhythmias and not a routine procedure. There is still concern in the small heart as to long-term complications of the lesions produced.¹³

In the older child, ablation offers cure of arrhythmia and thereby helps in preventing side effects of medications. Success rates for ablation of accessory pathways are as high

Table 2: Management of specific arrhythmias^{2,12}

<i>Arrhythmia</i>	<i>Medications, measures and comments</i>
Atrial ectopic tachycardia	Radiofrequency ablation, if leads to hemodynamic impairment
Atrial fibrillation	Rare in children, WPW syndrome, ibutilide, dofetilide, digoxin, beta-blockers, calcium channel blockers, ablation, maze procedure
Atrial flutter	Digoxin, amiodarone or flecainide, cardioversion
Chaotic ectopic atrial tachycardia	Very rare in children, amiodarone, if symptomatic
Re-entry tachycardia secondary to accessory pathway	Most common SVT, beta-blockers, flecainide, amiodarone or a combination in refractory cases. Ablation in older children
AV nodal re-entrant Tachycardia (AVNRT)	Beta-blockers, flecainide, digoxin, ablation, permanent pacemaker
Incessant junctional reciprocating tachycardia	Ablation
Junctional ectopic tachycardia	Usually postoperative. Cooling, minimize inotropes, overdrive atrial pacing, correct electrolytes, sotalol, amiodarone, procainamide, Ablation
Ventricular Tachycardia (non-genetic)	Amiodarone, lidocaine, beta-blockers, phenytoin, cardioversion, ablation, ICD

95 percent. Caution has to be employed where pathways are close to the AV node and when considering ablation for AVNRT. Ablation is applicable to some VTs and has a special role in the treatment of arrhythmias after surgery for congenital heart disease.¹³

MANAGEMENT OF VENTRICULAR TACHYARRHYTHMIAS¹¹

Acute Management

Without exception, this again begins with the ABCs of resuscitation. DC cardioversion should be urgently performed for hemodynamically compromised patients (can start with 1 to 2 J/kg and can go up to 4 J/kg). Reversible causes like electrolyte imbalance and acidosis should be treated. Intravenous lidocaine at 1 mg/kg is the first-line drug. Intravenous procainamide and amiodarone are also useful.

Chronic Therapy

This should be directed at the cause of the ventricular arrhythmia. In patients who initially responded to IV lidocaine, oral mexiletine is useful for long-term therapy. Ventricular tachycardia due to long QT syndrome responds to beta-blockers.

Amiodarone can be used as second-line therapy. It is a very powerful drug and should not be used irrationally. It has class III action and some degree of beta blockade. It acts on atrial myocardium, the AV node and ventricular myocardium and also has minimal negative inotropic effect. However, the drug has a potential for serious long-term adverse effects including hepatotoxicity, thyroid dysfunction and photosensitivity. Reversible corneal microdeposits, are also reported. In adults, pulmonary toxicity is a known problem. But it is not major concern in children.¹²

Amiodarone is effective intravenously with a very long half-life and builds up in the myocardium. It can be used

in combination with digoxin for added AV nodal effect. However, amiodarone increases the level of digoxin and maintenance doses need to be reduced. Similar effect is also seen with flecainide.¹² Table 2 summarises the management of common arrhythmias.

MANAGEMENT OF BRADYARRHYTHMIAS¹¹

The initial management of bradycardia should be directed towards identification of the cause and cardiopulmonary resuscitation. Choices of pharmacologic interventions are atropine (0.02 mg/kg, IV, minimum 0.1 mg; maximum single dose: 0.5 mg in children and 1 mg in adolescents) or isoproterenol given as an IV infusion 0.05 to 0.5 µg/kg/min, titrated to desired effect. Isoproterenol is a sympathomimetic agent known to increase the heart rate. If drug therapy does not improve the situation, then a temporary transvenous pacemaker is indicated.

Pacemakers are the treatment of choice for symptomatic bradycardia. They are aimed at restoring as close a physiologic rhythm as possible. The indications are defined by AHA/ACC guidelines.¹⁴

- Symptomatic second- or third-degree AV block
- Symptomatic sinus node dysfunction
- Postoperative second- or third-degree AV block persisting for at least 7 to 10 days
- Congenital complete AV block with a wide QRS escape rhythm, complex ventricular ectopy, ventricular dysfunction, or ventricular rate less than 50 to 55 beats/minute (bpm) in an infant or less than 70 bpm in a patient with congenital heart disease
- Sustained pause-dependent ventricular tachycardia, such as in long QT syndrome.

CONCLUSION

The diagnosis of arrhythmia is largely mathematical and an effective management can be worked out on an algorithmic basis. A high index of suspicion and alertness is

required for decision making. The decision should be based on a firm clinical judgment and meticulous ECG evaluation. Monitoring the child throughout the course of management is vital for effective care. Judicious use of medications and appropriate use of radiofrequency ablation goes a long way in optimal management. Refractory arrhythmias require multidisciplinary collaboration from pediatricians, pediatric cardiologists, electrophysiologists, and geneticists. Current advances in clinical and molecular genetics have started to offer improved screening and condition specific treatment for many potentially life threatening inherited arrhythmias.

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Surgical Management and Outcomes of Congenital Heart Diseases

Raja Joshi, Reena K Joshi

The prevalence of congenital heart disease (CHD) among live births is estimated at 4 to 9 percent.¹⁻⁴ These figures do not include the bicuspid aortic valve, with an incidence of 2 to 3 percent in live born infants.⁵⁻⁸ Congenital heart disease being defined as the presence at birth of a gross structural abnormality of the heart, great arteries, or great veins that is actually or potentially of functional significance. Included in this definition, though not being a structural heart problem are congenital complete heart block.^{9,10} Extrapolating from an average prevalence of 8 percent of live births there are approximately 200,000 new cases per year in India.¹¹ Approximately, half of these will require tertiary care attention in their early infancy. Surgery forms a major part therapeutic armamentarium for managing most of such lesions, hence a clear understanding of the type of surgeries, the optimum timing for these and their short and long-term outcomes are important to discuss.

Most heart surgeries for CHD can be classified as curative (No postoperative residua, sequel or complications), reparative (Anatomic repair or reconstruction with obligatory postoperative residua or sequel), palliative (basic morphologic anomaly is neither repaired nor reconstructed), reoperative (late reoperation after reparative or palliative surgery) and transplantations.

There are some common major late morbidities related to many types of repairs of congenital heart surgeries. These are late death, reintervention, heart failure/ventricular dysfunction, rhythm disturbances and need for pacemaker, endocarditis, exercise limitation and restrictions, neurocognitive impairment, decreased ability to tolerate pregnancy, need for chronic medications and impaired quality of life. Lesion specific outcome parameters are discussed below.

ATRIAL SEPTAL DEFECTS

Atrial septal defects of secundum variety are best closed at two years of age or anytime after that whenever diagnosed.

Indications of closure are symptomatic child, presence of cardiomegaly, dilated right atrium and right ventricle. Options available are surgical closure and percutaneous device closure. The surgical success for closure approaches 100 percent. Time related survival of patients operated for ASD during the first few years of life is that of the matched general population implying there is no late attrition of these patients and survival continues in the second decade and beyond. Features to follow carefully would be RV diastolic dimensions, (especially if the closure was performed at an older age), atrial arrhythmia. Those with atrial arrhythmias especially atrial fibrillation run the risk of thromboembolism and therefore need anticoagulation.

Sinus venosus atrial septal defects (SVASD) require to be surgically repaired as most of them will be associated with partial anomalous drainage of the pulmonary veins. A recently published study looking at long-term outcome of sinus venosus ASD noted outcomes which may be surprising. The authors reviewed outcomes of 115 patients (mean age 34 years) with SVASD who had repair. Complete follow-up was available in 95 percent patients at 144 + 99 months. Symptomatic improvement was noted in 83 patients (77%), and deterioration was noted in 17 patients (16%). At follow-up, 7 (6%) of 108 patients had sinus node dysfunction, a permanent pacemaker, or both and 15 (14%) of 108 patients had atrial fibrillation. Older age at repair was predictive of postoperative atrial fibrillation.¹²

Primum atrial septal defects also called partial atrioventricular septal defects need to be closed surgically. These infants get symptomatic earlier in case they have left atrioventricular valve regurgitation. Incidence of trisomy 21 with this lesion should also be kept in mind while working up these patients. Their follow-up reveals main reasons for long-term concern being left AV valve dysfunction (regurgitation/stenosis), left ventricular outflow tract obstruction and residual pulmonary hypertension.

VENTRICULAR SEPTAL DEFECTS

Ventricular septal defect is one of the lesions where the long-term outcome is excellent if no residual lesion has been left behind.¹³ Premature late death occurs in less than 2.5 percent of patient provided the pulmonary resistance was preoperatively judged to be low. Patient who had high preoperative pulmonary vascular resistance may succumb from progressive pulmonary vascular disease. Thus it must be emphasized that closure during the first year of life is curative.

If timely closure is done, physical growth normalizes for all parameters. Rarely, aortic or tricuspid valve regurgitation may be present related to preoperative or intraoperative issues.

Certain conduction defects can also be seen on the ECG in the long-term. These can be right bundle-branch block alone (about 40%) which are relatively benign, RBBB with left anterior hemiblock (about 15%) which run the theoretical disadvantage of a higher risk to develop late complete heart block ventricular arrhythmias (especially if the age at operation was older). Complete heart block is noted in small number of patients (<1%).

PATENT DUCTUS ARTERIOSUS

The preferred modality for closure of isolated patent ductus arteriosus (PDA) in a term infant is by a percutaneously delivered device. As an alternate therapeutic option surgical division can be undertaken. For very small for age and premature newborns with large PDA, the first line of management should be prostacyclin inhibitors. In case there is no response to the PCI therapy, a contraindication to such therapy or a recurrence after two courses of PCI, surgical ligation should be undertaken.

Follow-up should involve left pulmonary artery, coarctation and resolution of left ventricular dilatation. Life expectancy is normal after closure of an uncomplicated PDA in infancy or childhood with older age at operation or preoperative high pulmonary vascular resistance late deaths may result from progression of pulmonary hypertension. Comorbidities related to the prematurity of newborns are responsible for major long term issues.

COMPLETE ATRIOVENTRICULAR SEPTAL DEFECTS (AV CANALS)

These patients require early repair of the AV septal defect encompassing closure of the atrial and ventricular components and closure of the cleft in the left component of the common valve. Most long-term survivors (88%) are in excellent NYHA-status. These defect once repaired and are beyond the early hazard phase (which is steep for the initial 6 to 9 months after surgery) show a very small but appreciable constant hazard phase. This means that these patients need regular follow-up even in the long-term.

The main reasons for concern are left AV valve dysfunction (regurgitation/stenosis). Left ventricular outflow tract obstruction (more after a partial AV septal defect repair than complete), residual pulmonary hypertension, and rarely complete heart blocks or supraventricular arrhythmias.¹² It should be noted that presence of trisomy ²¹ does not adversely affect the outcome of these defects. Incidentally a study published in 1995 with follow-up of 203 patients concluded that mortality has decreased over the decades from 19 percent before 1980 to 3 percent after 1990. The 10-year survival is 90 percent and all patients are in NYHA class I or II. Late reoperation was required in only 8/203 patients and their results indicate that complete atrioventricular septal defects can be repaired with low mortality and good intermediate to long-term results.¹⁴

Coarctation of Aorta/Interrupted Aortic Arch

In isolated coarctation of aorta long-term survival is excellent. Long-term issues include resting and exercise induced hypertension. Recurrence of coarctation has to be sought for actively. Commonly associated bicuspid aortic valve may show signs of stenosis by the 2nd or 3rd decade of life and may also be a source to infective endocarditis. New or late onset subaortic stenosis is also an issue to be looked for. If patch aortoplasty was performed care should be taken to evaluate for aneurysm formation in the long run. Cerebrovascular accidents are more common in patients with persistent hypertension and in those with berry aneurysms.

In a late follow-up up to 50 years after coarctation repair, surprisingly 18 percent (45/274) patients died at a mean age of 34 years. Predictors of survival were age at operation and blood pressure at the first postoperative visit. The authors noted long-term survival is significantly affected by age at operation, with the lowest mortality rates observed in patients who underwent surgery between one and five years of age. More than one-third of the survivors developed significant late cardiovascular abnormalities.¹⁵

Interrupted arch mostly presents as a duct dependent lesion in a neonate. It is commonly associated with a ventricular septal defect. It is also commonly associated with DiGeorge syndrome. This cardiac lesion needs to be repaired in the neonatal period.

TRUNCUS ARTERIOSUS

Since a valved conduit is used for repair during the neonatal period, the issues related to the valve in the necessitate reoperation or intervention or both. Pulmonary vascular disease often develops and progresses in older infants

and children who did not undergo repair and therefore adversely affects survival in the long run. A recent single center review of 16 cases on intermediate-term follow-up indicate conduit and valve failure at mean follow-up of 2.5 years in 67 Percent of the patients.¹⁶

Tetralogy of Fallot

Tetralogy of Fallot (TOF) has the longest history of surgical treatment of any cyanotic lesion, with a 60 year history of palliation and a 50 year history of repair.¹⁷ The era of surgical therapy for cyanotic heart disease began in 1945 with Blalock and Taussig's report of palliation of three patients with TOF by systemic to pulmonary artery shunt.¹⁸ In 1955, Lillehei et al¹⁹ reported the first intracardiac correction of TOF. As the field moved into the 1990s, preoperative catheterization was replaced by echocardiography, and significant advances were made in postoperatively care. The fraction of patients palliated initially with a shunt continued to decline.

The Pediatric Cardiac Care Consortium (PCCC) reported that between 1991 and 1995, 22 percent of patients had a shunt before definitive repair.²⁰ The mean age at repair in this consortium decreased to 1.35 years, and mortality declined to 2.3 percent. Surgical management of neonates with critical CHD expanded, and several large centers adopted primary repair in cyanotic neonates with TOF as their preferred strategy.²¹ The optimal approach in this patient group—shunt followed by later repair or primary repair—continues to be debated in 2005, as illustrated elsewhere in this issue. Finally, the multiple genetic associations with TOF, most importantly the 22q11 deletion syndrome, were increasingly recognized.²² Many of these genetic abnormalities have significant implications for long-term outcomes that are hard to separate from the management of the cardiac malformation (e.g. neurodevelopmental outcomes).

Hirsch et al²¹ reported on their center's experience with complete repair of TOF in 61 neonates operated on between 1988 and 1999. There was one in-hospital death and four late deaths, with an actuarial survival of 95 percent at 5 years. Freedom from reoperation was 58 percent at 5 years. Excellent survival after TOF repair is achievable, even with operation in the neonatal period. However, the frequencies of morbidities well described among patients operated on circa 1975 are undefined for the infant who has undergone routine repair in the recent era.

Adults with TOF face the sequel of medical and surgical management strategies use during their infancy and childhood. From a clinician's perspective, they enjoy excellent actuarial survival rates, and reintervention has been infrequent. However, there is growing concern about the long-term effects of pulmonary regurgitation and ventricular dysrhythmias, with their attendant influences on functional status, exercise tolerance, and the risk (fear) of

sudden death. These late outcomes may or may not be applicable to the current generation of infants with TOF undergoing primary repair. Follow-up studies are needed in more contemporary cohorts to define their truly late outcomes.

This is a heterogeneous group of patients that behave in a variety of ways in long-term follow-up. To answer the difficult question regarding "surgical cure" of tetralogy we take lesson learnt from a large meta-analysis. This infers that time related survival of most patients after repair of TOF with pulmonary stenosis (not atresia) under proper circumstances is excellent, approaching that of general population, but the risk of death throughout life is "slightly greater" than general population.

During follow-up important point to be noted are RV function, RV outflow tract aneurysms, pulmonary insufficiency (especially if a transannular patch has been placed during the repair) residual right ventricular outflow tract (RVOT) obstruction and recurrent/residual VSDs, late aortic insufficiency, tricuspid valve competence and ventricular or supraventricular arrhythmias.

Progressive RV dilatation and dysfunction (preferably documented by MRI) should be sought for early. An ECG with QRS duration >180 ms puts these patients on a higher risk for sudden death from ventricular arrhythmias.

A recent study evaluated 95 patients with TOF on long-term follow-up for their RV function. Despite a large number of reoperations, this cohort of patients remained well with low incidence of sudden death with normal good RV and LV function. Aggressive intervention for right-sided hemodynamic abnormalities may have contributed to this outcome. Preserved ventricular function may herald a favorable long-term outlook in this group, the authors concluded.²³

In another multicenter study, 793 patients with tetralogy were reviewed for late arrhythmia complications. Thirty three patients developed sustained monomorphic ventricular tachycardia, 16 flutter or fibrillation. Pulmonary regurgitation was the main underlying hemodynamic lesion for patients with ventricular tachycardia and sudden death, whereas tricuspid regurgitation was for those with atrial flutter/fibrillation.²⁴

SINGLE VENTRICLE

This terminology comprises a wide variety of diagnosis. These patients have to be placed on what is termed as a single ventricle or Fontan palliation protocol.

The long-term survival issues cannot be simplified because of the heterogeneity of the primary diagnosis for which a Fontan pathway was offered. With the latest modification in the staged palliation towards Fontan operation mid-term survival is approaching and exceeding 90 percent. There is present the late slow rising phase of the baffle and this leads to some degree of acceptable cyanosis.

During the follow-up important facts to review and expect are development of supraventricular tachyarrhythmias, ventricular dysfunction, protein losing enteropathy, serous cavity effusions, thromboembolic and neurological complication (especially if a fenestrated Fontan is done). Development of AV valve regurgitation is detrimental and needs to be evaluated. Systemic hypertension and semilunar valve incompetence promote load on the ventricle and need prompt attention. Obstruction to the Fontan pathway and baffle leaks should also be looked into. These adolescents self learn to cope up with mild exercise intolerance.

In a recent review of 225 patients of double inlet single left ventricle (DILV) who underwent Fontan operation in Mayo Clinic between 1974 to 2011, median age at operation was 9 years and median follow-up was 12 year. The operative mortality after 1989 has decreased to 3 percent. Current health as described by the patients was good or excellent by authors concluded that, the Fontan operation for DILV is now performed with a low operative mortality rate. Long-term survival has improved, and most patients have good functional status.²⁵

TRANSPOSITION OF GREAT ARTERIES

Complete transposition of the great arteries is a relatively common anomaly, which comprises 5 to 7 percent of all instances of cardiac malformations. Palliation of D-TGA became possible in 1950 with the development of the Blalock-Hanlon atrial septectomy, which improved intercirculatory mixing.²⁶ A physiologic repair using native atrial tissue was first reported by Senning²⁷ in 1957, followed by Mustard's²⁸ success with an atrial switch using a pericardial baffle in 1963. Atrial switches became widely used in the 1960s and 1970s in a growing population of children stabilized in the neonatal period by a Rashkind transcatheter atrial septostomy.²⁹ In 1975, Jantene³⁰ reported the first successful arterial switch operation (ASO), ushering in a new era of surgery for D-TGA. Despite an initial difficulty with high operative mortality, the ASO had become the predominant surgical strategy at most institutions by the late 1980s.³¹

Given the decreasing mortality rates associated with a neonatal arterial switch operation and the unacceptable morbidity with atrial baffle operation and the unacceptable morbidity associated with atrial baffle operations, this operation has been accepted as the procedure of choice for the treatment of complete transposition of the great arteries. It restores the left ventricle to its natural systemic function. Long-term survival exceeds 90 percent. Translocation of the coronary arteries remains one of the most difficult aspects of the operation and late mortality appears to coincide with coronary artery events with sudden death secondary to acute myocardial infarction being

reported in 1 to 2 percent of hospital survivors. Supravalvar pulmonary Stenosis, neo-aortic root dilation and valvar regurgitation and myocardial perfusion abnormalities are aspects which require routine follow-up.³² Death hazard rate is extremely low by 6 to 12 months after an arterial switch operation and survival declined minimally after that time.

In the Third World countries, where timely referrals are difficult, there still is a role for the Senning's/Mustard's operations. The cardiac problem to be followed in these cases will be the failure of systemic right ventricle and systemic tricuspid valve regurgitation (pronounced more if repair was for TGA+VSD). Atrial arrhythmias are the next most long-term issue after these types of surgeries. A review of 40 years of experience of the atrial switch results highlighted 75 Percent 25 year survival. Late morbidity included issues mentioned above. Progressive heart failure necessitating surgery or late sudden death from arrhythmias is the main etiologies of late death.³³

By the mid 1990s the ASO had essentially completely replaced the atrial level switch, except in rare complicated anatomic or clinical situations. The first decade of routine use of the ASO was marked by a decline in the operative mortality rated in several large series^{34,35} and increasing success with complex coronary patterns. Dibardino et al³⁶ reported an overall 1.6 percent early mortality at their center since 1995; no patient was denied ASO on the basis of a coronary anomaly actuarial analysis of this series shows 96 percent survival and 90 percent freedom from reoperation at 7 years. In contrast, a publication from the PCCC using slightly older data (1992 to 1996) reported an overall hospital mortality of 15.1 percent with marked variation in mortality by center, ranging from 0 to 50 percent.³⁷ This study reminds us that publication bias favors good results, and although most results of the ASO in the literature are outstanding, a subset of patients may not be enjoying such outcomes. Finally, prenatal diagnosis became increasingly common in the 1990s and has been embraced by clinicians as a mechanism to improve outcomes; however, a beneficial effect on long-term outcome has yet to be demonstrated.³⁸ The medium- and long-term outcomes for D-TGA are reassuring, although older patients after atrial repair are at risk for arrhythmia, ventricular failure, and sudden death. Although these sequel are not likely to affect younger children with ASO to the same degree, new and emerging difficulties, such as coronary disease or aortic root dilation, may become the "Achilles heel" of the new approach. The transition of surgical management from the atrial to the arterial repair and its emerging sequel reminds us of two important facts: (1) Innovation based on past results is necessary to improve overall outcomes, and (2) naivete that the heart is "corrected" cannot replace systemic, comprehensive follow-up.

SUMMARY

Optimum late outcomes are the holy grail of medicine. Although the emphasis of innovation is often initially on short-term measures of success, the ultimate goal of therapy is improved long-term functional status and quality of life. Mortality associated with CHD has been declining approximately 39 percent over the past several years. This is true for all age groups and for all lesions. It would be safe to conclude that current practice patterns and strategies for patients of CHD offer them an excellent survival benefit and freedom from morbidities. Although these strategies have improved upon the natural history of most lesions, surgical (and now transcatheter) interventions have created an "unnatural history" that requires ongoing, lifelong, systematic follow-up.

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Interventional Cardiac Catheterization in Children

Mangesh Jadhav, Snehal Kulkarni

INTRODUCTION

In the past 2 to 3 decades, the field of pediatric interventional cardiology has experienced significant growth. Technological innovations have greatly advanced treatment of cardiovascular disease in both children and adults with congenital heart defects (CHD). Most of the diagnosis of congenital heart defects is mainly done with two dimensional echocardiography. Sometimes additional noninvasive imaging like computed tomography or magnetic resonance imaging is used as additional tools of diagnosis. As a result, diagnostic procedures in the catheterization laboratory are decreasing and the catheterization laboratory is mainly used for interventional procedures.

Therapeutic catheterizations were initiated by Dotter and Judkins in 1964. Now, interventional therapy has become an acceptable alternative treatment for many congenital heart defects. Many of the procedures have already replaced surgeries. While selecting the patients for these procedures the indications, contraindications, risks involved in the procedures and cost implications need to be considered. *Along with the technical skills, anatomic and hemodynamic understanding, the knowledge of operator about the selection of hardware are most important parameters for the successful outcomes.*

The interventional procedures can be classified into emergency procedures, palliative and corrective ones. The emergency procedure is balloon atrial septostomy which is used to create a communication between the two atria for improving the oxygen saturations in patients with transposition of great vessels.

Other procedures can be classified as:

- Opening the valves and vessels-balloon aortic and pulmonary valvotomy.
Balloon dilatation and stent implantation of coarctation.
Balloon dilatation/stent implantation of pulmonary arteries

- Closing the intracardiac or extracardiac communications like closure of atrial and ventricular septal defects and closure of patent ductus arteriosus.
- Miscellaneous interventions—Closure of pulmonary AV malformations.
Closure of coronary AV fistulae.
Stenting of patent ductus arteriosus

ATRIAL SEPTOSTOMY

Balloon atrial septostomy (BAS), which was introduced by Rashkind and Miller in 1966 is a life saving procedure for patients with restrictive interatrial communication in transposition of great arteries, tricuspid atresia, total anomalous pulmonary venous connections. This is one of the few indications for an emergency catheterization in neonates. The procedure can also be performed in the intensive care unit under echocardiographic guidance.

Indications for atrial septostomy):¹

- To enhance atrial mixing (e.g. transposition of the great vessels with restrictive/ intact atrial communication) or to decompress the left or right atrium.
- For relief of left atrial hypertension, for example, in patients on extracorporeal membrane oxygenation support and in patients with hypoplastic left heart syndrome with an intact or restrictive atrial communication.
- For decompression of hypertensive pulmonary or systemic venous chamber with restrictive atrial communication (e.g. tricuspid atresia, pulmonary atresia with intact ventricular septum, total anomalous pulmonary venous connection) if needed before surgery.
- In selected patients with pulmonary arterial hypertension to increase cardiac output at the expense of increasing systemic desaturation.

Procedure²

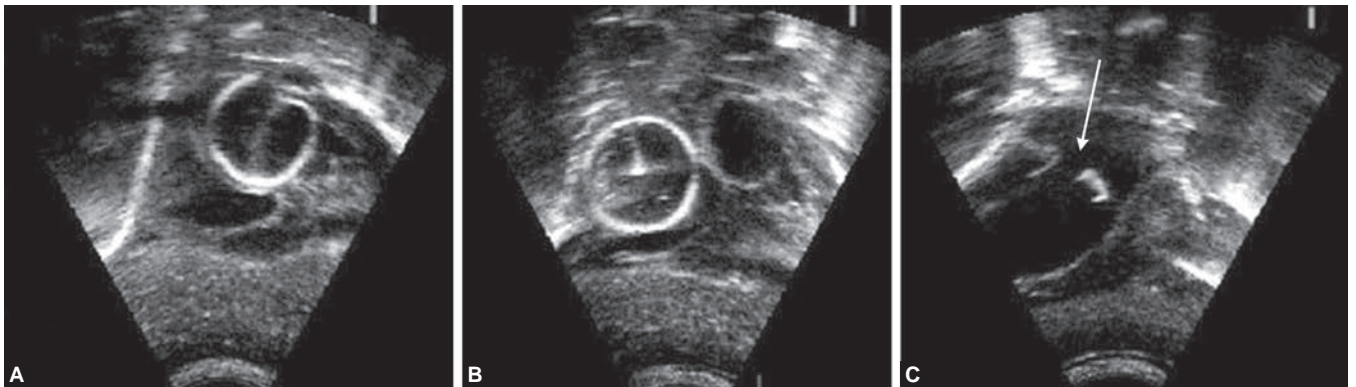
Balloon atrial septostomy (BAS) can be performed either by femoral or umbilical venous route. Usually Rashkind's septostomy balloon is used for the procedure. The deflated balloon is introduced in the left atrium through the patent foramen ovale under fluoroscopic or echocardiography guidance. A rapid, short and forceful jerk is given to pull the inflated balloon towards the right atrium (Figs 1A to C). The procedure can be repeated three to four times till there is no resistance and oxygen saturation is improved.

BALLOON AORTIC VALVOTOMY (BAV)

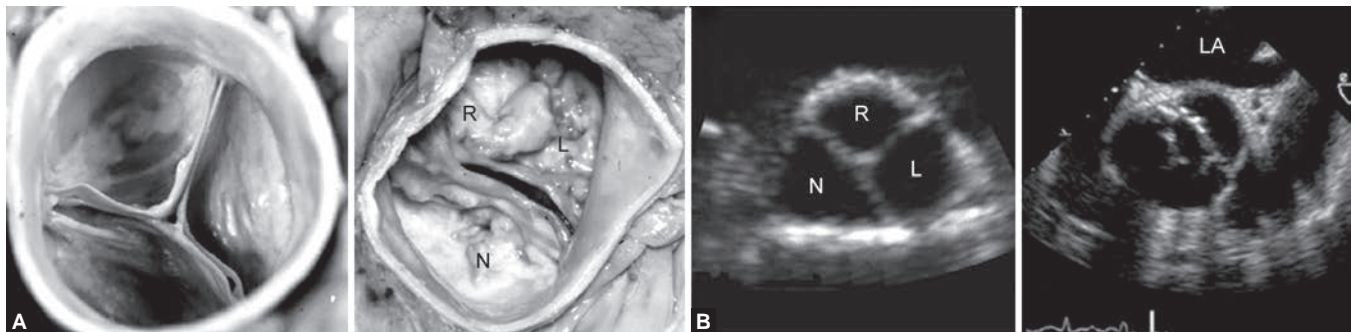
The clinical spectrum of congenital aortic stenosis varies from normal function of a malformed bicuspid aortic valve to severe aortic stenosis (AS) in fetal life resulting in hypoplastic left heart syndrome. Congenital bicuspid aortic valve occurs in 1.3 percent of the population and is one of the most common congenital heart malformations³ (Figs 2A and B). In neonatal critical AS, congestive heart failure and shock occurs around the time of natural PDA closure. In older children, the presentation could be detection of systolic ejection murmur characteristic for valvular AS.

N; noncoronary cusp, L; left coronary cusp, R; right coronary cusp, LA; left atrium, LV; left ventricle, Ao; aorta
American College of Cardiology/ American Heart Association guidelines for balloon aortic valvuloplasty:⁴

- Asymptomatic children and young adults with Doppler peak instantaneous gradients of 70 mm Hg and/or catheter measured peak-to-peak gradient of >60 mm Hg.
- Patients who desire to participate in competitive sports or are contemplating pregnancy and have Doppler peak gradients between 50 and 70 mm and/or peak-to-peak gradient is >50 mm Hg.
- Patients with symptoms (angina, syncope, dyspnea on exertion) or ischemic or repolarization changes on rest or exercise ECG, if the peak-to-peak gradient is >50 mm Hg.
- Other causes of the symptoms or ECG changes should be sought if the gradient is <50 mm Hg.
- Valvuloplasty is not recommended for asymptomatic patients with peak-to-peak gradients <50 mm Hg unless cardiac output is impaired, in which case the gradient underestimates true severity of the obstruction.



Figs 1A to C: Echocardiography guided balloon atrial septostomy: subcostal long axis view showing inflated balloon in the left atrium A, The balloon is pulled into the left atrium B, and the defect in the interatrial septum at the end (arrow) C.



Figs 2A and B: Morphological specimen showing normal tricuspid aortic valve A, stenosed bicuspid valve B and echocardiographic images showing normal tricuspid valve in parasternal short axis view A, and stenotic bicuspid aortic valve in parasternal short axis view B

Procedure I

It is usually performed retrogradely with a catheter introduced through the femoral artery. An end-hole catheter is passed from the femoral artery across the aortic valve to a stable position in the left ventricle. With the wire secured within the left ventricle, the deflated balloon is passed retrogradely over the wire. The balloon is chosen with a diameter of about 80 to 90 percent of the measured aortic annulus diameter.⁵ Once the balloon is positioned across the stenotic valve, the balloon is rapidly inflated to the recommended maximal pressure and then rapidly deflated (Figs 3A and B). The procedure could be repeated till disappearance of the waist. After the procedure the gradient should be reduced by 60 to 70 percent or to <30 to 40 mm of Hg without significant aortic insufficiency.²

Complications

Femoral artery damage, bleeding, limb ischemia and aortic insufficiency which may progress over a period of time.⁶ The procedure is safe with complication rate of <3 Percent with the newer catheters and balloons.⁷

Balloon Pulmonary Valvotomy (Figs 4A and B)

Pulmonary stenosis (PS) at some level, with and without other associated lesions, occurs in 25 to 30 percent of all patients with CHD. Isolated pulmonary valve stenosis is found in 80 to 90 Percent of all patients with right ventricular outflow obstruction (RVOTO). Most patients with valvar pulmonary stenosis are asymptomatic. Symptoms due to right ventricular failure typically present in those with severe stenosis. Children with valvar pulmonary stenosis usually have normal growth and development regardless

of the severity of obstruction. Infants with critical pulmonary stenosis are cyanotic at birth, and the cyanosis may be severe enough to be life-threatening.²

Balloon pulmonary valvotomy is safe and effective therapy (BPV) for valvar pulmonary stenosis.⁸

Recommendations for pulmonary valvuloplasty¹ (Fig. 5):

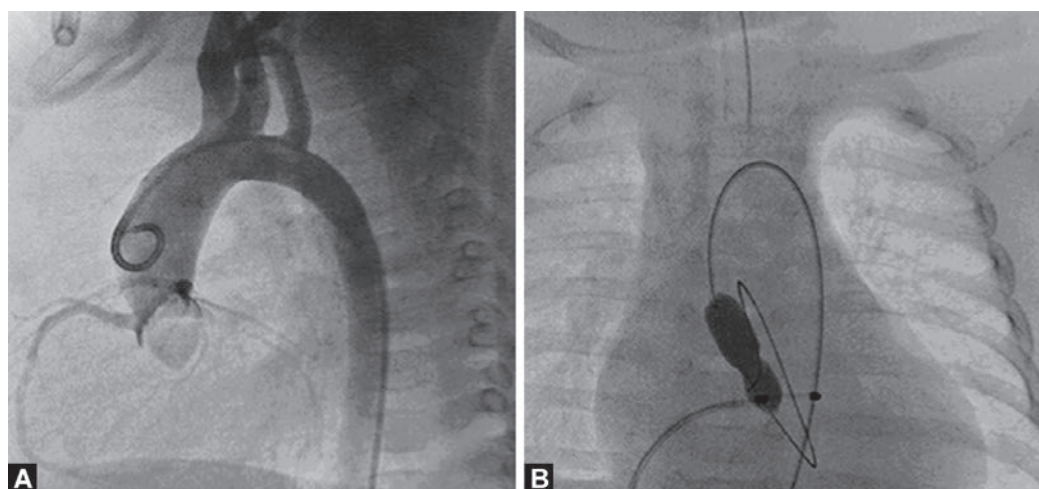
- Indicated in patients with critical PS (presenting in neonatal age with cyanosis and ductal dependent circulation), severe PS with mean Doppler gradient of >40 mm Hg or with significant RV dysfunction.
- Reasonable in patient with dysplastic pulmonary valve and who satisfies above mentioned criteria.
- May be considered in cyanotic patients as a palliative measure, for example, tetralogy of Fallot.
- Contraindicated in patient with pulmonary atresia and RV dependent coronary circulation.

The balloon selected for the procedure is ideally 120 to 130 percent of the size of pulmonary valve annulus.⁹ Neonates with critical PS and a closed arterial duct, a low-profile balloon with fairly rapid deflation characteristics such as the Tyshak II balloon should be used. High-pressure balloons may also be more beneficial when dealing with very dysplastic, thickened pulmonary valves in the older patient, or if there is associated supralvalvar narrowing (Fig. 6).

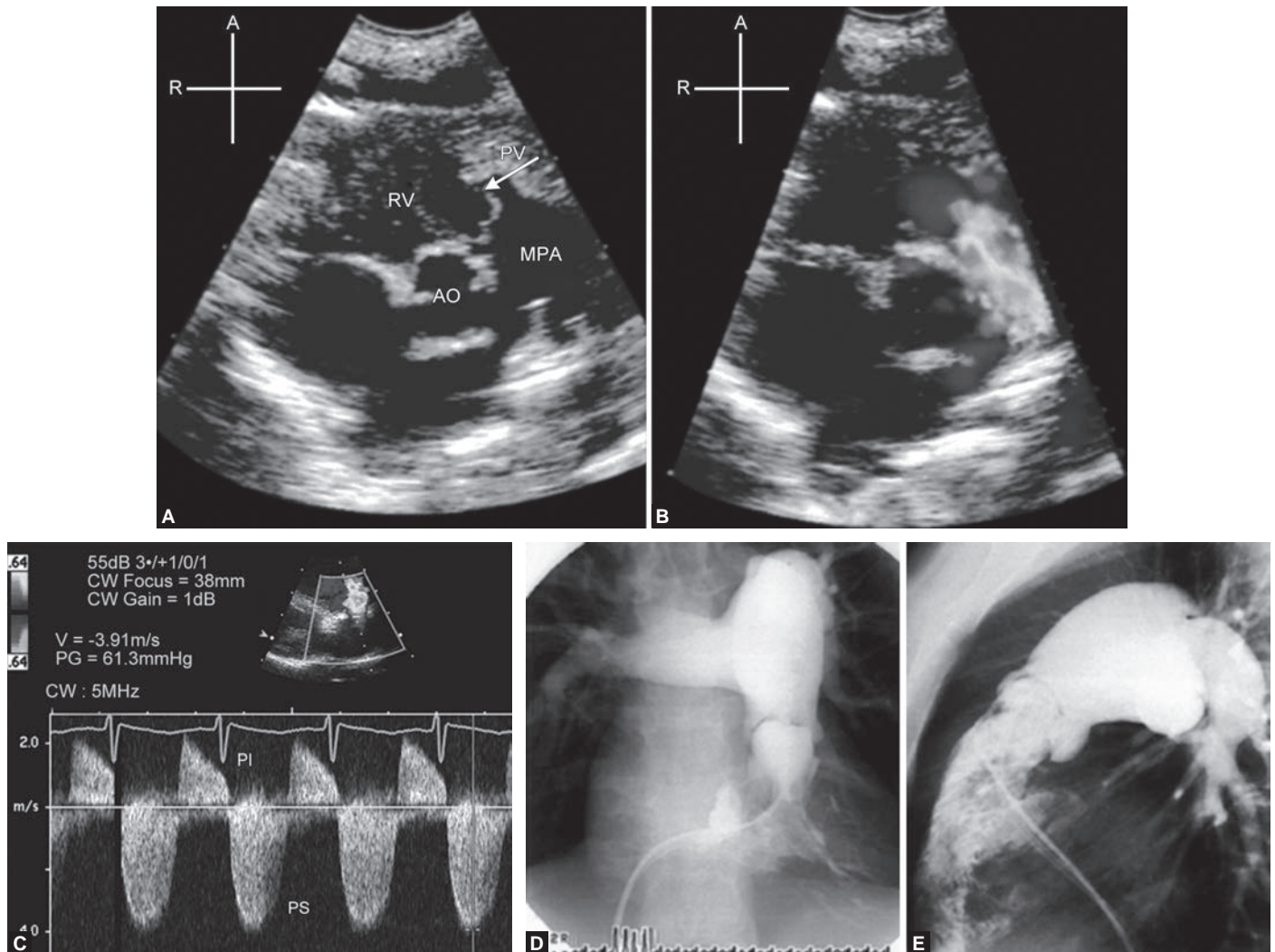
Restenosis after balloon dilation is rare. Pulmonary regurgitation after dilation is common, which occurs in 10 to 40 percent of patients. Compared with surgical valvotomy, however, the incidence and severity of regurgitation is much lower in the group treated with valvuloplasty.¹⁰

Complications

Vessel injury, bleeding, limb ischemia.



Figs 3A and B: (A) Aortogram in lateral projection profiling the doming aortic valve annulus, (B) Balloon inflation centered across the aortic valve



Figs 4A to E: A and B: The echocardiography image of pulmonary valve in parasternal short axis showing stenotic valve with doming of cusps A, Color Doppler through the stenotic pulmonary valve shows a mosaic pattern; C: Continuous wave Doppler imaging in a patient with pulmonary valve stenosis. Note the peak pressure gradient of 61 mm Hg with concurrent pulmonary valve insufficiency; C and D: The ventriculogram in anteroposterior view D and lateral view E, showing stenotic pulmonary valve and characteristic doming of the cusps and dilated segment of MPA. RV: Right ventricle, Ao: aorta, MPA: main pulmonary artery, PV: pulmonary valve. (For color version see plate 17)

TRANSCATHETER DEVICE CLOSURE OF SEPTAL DEFECTS

Secundum Atrial Septal Defect

Secundum atrial septal defect (ASD) account for 7 percent of all congenital heart defects. The most common ASD is a secundum defect followed by defects located in the septum primum, sinus venosus defects, or unroofed coronary sinus. If left untreated, these defects may result in right-sided heart failure, arrhythmias, and pulmonary arterial hypertension. The first transcatheter closure of ASD in humans by double umbrella device was done by King et al in 1976.¹¹ Device closure of secundum ASD is associated with low complication rates, short anesthetic times, and short hospitalizations. When conditions are favorable,

transcatheter secundum ASD closure has become the treatment of choice. Echocardiography, either intracardiac or transesophageal (TEE), plays a significant role in the guiding these procedures.

Indications for Transcatheter Closure of ASD¹

- In patients with hemodynamically significant ASD with suitable anatomic features. The most important criteria to decide regarding the suitability is presence of adequate sized surrounding rims which will hold the device after deployment.
- In patients with transient right-to-left shunting at the atrial level who have experienced sequelae of paradoxical emboli such as stroke or recurrent transient ischemic attack.

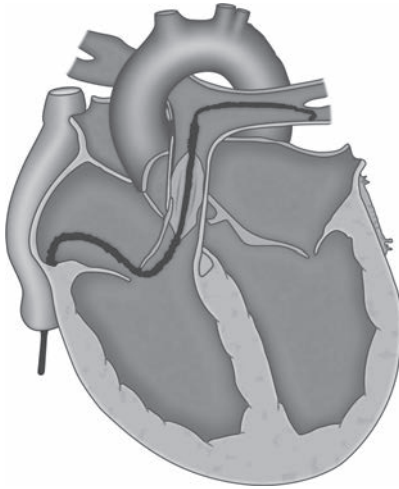


Fig. 5: Schematic illustration of the catheter course and the position of balloon valvuloplasty catheter across the pulmonary valve.

Procedure: After prograde catheterization RV angiogram in lateral and AP projection is obtained. After assessing the details of valve size and location a long exchange guidewire is passed through an end-hole catheter into a distal pulmonary artery, preferably the left pulmonary artery. The balloon catheter is then negotiated over the wire and balloon is positioned across the valve. The balloon is later inflated and deflated rapidly till the disappearance of waist

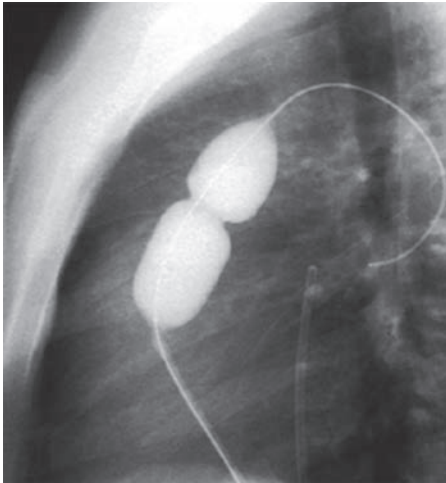


Fig. 6: Single balloon technique of balloon pulmonary

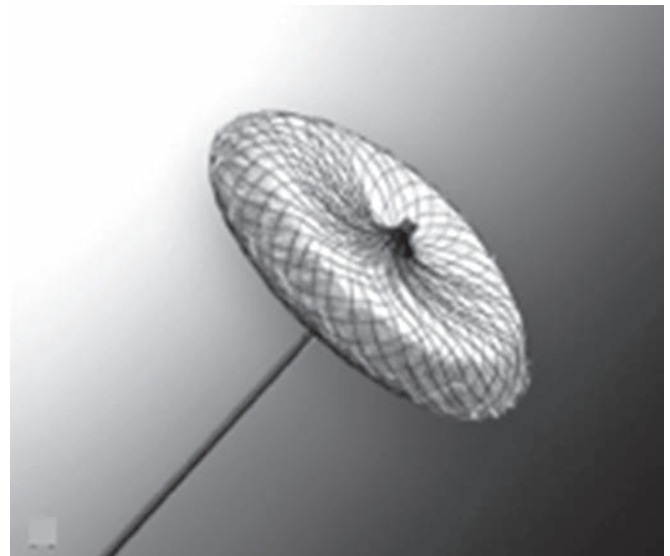


Fig. 7: The amplatzer septal occluder (ASO) is a double-disc device formed of 0.005-inch nitinol mesh. It consists of two disks that are linked to each other through a central connecting waist. Dacron fabric is incorporated into each disk as well as the connecting waist to enhance thrombosis. The device size is defined by the diameter of the connecting waist and is available from 4 to 40 mm. The connecting waist has a length between 3 and 4 mm with the diameter of the left atrial disk exceeding the connecting waist by 12 to 16 mm, whereas the diameter of the right atrial disk exceeds the connecting waist by 8 to 10 mm

Devices for Secundum ASD Closure

Various devices have developed after efforts by King et al.¹¹ Currently, amplatzer septal occluder (AGA Medical) (Fig. 7) is the most widely used device worldwide. Other devices like HELEX septal occluder (WL Gore and Associates) (Fig. 8), cardioseal devices are also approved for secundum ASD closure in certain situations.¹ Both devices can be implanted successfully in children less than 2 years of age, although common practice suggests that a weight of 15 kg may offer some technical advantages and simplify the procedure.²

Procedure²

It is usually performed under general anesthesia under transesophageal echocardiography (TEE) or intracardiac echocardiography (ICE) as guidance. Complete prior echocardiographic assessment for the defect size, surrounding rims, pulmonary venous drainage, atrioventricular valves and associated cardiac malformation needs to be done.

Through the femoral venous access, the left upper or lower pulmonary vein is entered using either a wedge, multipurpose, or Judkins right coronary catheter, and a preshaped exchange length, extrastiff, J tipped wire is advanced. The device size is 125 percent of the average diameter of ASD assessed on TEE. Once the device size has been determined, the appropriate delivery sheath is

- In patients with a small secundum ASD who are believed to be at risk of thromboembolic events (e.g. patients with a transvenous pacing system or chronically indwelling intravenous catheters, patients with hypercoagulable states).

Contraindications for Transcatheter Device Closure of ASD

- In patients with ASD's other than those of the secundum variety like sinus venosus or ostium primum defects.
- Patients with advanced pulmonary vascular obstructive disease.
- Insufficient surrounding rims.

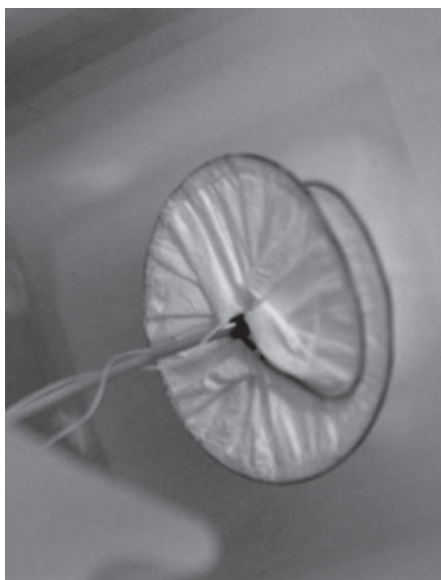


Fig. 8: Helex septal occluder: Its frame is made of a long nitinol wire, with a strip of polytetrafluoroethylene (PTFE) fabric attached alongside. Three eyelets are embedded along the device to facilitate accurate positioning, one at each end and one in central position between both disks. In its deployed status, the device forms two circular disks that are composed of the spiraling nitinol wire with its attached PTFE membrane. The device is available in sizes from 15 to 35 mm. It is used for closure of defects less than 18 mm in size¹²

placed over the guidewire. The dilator and wire are gently removed, and extreme care has to be taken to avoid any inadvertent air entry into the sheath and left atrium at this stage. The device is then prepared for delivery. The device is then loaded into the delivery sheath pushed forward under fluoroscopic guidance to the tip of sheath. The deployment is conducted under simultaneous echocardiographic and fluoroscopic guidance.

Complications

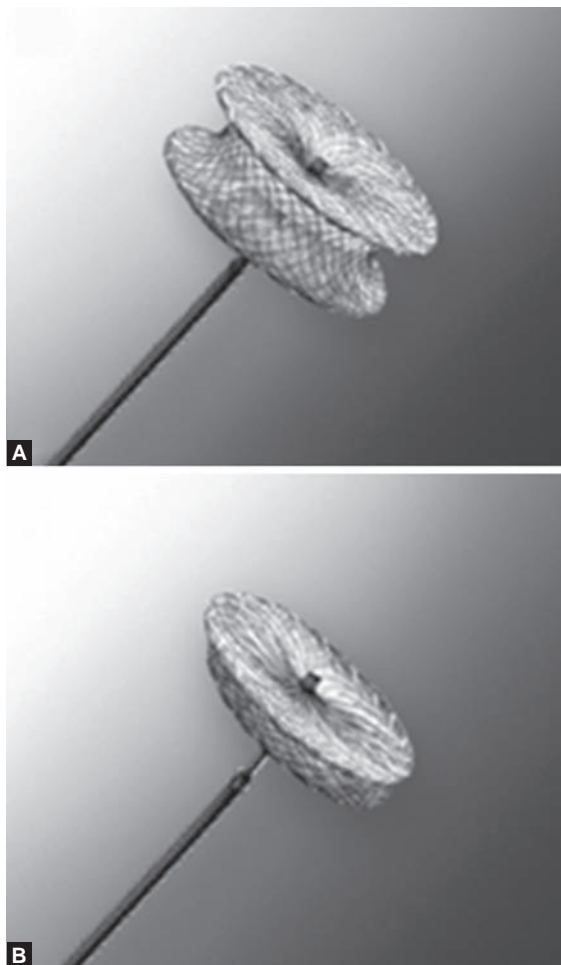
Device migration; device malposition; cardiac erosion/perforation leading to tamponade and death; atrioventricular block; and the complications encountered from a cardiac catheterization, including air embolism, infection, and hematomas.¹

Postprocedure Care

Usually the patients are advised to take tab aspirin 3 to 5 mg/kg daily for 6 months. They can do daily regular activities but they are advised not to participate in heavy competitive sports for six months.

Ventricular Septal Defects (VSDs)

Ventricular septal defects (VSDs) account for 20 percent of all forms of CHD.¹³ The ventricular septum can be divided into 4 regions: Membranous, inlet, trabecular, and outlet. Amongst all types of VSDs, only muscular and some types



Figs 9A and B: Device description:

A. Amplatzer MVSD occluder: It is a double-disk device made of 0.0005-inch nitinol mesh wire. Both disks are equal in size and exceed the diameter of the central connecting waist by 8 mm. Dacron fabric is incorporated into both disks as well as the central connecting waist, which has a length of 7 mm to accommodate the increased septal thickness of muscular VSD. It is available from 4 to 18 mm sizes.²

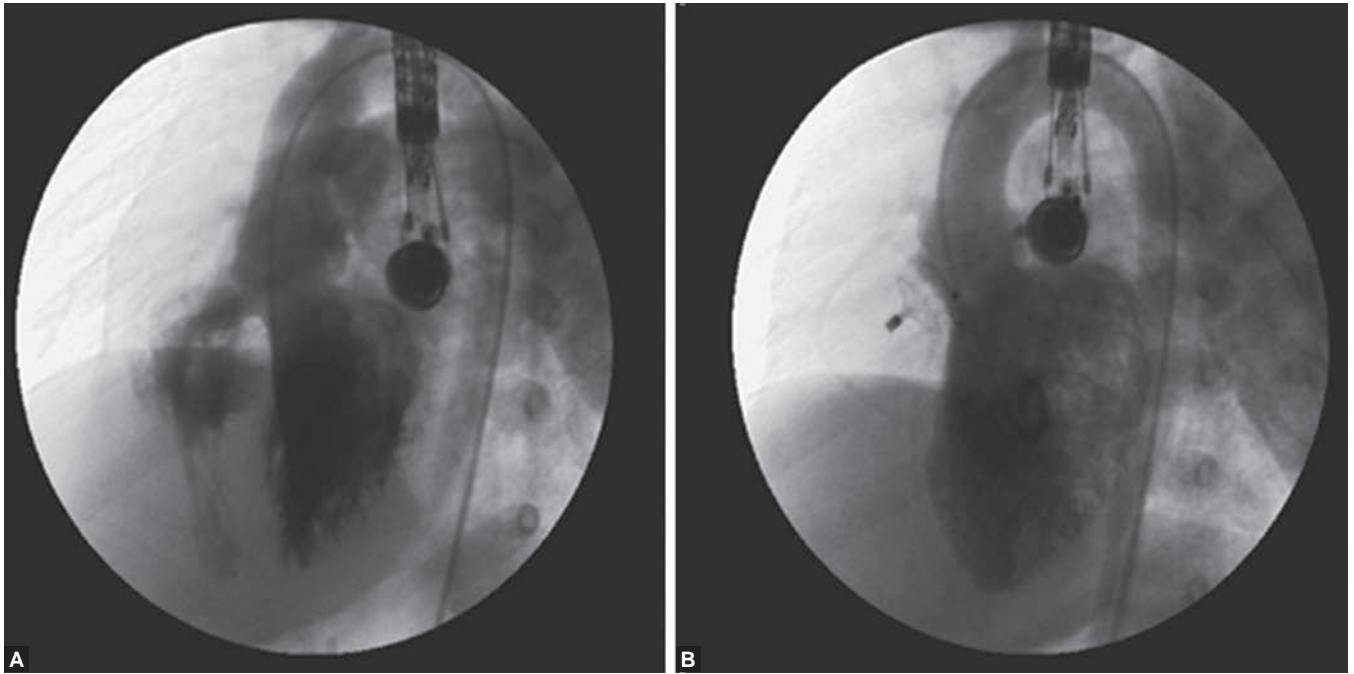
B. Amplatzer membranous VSD occluder: The membranous VSD occluder is an asymmetrical double-disk device made of 0.004-inch nitinol wire mesh. The asymmetrical LV disk exceeds the central connecting waist at the superior, aortic end by just 0.5 mm and at the inferior, apical end by about 5.5 mm. The RV disk is symmetrical to the connecting waist and exceeds its diameter by 4 mm at both the ends.²

of membranous VSD's are suitable for transcatheter closure with the help of device.

Patient selection for device (Figs 9A and B) closure (Figs 10A and B) is mainly done on the basis of transthoracic echocardiography.

Recommendations for Device Closure of MVSDs¹

- Weigh >5 kg child with hemodynamically significant* mid-muscular ventricular septal defect (MVSD) (*hemodynamically significant—left ventricular or left



Figs 10A and B: Procedure:² The procedure is performed under general anesthesia using continuous TEE and fluoroscopy guidance. Through retrograde approach the VSD is usually crossed from the LV using a Judkins RCA catheter with the help of a guide wire which is snared from the venous side. The appropriate-diameter long-delivery sheath is advanced over the guidewire through the defect into the left ventricle. Rest of the device delivery is similar to that of the Amplatzer septal occluder for ASD closure

atrial volume over-load or pulmonary-to-systemic blood flow ratio $>2:1$)

- Weight <5 kg child with hemodynamically significant MVSD and associated cardiac defects requiring cardiopulmonary bypass and may be considered for hybrid periventricular closure of the VSD off bypass.
- Distance of >4 mm between the margins of VSD and the aortic, pulmonic, mitral, or tricuspid valves.
- Pulmonary vascular resistance <7 indexed wood units.

Exclusion Criteria

- Weight <3.0 kg (unless the hybrid periventricular approach is used in this case);
- Sepsis
- Inlet VSD's with inadequate space between the defect and the atrioventricular or semilunar valves should not undergo device closure (hybrid or percutaneous).
- Small to moderate-sized MVSD (without symptoms) in whom there is a reasonable expectation that the defect will become smaller or may close over time.
- The angiogram showing closure of PM VSD. Left before closure and right after closure.

Complications¹

Device migration/embolization, tricuspid and mitral valve regurgitation, hemolysis, transient ischemic attack/ stroke, ventricular tachycardia, and complete atrioventricular

heart block especially with perimembranous VSD. The reported incidences of complete heart block is 4 to 6 percent.

TRANSCATHETER PATENT DUCTUS ARTERIOSUS OCCLUSION

Except in newborns and small infants, most of the transcatheter patent ductus arteriosus (PDAs) are closed by transcatheter closures in the cardiac catheterization laboratory (Fig. 11). For small PDAs either single or multiple coils are used for closures. For larger PDAs a device is used for closure.¹⁴ The most commonly used device to close medium- or larger-sized arterial ducts is the amplatzer duct occluder (ADO).² Although original recommendation for ductal occlusion excludes patients weighing less than 6 kg, successful use in infants as small as 2.5 kg has been reported, although such patients are more challenging technically.¹

RECOMMENDATIONS FOR TRANSCATHETER PDA OCCLUSION¹

- All the auscultable PDAs need to be closed for the risk of infective endocarditis.
- All small to large sized PDAs with left-to-right shunt can be closed by transcatheter closure provided the anatomy and patient size are suitable.

PDA closure is not recommended in a patient with a PDA with severe pulmonary hypertension associated with bidirectional shunt or PDA dependent systemic or pulmonary circulation.

Procedure²

Coil occlusion of the arterial duct can be performed using either an antegrade or retrograde approach. For very small PDAs, a retrograde arterial approach is usually sufficient.



Fig. 11: The device is mushroom shaped and made of 0.005-inch nitinol wire mesh. The central skirt of the device is cone shaped with the pulmonary end being about 1 to 2 mm smaller than the aortic end. The aortic end exceeds the diameter of central skirt by 4 to 6 mm. A micro screw for attachment of the delivery cable is recessed into the pulmonary end of the device. It is available from 5/4 mm to 16/14 mm. The total length of the device ranges from 5 to 8 mm²

Before crossing the patent arterial duct an aortogram is performed. Measurements are obtained at the pulmonary arterial end and the aortic end, as well as the total length of the arterial duct. A coil usually twice the size of the pulmonary end of the duct is chosen, and coils are deployed in a way to usually allow about one loop being placed distal to the pulmonary arterial end, while the remainder of the loops are placed in the ductal ampulla. For the device closure, the PDA is crossed by antegrade approach and a 0.035-inch exchange-length wire is advanced into the descending aorta. The appropriate delivery sheath is advanced over the wire. The selected device size is 2 mm larger than the size of the narrowest pulmonary arterial end of the arterial duct and the device is deployed through the sheath (Figs 12A and D).

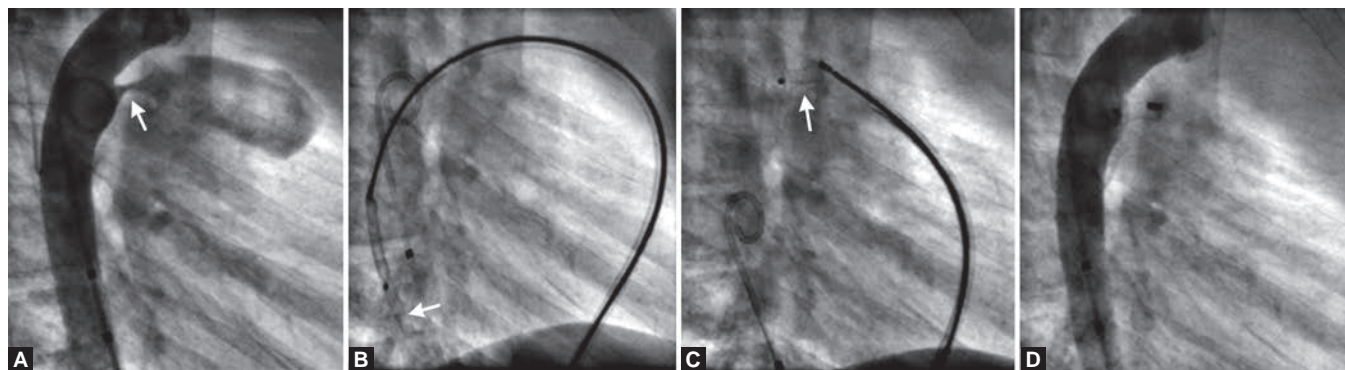
Complications

Inadvertent device embolization into the pulmonary and systemic circulation; obstruction of the descending aorta or left pulmonary artery due to protrusion of disc especially in small infants; transient left ventricular systolic dysfunction; hemolysis; and recanalization of PDA.¹

Coarctation/Recoarctation of Aorta

Coarctation of the aorta is a common form of CHD, accounting for 6 to 8 percent of all cardiac defects (Figs 13A and B). Clinical manifestations of coarctation are age dependent. Neonates with coarctation of the aorta may present with signs and symptoms of low cardiac output and shock once the ductus arteriosus closes. Older infants and children may present with signs and symptoms of failure to thrive, and older children and adults may present with hypertension, headaches, and claudication.¹

Treatment of coarctation of the aorta has evolved over the last few years. Surgical repair of coarctation is the treatment of choice for neonates and small infants with



Figs 12A to D: (A) Angiogram in the descending aorta demonstrating a 2-mm patent ductus arteriosus (PDA) at its narrowest diameter (arrow), angiographic type A, (B) A 6 F delivery sheath across the PDA into the descending aorta with the device near the tip of the sheath (arrow), (C) Deployment of the retention disk and tubular part of a 6- to 4-mm Amplatzer duct occluder (arrow), (D) Final angiogram after the device has been released, demonstrating complete closure of the ductus

severe coarctation due to very high risk of recoarctation and femoral artery damage in this age group.¹⁵ Balloon dilatation with or without stent implantation is the treatment of choice in all children and young adults and in small children who develop recoarctation after initial surgical repair (Figs 14A and B and Figs 15A to D).¹

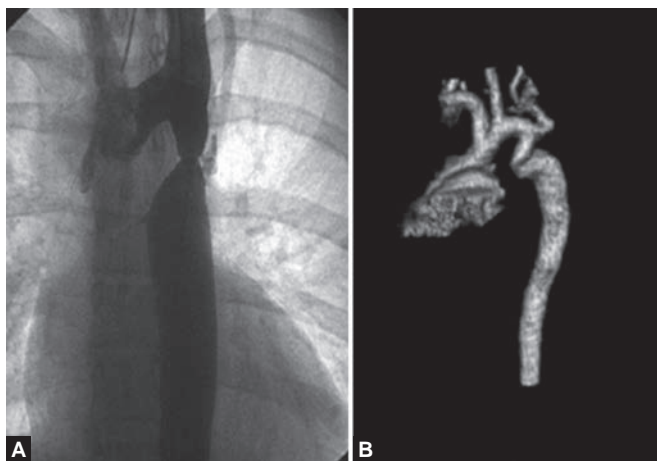
RECOMMENDATIONS FOR TRANSCATHETER BALLOON ANGIOPLASTY OF COARCTATION/ RECOARCTATION OF THE AORTA¹

- Transcatheter systolic coarctation gradient of >20 mm Hg and suitable anatomy.
- Transcatheter systolic gradient of <20 mm Hg and in the presence of significant collateral vessels and suitable angiographic anatomy or with significant ventricular dysfunction.
- In patients beyond 6 months of age when associated with a transcatheter systolic coarctation gradient >20 mm Hg and suitable anatomy.

Stent placement is indicated in patients with recurrent coarctation in bigger children or young adults in whom the stent can be expanded to an adult size, and who have a transcatheter systolic coarctation gradient >20 mm Hg.¹

COMPLICATIONS

Femoral artery injury, dissection, and aneurysm formation at the site of angioplasty, potential risk of stent malposition. The incidence of aneurysm formation after stent implantation is, less than for balloon angioplasty alone. The recoarctation rate after balloon dilatation is higher for younger patients (<6 months of age), and there is a small but definite risk of aneurysm formation after balloon dilation of native coarctation at any age.



Figs 13A and B: (A) The Three-dimensional reformatted CT angiogram in a left-lateral projection showing discrete coarctation and a tortuous transverse arch and isthmus, (B) The aortogram showing typical discrete juxtraductal coarctation with moderated poststenotic dilatation. (For color version see plate 17)

MISCELLANEOUS PROCEDURES

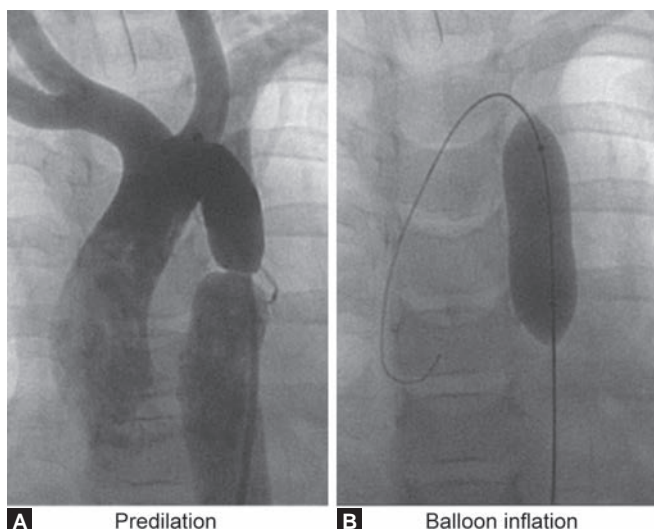
Patent Ductus Arteriosus Stenting

Stenting of the ductus arteriosus is considered in neonates and small infants to establish a reliable source of pulmonary blood flow for palliation of cyanotic heart disease with PDA dependent pulmonary circulation. This procedure is performed instead of doing a BT shunt operation to restore the pulmonary blood flow. Most of these patients are prostaglandin dependent or are severely cyanotic due to significant restriction of pulmonary blood flow. It is contraindicated in patients whose pulmonary arteries are of very small size.

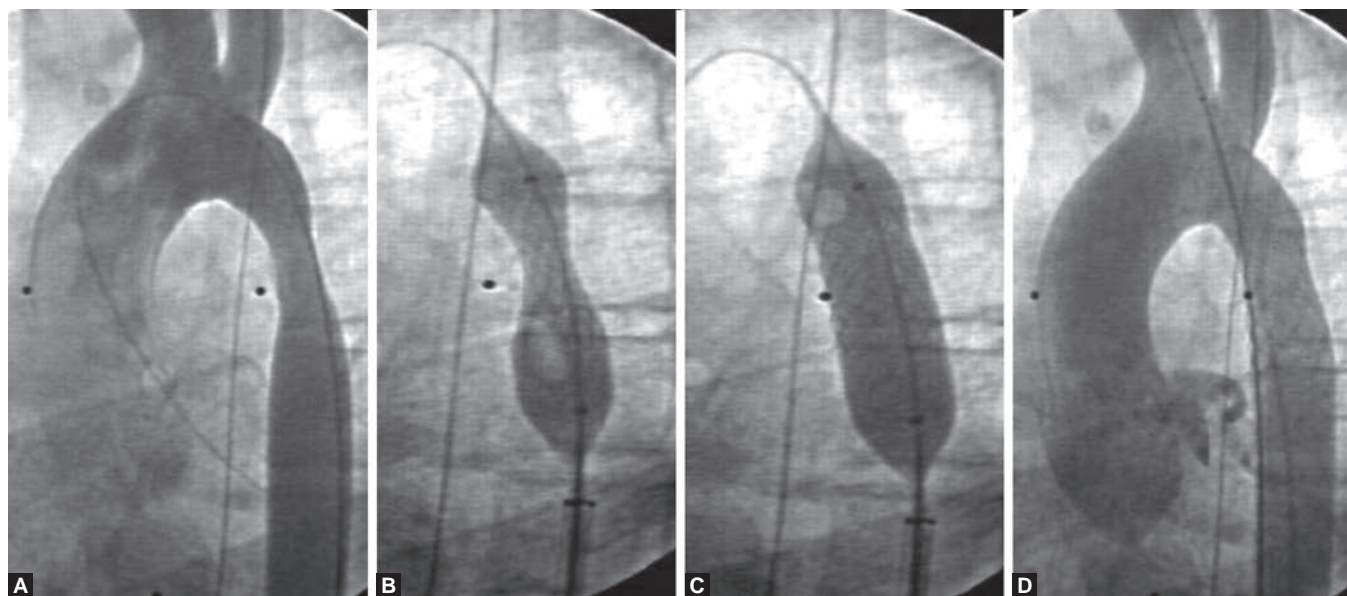
Procedure

The PDA stenting can be done by retrograde or antegrade approach depending upon the anatomy of the duct.¹⁶ A preliminary angiogram is obtained to assess ductal anatomy.

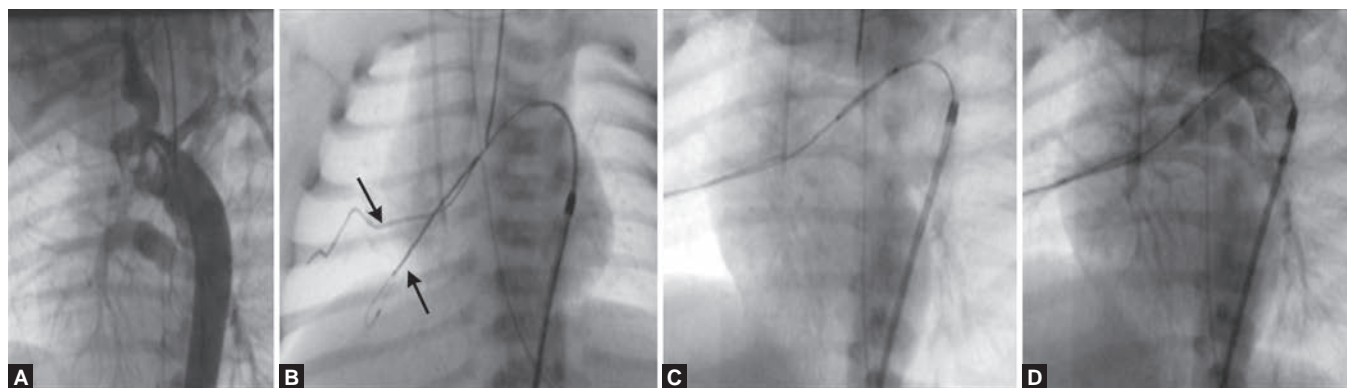
The duct is crossed by appropriate wire (0.014" coronary wire) and premounted coronary stents is advanced over the wire (Figs 16A to D). Once satisfactory position is acquired (both the pulmonary and the aortic ends of the ductus are covered) the stent is deployed by inflating the balloon to appropriate recommended pressure.



Figs 14A and B: Procedure²: The coarctation and adjacent aorta are defined by quantitative angiography. A balloon of the same diameter as the narrowest aortic diameter adjacent to the coarctation is prepared. A "J" or curved-tip stiff guidewire is positioned retrogradely through the coarctation, around the aortic arch, and into the aortic root or occasionally into the right innominate artery. The dilation balloon catheter is passed over the wire and across the area of coarctation. When the balloon is centered, balloon is inflated several times until the waist in the balloon or the gradient disappears



Figs 15A to D: Angiographic pictures of stent insertion for re-coarctation following surgical repair; (A) preprocedure, (B) stent insertion, (C) stent expansion by inflation of internal balloon, (D) final result



Figs 16A to D: (A) LAO-cranial projection—ductus arteriosus in PA-IVS with severe hypoplasia of the RV. Proximal origin of ductus, (B) The tip of a cut pigtail is engaged in the ductal ampulla, (C) Balloon-stent positioned along ductal length ready for expansion, (D) fully expanded stent

Complications^{1,16}

Femoral vessel injury or occlusion, stent thrombosis, ductal spasm, ductus perforation or occlusion, stent migration, early restenosis.

Balloon Mitral Valvotomy

Mitral valve stenosis in children can be either rheumatic or congenital. Although rheumatic mitral valve stenosis is commonly due to the development of thickened mitral leaflets and fused commissures, congenital mitral stenosis encompasses a broad spectrum of anatomic variants, including the “typical” variant with thickened leaflets, shortened chordae, and decreased interchordal spaces, parachute mitral valve; and the hypoplastic mitral valve associated with HLHS.¹ This procedure was extended to

patients with congenital mitral valve stenosis.¹⁷ Though the incidence of rheumatic heart disease is decreasing significantly, we still have a major burden of juvenile mitral stenosis in India. The commonest used balloon is Inoue balloon (Toray International America). Because surgical repair of congenital mitral valve stenosis in infants and young children has high mortality and morbidity, the less invasive transcatheter technique remains a reasonable alternative, although the results remain variable, in part because of the varied morphology of the mitral valve stenosis.¹⁷ In general, balloon dilation is more favorable in those variants of mitral stenosis with commissural fusion and more balanced chordal attachments, and worse outcome is seen with parachute mitral valves, supramitral rings, or small mitral annulus; in younger patients; and in those who develop significant mitral regurgitation.¹⁸

RECOMMENDATIONS FOR MITRAL VALVULOPLASTY¹

- Symptomatic patients with moderate to severe isolated rheumatic mitral stenosis or asymptomatic patients with moderate to severe rheumatic mitral valve stenosis/restenosis associated with pulmonary hypertension.
- Symptomatic children >5 years of age with congenital mitral stenosis or restenosis who have mitral valve morphology that is favorable for balloon valvuloplasty.
- It can be considered for patients <5 years of age with congenital mitral valve stenosis with moderate to severe residual stenosis or with valve restenosis who have already undergone surgical valvuloplasty.

Complications¹

Iatrogenic mitral regurgitation, atrial or ventricular perforation, transient rhythm abnormalities, stroke, and femoral artery or vein trauma.

TRANSCATHETER OCCLUSION OF OTHER VASCULAR ABNORMALITIES**Coronary AV Fistula**

Coronary fistulae may arise from the right or left coronary artery and drain most commonly into the right atrium, ventricle, or pulmonary artery. Most patients are asymptomatic, and spontaneous regression has been reported.¹⁹ They can be symptomatic due to large left to right shunt in few cases and symptoms of coronary steal in others. In the adult population, the frequency of symptoms increases. Thrombosis within the fistula is rare but may cause acute myocardial infarction, paroxysmal atrial fibrillation, and ventricular arrhythmias.¹

Embolization can be performed with coils or other occluding devices.²⁰ Incomplete occlusion with residual shunting, myocardial ischemia due to inadvertent distal coronary artery occlusion are the important complications.¹

Pulmonary Arteriovenous Malformations

Pulmonary arteriovenous malformations (PAVMs) are abnormal direct connections between the pulmonary arteries and veins (bypassing the capillaries). Although uncommon, they may be life-threatening. PAVMs may be congenital and isolated or associated with liver disease, palliated CHD (in which no hepatic flow travels through the lung), cancer, or trauma. There is a strong association between PAVMs and Osler-Weber-Rendu syndrome. Manifestations of PAVMs include cyanosis (most commonly), paradoxical embolization, brain abscess, and rupture. Coil embolization of pulmonary arteriovenous malformations is effective in reducing right-to-left anatomic shunt fraction and in

improving arterial oxygenation.¹ It is well tolerated with low complication rate.²¹

TRANSCATHETER CLOSURE OF RUPTURED SINUS OF VALSALVA

Ruptured aneurysm of the sinus of Valsalva has is a very rare cardiac lesion. Majority of the aneurysms of sinus of Valsalva arise from the right coronary sinus and rupture into right ventricle.² Till now surgical repair was the only option for repairing these aneurysms, but recently there are attempts to close these fistulae by transcatheter closures. Various devices are used to close these fistulae effectively. Transcatheter procedures involve relatively low risks but need lot of technical expertise.

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Section 14

Ambulatory Pediatrics

Editor
SC Arya

Clinical Examination: A Forgotten Art

YK Ambdekar

Over the last several years, medical science has rapidly marched forwards not only in the field of therapeutics but also in the field of diagnostics. But somewhere along the way, art of clinical examination has been left behind. Physicians in older generation practiced medicine without much diagnostic aids and had inevitably mastered art of clinical examination. Modern physician has an “exposure” to lots of “aids.” Easy availability of plethora of diagnostic tools has made the modern physician feel that clinical examination is superfluous for accurate diagnosis. However, in the absence of provisional diagnosis made on sound analysis of history and detailed structured physical examination, indiscriminate use of laboratory tests and polytherapy can be expensive and dangerous for the patient and disastrous for the community. Therefore, scientific advances are intended to facilitate and not eliminate the process of history taking and physical examination. Art of clinical examination must include ability to analyze information obtained through detailed history and abnormal findings on physical examination.

PURPOSE OF CLINICAL EXAMINATION

Detailed history taking and structured physical examination is a prerequisite of provisional diagnosis. It helps to select specific laboratory tests and plan rational therapy. It is ideal to analyze history to a point that it should help anticipate abnormal physical findings and then try to match results of physical examination. In case of discrepancy between anticipated and actual physical examination findings, one may have to cross check both history and physical examination. This becomes a self-learning exercise. It builds confidence and promotes transparency in medical practice.

DETAILED HISTORY TAKING

History taking should start with age of the patient as similar complaints at different age may connote varying

probabilities. Chief complaint has its own significance. Fever, pain in abdomen and vomiting may be common triad of symptoms in hepatitis, appendicitis and viral influenza. However, vomiting may be a chief complaint in hepatitis, abdominal pain in appendicitis and fever in influenza. Origin, duration and progress can add adjectives such as acute or subacute onset, short or long duration of symptoms and improving, worsening or stable progress that may narrow down the probable etiology of disease. Past history of similar disease points to recurrent diseases such as hyper-reactive airway disease or asthma or epilepsy. Every major illness in the past must be made note of as some of the diseases may present with varying forms of manifestations though related to the same disease. Systemic lupus erythematosus may present sequentially with apparently different organ involvement and a child presenting with renal disease but has a past history of skin rash, arthritis and mouth ulcers may point to varying manifestations at different times of the same disease. Family history helps to consider hereditary disorders. Personal history at times would offer clue to the diagnosis and often not volunteered by parents unless specially enquired by the physician. A child suffering from diabetes may present to the physician with fatigue and general weakness or coma and unless asked for, polyuria, polydipsia and polyphagia are often overlooked with resultant missing of diagnosis. Nutritional history is relevant in pediatric practice as many diseases are accompanied with nutritional deficiency and total care demands advice on proper nutrition irrespective of primary disease for which child may have presented. Birth history and developmental history are important especially in infants and young children. Birth events may have direct relation to the presenting disease. Developmental history helps to pick up subtle abnormalities such as mild developmental delay or autism and attention deficit disorder or learning disability. Socioeconomic

history contributes to understanding of diseases that may be the result of adverse socioeconomic status. It is important to realize that even the complicated problems are better solved by detailed history taking and proper analysis. Besides there are diseases that would be totally missed if one did not take into account analysis of history.

STRUCTURED PHYSICAL EXAMINATION

There cannot be a short cut to physical examination. Each part of physical examination is important and may offer a clue to proper diagnosis. Every physician must follow systematic pattern of physical examination, more so if diagnosis is elusive. However, due importance may not be given to some parts of physical examination and they would be emphasized in the following discussion. Unless every abnormal finding is noted correctly and analyzed properly, correct diagnosis may not be possible.

GENERAL EXAMINATION

It begins with description of “first look” of the patient with adjectives such as healthy, comfortable, acutely sick, chronically sick, anxious, breathless, confused, drowsy, etc. “First look” guides immediate plan of action. Anthropometric measurement and nutritional assessment is the integral part of physical examination in pediatric patients. It offers clue to the acuity or chronicity of the problem. Often hidden problems like chronic infection or organ dysfunction can be picked up by these measurements. Growth charts serve great purpose and must be maintained throughout childhood till adulthood. Developmental assessment is another important part of physical examination and basic screening tests can bring forth issues that parents may not have noticed or complained of subtle behavior changes or delayed language development may be the only pointer to learning disorder that must be picked up early in childhood for better outcome. Vital parameters such as pulse, respiratory rate and temperature must be noted with precision as in normal health they are maintained in a balanced proportion. Disproportionate increase in pulse and respiratory rate may suggest systemic inflammatory response and may warn against impending shock. Differential body temperature (central and peripheral temperature or core and skin temperature) and capillary refill time. Marked increase in pulse rate as compared to respiratory rate may point to primary cardiac problem as against marked increase in respiratory rate compared to pulse rate may be due to primary respiratory disorder. Such simple observations should not be missed. Unless special efforts are made to examine skin for any rash, it is easily missed. Purpuric rash of meningococcemia if not noted may prove to be a fatal mistake. Edema of feet may have to be looked for with care as it could be easily missed in early stages. Neck should be specially examined for engorged veins, as they are not noticed by cursory examination. Pallor is best

evaluated on ventral surface of the palm. Mild cyanosis may be difficult to appreciate unless carefully looked for and so also icterus.

In a neonate, physical examination should specially focus on cataract, cleft palate, congenital dislocation of hip, coarctation of aorta, lumbosacral spine and genitalia as these abnormalities are likely to be easily overlooked.

Systemic Examination

It should follow uniform pattern of inspection, palpation, percussion and auscultation. It is only when all these maneuvers are properly carried out and analyzed together that proper diagnosis may be achieved as many abnormal findings are shared by different pathologies. Following discussion will emphasize issues that may be routinely ignored.

Respiratory System

Sound produced during respiration suggests anatomy and pathology of the disease. Stridor indicates upper airway inspiratory obstruction; wheeze denotes lower airway expiratory obstruction and grunt is an attempt to increase end-expiratory pressure to prevent alveolar collapse (natural PEEP) as in pneumonia. Chest retraction suggests respiratory distress. Isolated suprasternal retraction indicates extrathoracic upper airway inspiratory obstruction. Isolated subcostal retraction denotes lower airway expiratory obstruction. Generalized intercostal retraction is seen in alveolar diseases. Severity and extent of chest retraction is proportionate to the severity of the disease. Chest retractions may be observed in a malnourished infant due to compliant chest wall even without any respiratory disease. Tachypnea needs cautious interpretation. When present in respiratory or cardiac disease, it is often accompanied with respiratory distress. Tachypnea without respiratory distress suggests metabolic acidosis. Deep and rapid respiration without any abnormal findings on physical examination of chest favors such a possibility. Loss of voice with tachypnea (silent tachypnea) indicates respiratory muscle paralysis and is easily mistaken for pulmonary or cardiac disease.

Abnormal chest findings should be analyzed by their distribution as it helps to localize the disease to lung, pleura or mediastinum. This is depicted as lobar, pleural or nonlobar nonpleural distribution. Disease affecting upper lobe of the lung results in abnormal physical signs restricted to upper half of the chest anteriorly, middle lobe affection to the lower-half of chest anteriorly and lower lobe involvement to mainly posterior part of the chest (as in lobar pneumonia). Abnormal findings are not restricted to lobar pattern in pleural disease, but are found anteriorly, laterally and posteriorly below a particular intercostal space (as in pleural effusion). However, physical findings in small pleural effusion may be restricted to few lower

intercostal spaces posteriorly. Abnormal chest signs not restricted to either lobar or pleural pattern may suggest mediastinal disease as in case of mediastinal space occupying lesion.

Hepatobiliary System

Anatomically four components need consideration for proper diagnosis—liver cell parenchyma, biliary tract, venous channels and reticuloendothelial cells. Each of these sites present with characteristic findings though there may be an overlap.

Hallmark of liver disease is enlarged liver. Liver size is better judged by liver span rather than extent of palpability of liver below the costal margin. Normal liver is of soft consistency while pathological enlarged liver is firm or hard. Enlarged soft liver is unusual and may suggest “pushed down” liver, in which case liver span is normal. Impalpable shrunk liver due to end stage liver disease is rare in pediatric patients. Normal liver has an edge, which is well defined but not sharp. Sharp edge denotes cirrhosis and rounded edge fatty liver.

Careful palpation of spleen is essential as it may add information in liver disease and so also detection of free fluid in peritoneal cavity—ascites.

Hepatomegaly, splenomegaly and ascites may be present in varying combinations.

All three signs indicate cirrhosis with portal hypertension and liver cell failure. Hepatosplenomegaly without ascites suggests either storage disorder or infection induced reticuloendothelial hyperplasia. Hepatomegaly with ascites without splenomegaly indicates sinusoidal venous obstruction (when associated with liver cell dysfunction) or post-sinusoidal venous obstruction (with normal liver function). Isolated splenomegaly may be a pointer to extrahepatic portal hypertension.

It is important to examine neck veins in every case of enlarged liver as disease like constrictive pericarditis may be easily mistaken for cirrhosis but for the presence of engorged neck veins.

Neurological System

Observation and play techniques are essential means of monitoring intellectual, behavioral and motor functions, especially in infants and young children. Beyond 4 to 5 years of age, neurological examination is more conventional and routine.

Gross motor functions are easily screened by simple maneuvers such as hopping on each foot, tandem walking forwards and backwards, toe and heel walk. Thereafter child should be asked to stand with his feet together, eyes closed and hands outstretched. This allows simultaneous assessment of abnormal movements and Romberg sign. Finger-nose test adds further information. Observing gait offers important information as it helps to localize the

disease to upper motor neuron, extrapyramidal system or peripheral lesion such as anterior horn, nerve or muscle.

Special attention is necessary to spine, skull, signs of meningeal irritation and increased intracranial pressure, papillary dysfunction, autonomic nervous system (vasomotor changes, blood pressure and temperature changes) and pattern of respiration.

Abnormal movements may be classified by the pattern as slow (dystonia, athetosis), rapid and jerky (tics, chorea) or rhythmic oscillatory (tremors, myoclonus).

Developmental reflexes are patterned responses that help assessment of general development of nervous system in first two years of life. Most of these reflexes appear at birth and disappear at sometime in first year. They include truncal incurvation, rooting, moro, palmer and plantar grasp, tonic neck reflex. However, few of them are not present at birth such as parachute and Landau reflex. They appear late in infancy, while Landau reflex disappears by 2 years of age, parachute reflex persists for life. Abnormality in developmental reflexes may be in the form of continued presence of a reflex that should have disappeared, absence of expected response or asymmetrical response. Usually they do not signify any localizing value.

Developmental assessment is an integral part of neurological examination. Parental concern about development needs to be addressed seriously as it often represents genuine abnormality. Language assessment is very important. If child does not attain first word by 18 months of age, detailed evaluation is necessary that should include hearing assessment, global brain function and behavioral assessment. Spectrum of autism, attention deficit hyperactivity disorder, pervasive developmental disorder and learning disability are easily missed unless suspected and evaluated properly.

Visual impairment must be differentiated from visual inattention. Roving eye movements and nystagmus suggest visual impairment.

Cardiovascular System

With easy availability of echocardiography, clinical examination is often ignored. However, unless clinical examination suspects heart disease, echocardiogram may not be asked for and hence it is equally relevant to master the art of clinical examination of cardiovascular system. While obvious abnormal findings may not be missed, it is important to focus attention on subtle signs that may be easily overlooked.

Soft short systolic murmur of ASD is often missed unless looked for carefully. Palpation of peripheral pulses can pick up coarctation of aorta or aortoarteritis. In fact pulse, blood pressure and neck veins offer lots of information along with inspection and palpation of precordium. Auscultation of heart may be confusing especially in case

of tachycardia but other clinical findings may predict auscultatory abnormalities.

Neonatal cardiac examination is tricky as “abnormal” findings may be transient while on the other hand, abnormality may appear later. Ideally, persistence of single second pulmonary heart sound beyond days 3 to 4 may suggest pulmonary outflow obstructive lesions that may be apparent after few weeks. Similarly, persistence of parasternal heave indicating right ventricular hypertrophy may signify congenital heart defect with right heart predominance.

Musculoskeletal System

Rheumatological diseases demand careful examination of joints. Early mild involvement may be evident only by performing different maneuvers to demonstrate restriction of extreme movements. Examination of spine and temporomandibular joints is as important; so also site of insertion of tendons. There are several accompanying physical findings that must be looked for and they include skin rash, mouth ulcers, alopecia, eye findings and involvement of skeletal muscles. Renal involvement in particular is of

paramount importance for proper management and may be picked up by periorbital edema that may have to be specially looked for.

Other Systems

Renal, hematological and endocrinal diseases offer clue in general examination. Edema and blood pressure may point out to renal disease, pallor with or without hepatosplenomegaly and bleeding manifestations signify hematological disorder and growth parameters and examination of genitalia and sexual maturity rating would help in diagnosing endocrinal disease. Gastrointestinal diseases present with nonspecific physical findings such as abdominal distension or tenderness that need careful evaluation.

In conclusion, there is a need to revive the art of clinical examination. Detailed history taking and physical examination should be followed with analysis of observed facts. Laboratory tests are no substitute to clinical examination and taken into account without correlation may misguide the physician. Empirical therapy without provisional diagnosis may result in harm to the patient and physicians must revive the forgotten art of clinical examination.

Rational Drug Therapy

Vikas Dua, Satya Prakash Yadav, Anupam Sachdeva

Irrational use of medicines is a major problem world-wide. World Health Organization (WHO) estimates that more than half of all medicines are prescribed, dispensed or sold inappropriately, and that half of all patients fail to take them correctly. The overuse, underuse or misuse of medicines results in wastage of scarce resources and widespread health hazards. Examples of irrational use of medicines include: use of too many medicines per patient (“poly-pharmacy”); inappropriate use of antimicrobials, often in inadequate dosage, for non-bacterial infections; over-use of injections when oral formulations would be more appropriate; failure to prescribe in accordance with clinical guidelines; inappropriate self-medication, often of prescription—only medicines; nonadherence to dosing regimes. In both the developed and the developing world, medically inappropriate, ineffective and economically inefficient use of pharmaceuticals commonly occurs in health care facilities. The costs of such irrational drug use are enormous in terms of both scarce resources and the adverse clinical consequences of therapies that may have real risks but no objective benefits. Only through a thorough understanding of the existing patterns of therapy, the magnitude of the ways in which such therapy departs from optimal practice, and the factors (clinical, psychological, political, economic, and cultural) which underlie them can an attempt be made to improve the quality and efficiency of drug therapy.

PROBLEMS OF IRRATIONAL DRUG USE

Background

Medically inappropriate, ineffective, and economically inefficient use of pharmaceuticals is commonly observed in the health care system throughout the world especially in the developing countries. However, various forms of inappropriate prescribing often remain unnoticed by

those who are involved in health sector decision-making or delivery of health services. This problem will usually come to the attention of health decision-makers or managers when there is an acute shortage of pharmaceutical budget and action for cost efficiency is required.¹

The need for promoting appropriate use of drugs in the health care system is not only because of the financial reasons with which policy makers and managers are usually most concerned. Appropriate use of drugs is also one essential element in achieving quality of health and medical care for patients and the community. Obviously, this should also become the concern of practitioners. Actions or intervention programs to promote the appropriate use of drugs should, therefore, be continuously implemented and systematically incorporated as an integral part of the health care system.²

Defining Rational Use of Drugs

The terms “appropriate” and “rational” use of drugs will be used interchangeably throughout the chapter. What is rational use of drugs? What does rational mean? People may have different perceptions and meanings regarding rational use of drugs, or more specifically regarding rational prescribing. However, the Conference of Experts on the Rational Use of Drugs, convened by the World Health Organization in Nairobi in 1985 defined that

“Rational use of drugs requires that patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements for an adequate period of time, and the lowest cost to them and their community”³

This is very much a medical model definition.

These requirements will be fulfilled if the process of prescribing is appropriately followed. This will include steps in defining patient’s problems (or diagnosis); in defining effective and safe treatments (drugs and non-drugs); in selecting appropriate drugs, dosage and duration; in

writing a prescription; in giving patients adequate information; and in planning to evaluate treatment responses.

The definition implies that rational use of drugs, especially rational prescribing should meet certain criteria as follows:³

- *Appropriate indication:* The decision to prescribe drug(s) is entirely based on medical rationale and that drug therapy is an effective and safe treatment.
- *Appropriate drug:* The selection of drugs is based on efficacy, safety, suitability and cost considerations.
- *Appropriate patient:* No contraindications exist and the likelihood of adverse reactions is minimal, and the drug is acceptable to the patient.
- *Appropriate information:* Patients should be provided with relevant, accurate, important and clear information regarding his or her condition and the medication(s) that are prescribed.
- *Appropriate monitoring:* The anticipated and unexpected effects of medications should be appropriately monitored.

Unfortunately, in the real world, prescribing patterns do not always conform to these criteria and can be classified as inappropriate or irrational prescribing. Irrational prescribing may be regarded as “pathological” prescribing, where the above-mentioned criteria are not fulfilled. Common patterns of irrational prescribing, may, therefore be manifested in the following forms:

- The use of drugs when no drug therapy is indicated, e.g. antibiotics for viral upper respiratory infections.
- The use of the wrong drug for a specific condition requiring drug therapy, e.g. tetracycline in childhood diarrhea requiring oral rehydration solution (ORS).
- The use of drugs with doubtful/unproven efficacy, e.g. the use of antimotility agents in acute diarrhea.
- The use of drugs of uncertain safety status, e.g. use of dipyrrone (Baralgan, etc.).
- Failure to provide available, safe, and effective drugs, e.g. failure to vaccinate against measles or tetanus, failure to prescribe ORS for acute diarrhea.
- The use of correct drugs with incorrect administration, dosages, and duration, e.g. the use of IV metronidazole when suppositories or oral formulations would be appropriate.
- The use of unnecessarily expensive drugs, e.g. the use of a third generation, broad-spectrum antimicrobial when a first line, narrow spectrum, agent is indicated.

Some examples of commonly encountered inappropriate prescribing practices in many health care settings include:

- Overuse of antibiotics and antidiarrheals for non-specific childhood diarrhea.
- Indiscriminate use of injections, e.g. in malaria treatment.
- Multiple drug prescriptions.
- Excessive use of antibiotics for treating minor acute respiratory infection (ARI).

- Minerals and tonics for malnutrition.
- Consumers may have a very different perspective as to what is rational.

The drug use system is complex and varies from country to country. Drugs may be imported or manufactured locally. The drugs may be used in hospitals or health centers, by private practitioners and often in a pharmacy or drug shop where over the counter (OTC) preparations are sold. In some countries all drugs are available over available over the counter! Finally, the public includes a very wide range of people with differing knowledge, beliefs and attitudes about medicines.

Monitoring the Use of Medicines

From 1990 to date, the World Health Organization (WHO) has created a database of more than 700 published and unpublished surveys of medicine use carried out in developing countries and countries with economies in transition. Results from this database were initially presented at the second International Conference on Improving the Use of Medicines (ICIUM) that took place in Thailand in 2004.³ Some updated results from this database indicate that the use of medicines has remained much the same, slightly increasing over the last 15 years. The results further indicate that in Africa, Asia and Latin America, only about 40 percent of all patients were treated in accordance with clinical guidelines.

Factors Underlying Irrational Use of Drugs

There are many different factors which affect the irrational use of drugs. In addition, different cultures view drugs in different ways, and this can affect the way drugs are used.

The major forces can be categorized as those deriving from patients, prescribers, the workplace, the supply system including industry influences, regulation, drug information and misinformation, and combinations of these factors:³

- Patients
 - Drug misinformation
 - Misleading beliefs
 - Patient demands/expectations
- Prescribers
 - Lack of education and training
 - Inappropriate role models
 - Lack of objective drug information
 - Generalization of limited experience
 - Misleading beliefs about drugs efficacy
- Workplace
 - Heavy patient load
 - Pressure to prescribe
 - Lack of adequate lab capacity
 - Insufficient staffing
- Drug supply system
 - Unreliable suppliers

- Drug shortages
- Expired drugs supplied
- Drug regulation
 - Non-essential drugs available
 - Non-formal prescribers
 - Lack of regulation enforcement
- Industry
 - Promotional activities
 - Misleading claims

All of these factors are affected by changes in national and global practices. For example, the frequent use of injections is declining in many African countries because of the fear of AIDS. In some countries, however, the use of injectibles remains high due to false assumption of prescribers that injections will improve patient satisfaction and that they are always expected by the patients.

Impact of Inappropriate Use of Drugs

The impact of this irrational use of drugs can be seen in many ways:

- Reduction in the quality of drug therapy leading to increased morbidity and mortality.
- Waste of resources leading to reduced availability of other vital drugs and increased costs.
- Increased risk of unwanted effects such as adverse drug reactions and the emergence of drug resistance, e.g. malaria or multiple drug resistant tuberculosis.
- Psychosocial impacts, such as when patients come to believe that there is “a pill for every ill”. This may cause an apparent increased demand for drugs.

Examples of Irrational Drug Use

There are various forms of irrational use of drugs. Drug use can be measured in general and also for specific diagnoses. The following examples illustrate the extent of problems of misuse and overuse in studies from around the world.

All Diseases

- *Polypharmacy*: The number of drugs per case or per episode describes the pattern of polypharmacy, where more than one drug is prescribed (often unnecessarily) for a

condition. In one study in Indonesia,⁴ the occurrence of polypharmacy or multiple prescribing was obvious, where the average number of drugs per case was 3.8 both for under fives and for the over five age group.

When the number of drugs per case was broken down by diagnosis, very little change was noted. The general pattern of polypharmacy occurs almost independent of diagnosis⁴ (Fig. 1).

- Antibiotic use is a common drug use indicator.⁴ Excessive antibiotic use leads to resistance (Fig. 2).
- Injection use is another simple indicator of therapeutic practices. In the study from Indonesia mentioned above, almost half of the under fives and more than 70 percent of the over five age group received at least one injection⁴ (Fig. 3).

When injection use was broken down by diagnoses, overuse was seen to be common for many illnesses. The reasons for the overuse of injections are complex. Prescribers tend to believe that patients expect and are satisfied by receiving injections. Some patients do ask for injections. However, many dislike injections but accept them because “the doctor knows best”. There appears to be great variation in attitudes toward injections across different societies⁴ (Figs 4 and 5).

Disease-specific Indicators

When drug use is studied for specific illnesses, useful insight can be gained.

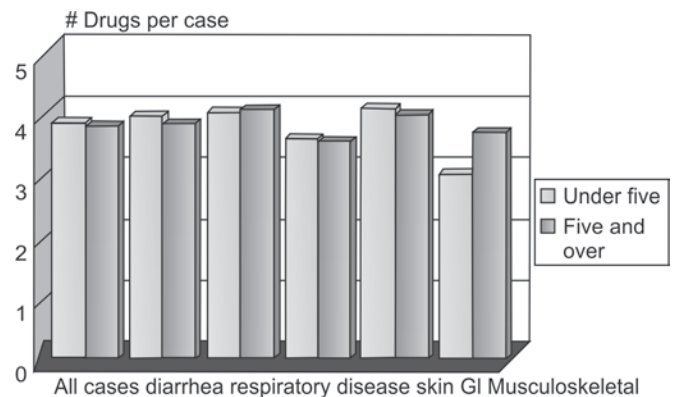


Fig. 2: Drugs per case by diagnosis, Indonesia 1987

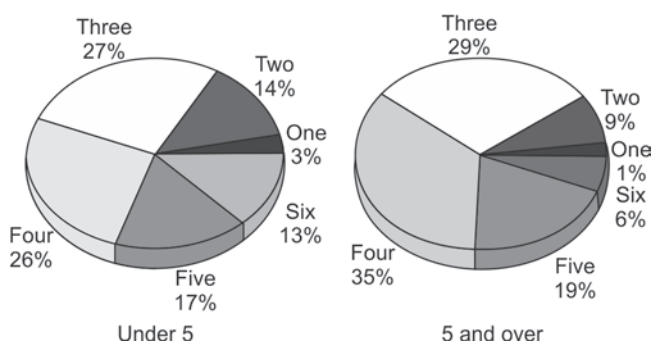


Fig. 1: Drugs per case by age group, Indonesia 1987

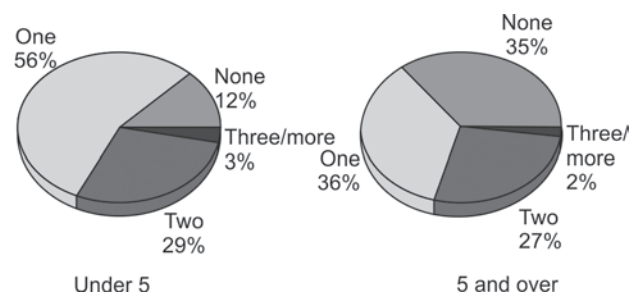


Fig. 3: Percentage of patients receiving antibiotics, Indonesia 1987

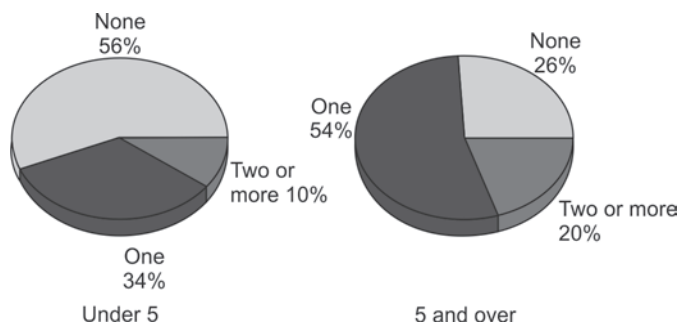


Fig. 4: Percent of patients receiving injections, Indonesia 1987

Drug Use in Acute Respiratory Infection

Many drugs, particularly antibiotics, are used to treat minor upper respiratory tract infections. A major portion of the cost of ARI treatment is due to excessive use of antibiotics⁴ (Fig. 6).

Incorrect Treatment of Malaria

In many African countries, malaria is treated with injectible chloroquine rather than adequate doses of oral chloroquine. This leads to apparent treatment failure, which in Ghana is called “go slow malaria”.

Poor Compliance with Tuberculosis Therapy

In many countries with tuberculosis programs, less than 50 percent of patients fully complete their course of therapy which may last for 6 to 8 months. This results in treatment failures and the emergence of multiple resistant organisms (MDRTB). To counteract this dangerous trend, WHO and the International Union against tuberculosis have popularized the use of Directly Observed Treatment Short course (DOTS).⁵ In this system, TB patients are directly supervised taking their medication. When this is done, cure rates of over 90 percent are possible. However, effectiveness has varied widely across different environments.

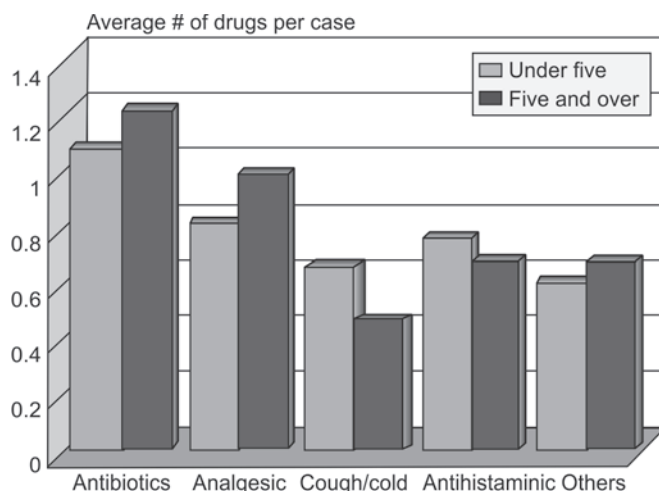


Fig. 6: ARI treatment pattern, Indonesia 1987

Underuse of Effective Drugs

In both developed and developing countries, some conditions for which effective medicines exist are undertreated. Examples of these include hypertension, depression or anemia during pregnancy. These conditions can be life threatening and severely disabling. They are under diagnosed because they are not checked for regularly and health workers do not consider these conditions. However, these conditions are very amenable to therapy. Thus, failure to treat serious conditions is another form of irrational drug use.

Hospital Problems

Drug use in hospitals has been a neglected area. However in both developed and developing countries the misuse of antibiotics, particularly for surgical prophylaxis, has been widely reported. Hospitals have been able to improve antibiotic use through the use of formularies.

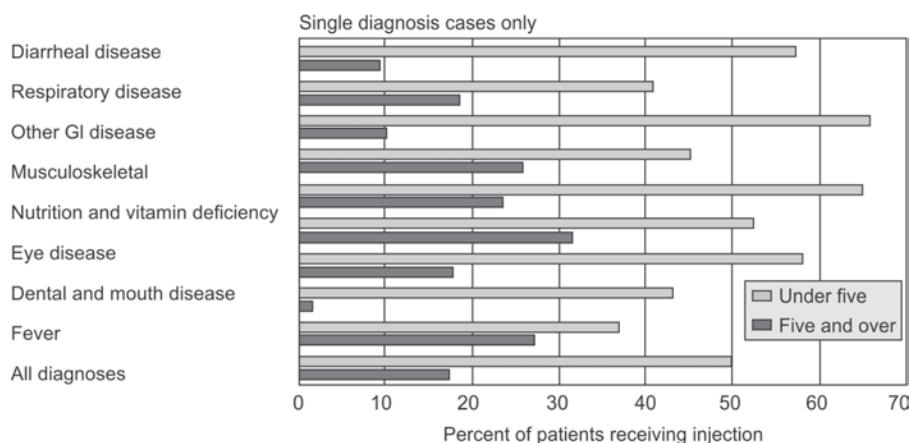


Fig. 5: Injection use by diagnosis, Indonesia 1987

Drug Use Patterns in Developing Countries

In order to encourage a standard approach to measuring problems in drug use, the International Network for the Rational Use of Drugs (INRUD) coordinated the development of standard drug use indicators and encouraged indicator studies in a number of developing countries during the period 1990-1992.⁶⁻⁹ These results are presented below:

The average number of drugs prescribed in public sector facilities in most of these countries ranges from 1.3 to 2 drugs. However, Indonesia, Nigeria and Ghana differ

significantly from this average. The use of generics varies from 37 to 94 percent. This tends to depend on government regulations and the enforcement efforts in the country (Fig. 7).

Antibiotics are commonly used in developing countries due to the high load of infection. Most countries tend to lie in the range of 25 to 40 percent, though some are considerably higher (Fig. 8).

The use of injections varies considerably, and seems to be declining in many countries. The use of injections is also affected by the availability of injectable drugs and

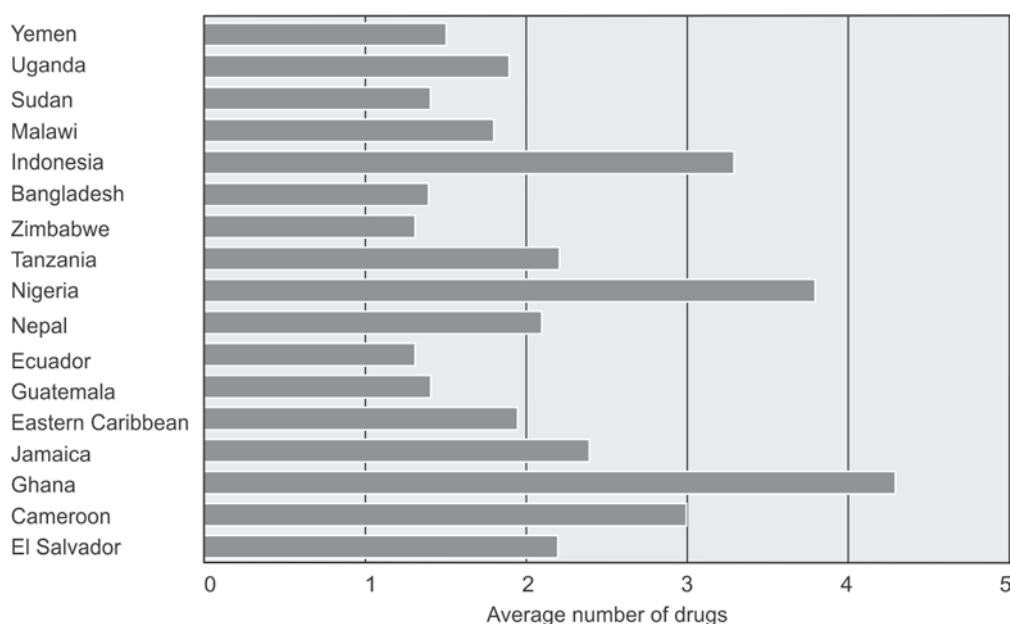


Fig. 7: Average number of drugs per patient, 1990-1992

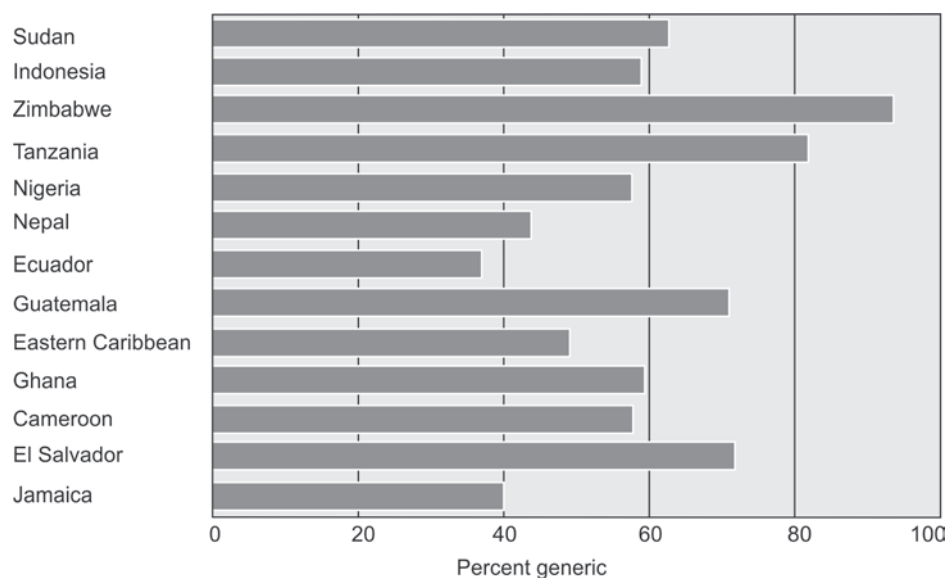


Fig. 8: Percent prescribed as generics, 1990-1992

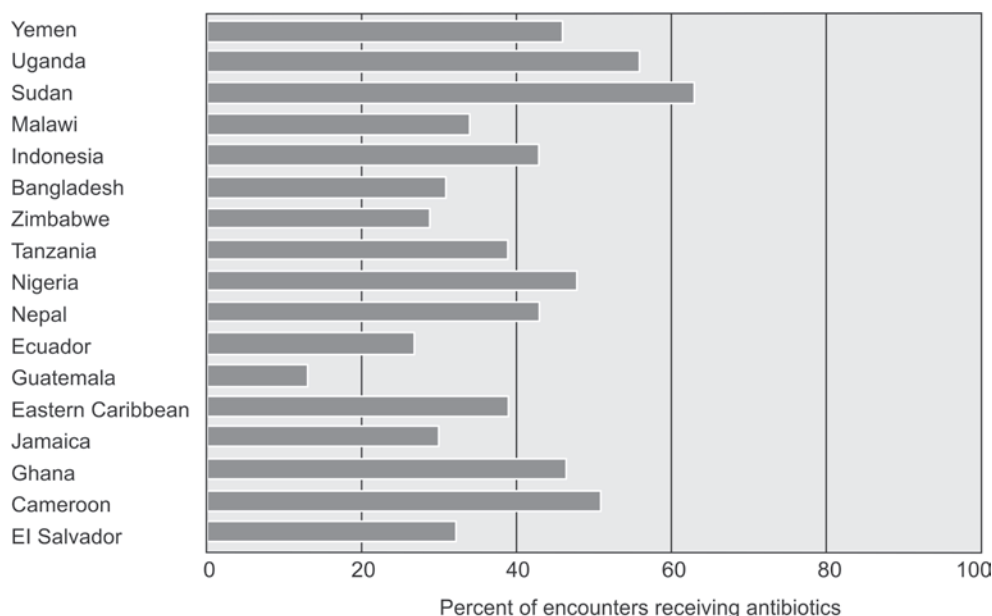


Fig. 9: Percent receiving antibiotics, 1990-1992

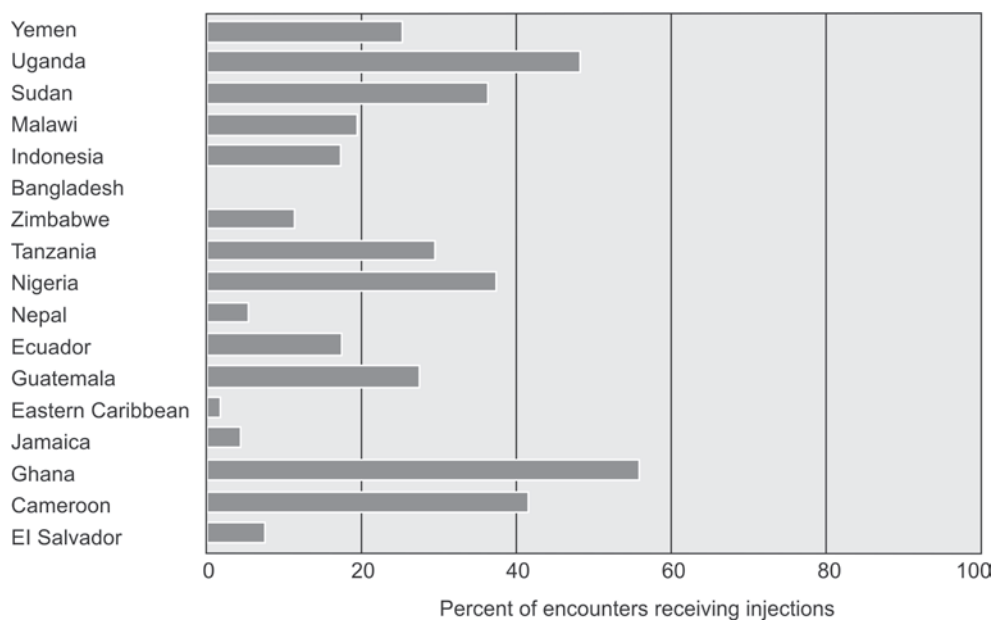


Fig. 10: Percent receiving injections, 1990-1992

syringes and needles. However, rates as high as 48 percent, as occurred in Uganda in September 1990, are clearly too high, particularly in the HIV/AIDS era (Fig. 9).

Percentage receiving injections, 1990-1992 is shown in (Fig. 10).

Patient Care Indicators

More recently efforts have been made to quantify the consulting and dispensing process. The consultation time in most country studies varies from 2.3 to 3.5 minutes.

The events occurring during this time frequently do not include physical examinations.

Dispensing has been observed in a limited number of countries. The average times vary from 12 to 86 seconds, which is a short time to convey what may be complex information about prescribed drugs to the patient (Fig. 11).

When patients are assessed as to their knowledge of how they should take drugs, between 27 and 83 percent know how and when to take their drugs. Potentially, this could result in major misuse of drugs (Fig. 12).

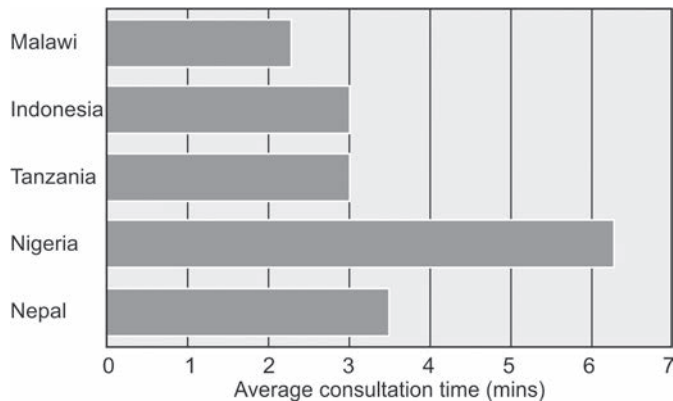


Fig. 11: Average consultation time, 1990-1992

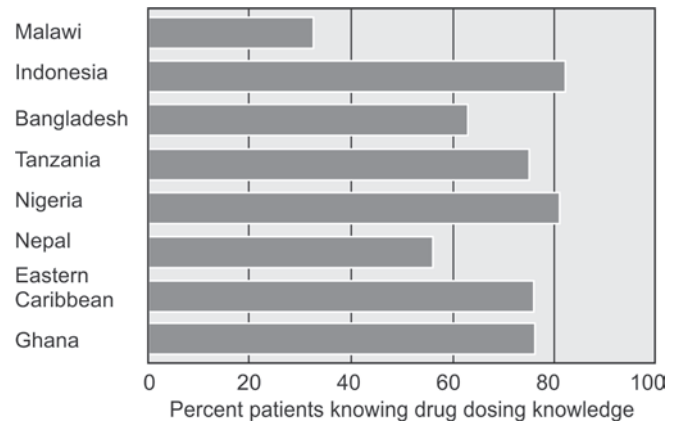


Fig. 13: Percent patients knowing drug dosing, 1990-1992

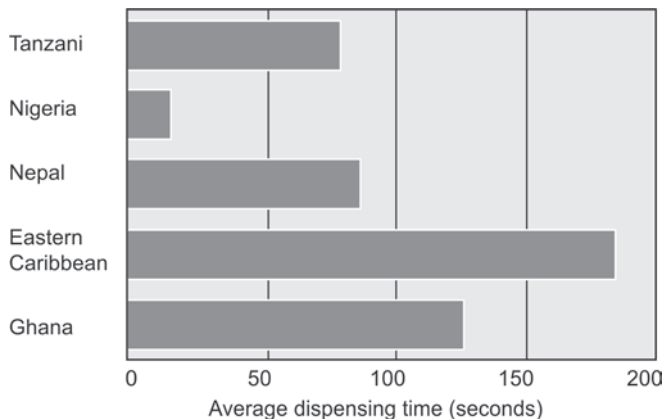


Fig. 12: Average dispensing time, 1990-1992

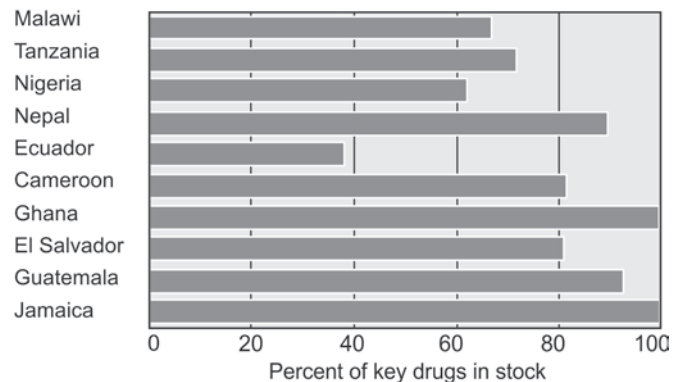


Fig. 14: Percent of key drugs in stock, 1990-1992

Percent patients knowing drug dosing, 1990-1992 is shown in (Fig. 13).

Facility Indicators

Drug treatment may vary according to the availability of drugs. In a series of surveys of the availability of 10 to 15 key drugs, the drugs were available between 60 and 90 percent of the time, except in Ecuador. These data from different countries reflects the present situation in prescribing (Fig. 14).

DECISION MAKING FOR RATIONAL USE INTERVENTIONS

Introduction

Once a determination has been made that a drug use problem exists in an institution, an area, or a country, action to remedy the problem usually follows. Unfortunately, it is not always clear what intervention will be most effective. To decide which intervention(s) should be undertaken, preliminary work is required.

First, the drug use problem should be clearly defined. After this, the various motivating factors should be

identified and assessed. Then comes the stage of listing interventions. There are usually multiple options for dealing with any specific problem. Once these possibilities have been listed, the difficult task of choosing one or two interventions should occur. When more than one intervention is selected, each should be of a different type (regulatory, managerial, or educational).

When the intervention is undertaken it is important that there be a control group and that the sample sizes are adequate to detect differences if they exist. Once the control study has been undertaken, the results should be assessed and follow-up decided. Three outcomes are likely. First, the intervention may be ineffective and should be dropped; second, the intervention might require revision and restudy; third, in a few cases the intervention may be clearly effective, and such interventions can then be translated into national programs.

Choosing Strategies to Test and Implement

You might find that, in addition to the above techniques, there are other managerial and regulatory strategies that could be considered for your country or your program. It is important to choose a small number of strategies likely

to succeed, test them on a pilot basis, and then to implement the strategy as effectively as possible.

The following factors should be considered in choosing strategies:¹⁰⁻¹²

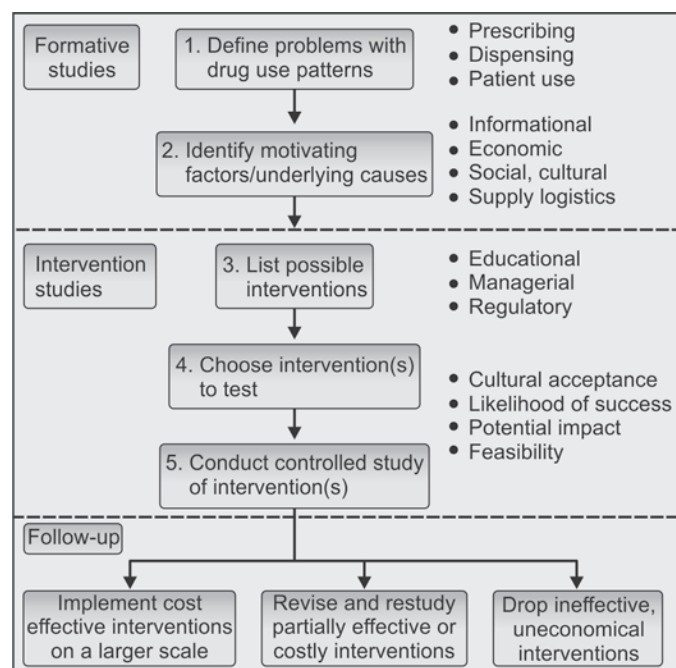
- *Expected magnitude of impact*: If the strategy is successful, what is the likely impact? That is, will it affect only a few drugs, only a few providers, or only save a small amount of money? Or will the impact be great? Obviously, preference goes to strategies likely to have greater impact on priority drug use problems.
- *Likelihood of success*: All things considered, how likely is success? Will opposition be so great or the task so complex that success is unlikely?
- *Unintended effect*: What are the unintended effects that might occur? How can these effects, if any, be minimized?
- *Political and cultural feasibility*: How acceptable is the strategy in the local context? Will political and cultural factors favor development and implementation of the strategy, or will they severely hinder it?
- *Technical feasibility*: What are the technical requirements of the strategy? Computers? A highly developed information system? How much technical help (people, systems, equipment) will be needed?
- *Cost (economic feasibility)*: What is the cost, particularly compared to available resources and to the potential benefits of successfully implementing the strategy?
- *Potential for donor support*: Will donor support be needed? Requested? How likely is it that the donors with whom you work will support the proposed approaches?

If an informal review of possible strategies has reduced the number to relatively few (perhaps two to eight), then a decision matrix could be made using the alternative strategies as one dimension and the above six selection factors as the other dimension. Whatever strategies are chosen, they should be tested in advance wherever possible and the impact of their implementation should be carefully monitored.

Stages in Attacking a Drug Use Problem¹³ (Flow chart 1)

- The initial action required is to characterize the drug use situation with a general drug use indicator study (*quantitative*).
- The problem may require clarification which can be done through follow-up *quantitative* studies (disease specific or level specific).
- Following this stage it is essential that the motivations of prescribers and the constraints within the system are investigated. This requires *qualitative* studies.
- With the available data you can then identify the key factors to change. This requires synthesis of data

Flow chart 1: Framework for formative and intervention studies



and prioritization of problems. Are they: important, changeable, feasible?

- Intervention selection should ensure that they are targeted to identified factors and constraints.
- Study design should take into account the available resources both financial and human and the administrative structure.
- Monitor progress of the intervention closely as unexpected changes may complicate the result of the intervention.
- Evaluate the results carefully, obtaining assistance in data analysis if necessary.
- Feedback the results of the intervention (positive or negative).

WHO Advocates 12 Key Interventions to Promote More Rational Use¹⁴

- Establishment of a multidisciplinary national body to coordinate policies on medicine use.
- Use of clinical guidelines.
- Development and use of national essential medicines list.
- Establishment of drug and therapeutics committees in districts and hospitals.
- Inclusion of problem based pharmacotherapy training in undergraduate curricula.
- Continuing in service medical education as a licensure requirement.
- Supervision, audit and feedback.
- Use of independent information on medicines.

- Public education about medicine.
- Avoidance of perverse financial incentives.
- Use of appropriate and enforced regulation.
- Sufficient government expenditure to ensure availability of medicines and staff.

A Mandated Multi-Disciplinary National Body to Coordinate Medicine Use Policies

Many societal and health system factors, as well as professionals contribute to how medicines are used. Therefore, a multi-disciplinary approach is needed to develop, implement and evaluate interventions to promote more rational use of medicines. A national regulatory authority (RA) is the agency that develops and implements most of the legislation and regulation on pharmaceuticals. However, ensuring rational use requires coordination with other stakeholders in more activities than those normally covered by RA's. Thus a national body is needed to coordinate policy and strategies at national level, in both the public and private sectors. The form this body takes may vary with the country, but in all cases it should involve government (ministry of health), the health professions, academia, the RA, pharmaceutical industry, consumer groups and non-governmental organizations involved in health care. The impact on medicine use is better if many interventions are implemented together in a coordinated way, single interventions often having little impact.

Clinical Guidelines

Clinical guidelines (standard treatment guidelines, prescribing policies) consist of systematically developed statements to help prescribers make decisions about appropriate treatments for specific clinical conditions. Evidence-based clinical guidelines are critical to promoting rational use of medicines. Firstly, they provide a benchmark of satisfactory diagnosis and treatment against which a comparison of actual treatments can be made. Secondly, they are a proven way to promote more rational use of medicines provided they are:

- Developed in a participatory way involving end-users;
- Easy to read;
- Introduced with an official launch, training and wide dissemination;
- Reinforced by prescription audit and feedback.

Essential Medicines List Based on Treatments of Choice

Essential medicines are those that satisfy the priority health care needs of the population. The use of an essential medicines list (EML) makes medicine management easier in all respects. Procurement, storage and distribution are easier to do with fewer items, and prescribing and dispensing are easier for professionals as they have to know about fewer items. A national EML should be based

upon national clinical guidelines and should be the focus for government activities in the public sector, e.g. procurement, distribution, insurance reimbursement policies and training. Only health workers who are approved to use certain medicines should be supplied with them. Medicine selection should be done in a transparent way by a central committee with an agreed membership and using explicit, previously agreed criteria, based on efficacy, safety, quality, cost (which will vary locally) and cost-effectiveness.

Drugs and Therapeutics Committees in Districts and Hospitals

A drugs and therapeutics committee (DTC) is a committee designated to ensure the safe and effective use of medicines in the facility or area under its jurisdiction. Such committees are well established in industrial countries as a successful way of promoting more rational, cost effective use of medicines in hospitals. Governments may encourage hospitals to have DTC's by making it an accreditation requirement to various professional societies. DTC members should represent the administration and all the major specialties in any given facility. The members should also be independent and declare any conflict of interest. A senior doctor would usually be the chairperson and the chief pharmacist, the secretary. Unfortunately many DTC's are procurement committees. Their activities should however be much broader and should include developing or adapting clinical guidelines, medicines selection, monitoring medicines use and taking corrective action, staff education, controlling drug promotional activities by pharmaceutical industry within the premises of the health facility and monitoring adverse drug reactions.

Problem-based Training in Pharmacotherapy in Undergraduate Curricula

The quality of basic training in pharmacotherapy for undergraduate medical and paramedical students can significantly influence future prescribing. Rational pharmacotherapy training, linked to clinical guidelines and essential medicines lists, can help to establish good prescribing habits. Training is more successful if it is problem based, concentrates on common clinical conditions, takes into account students' knowledge, attitudes and skills, and is targeted to the students' future prescribing requirements (WHO 1994).

Continuing In-service Medical Education as a Licensure Requirement

Continuing in-service medical education (CME) is a requirement for licensure of health professionals in many industrialized countries. In many developing countries opportunities for CME are limited. In these countries no incentives are offered for CME since it is not required for continued licensure. CME is likely to be more effective if it

is problem based, targeted, involves professional societies, universities and the ministry of health, and is face-to-face. Printed materials, such as bulletins or newsletters, that are unaccompanied by face to face interventions, have been found to be ineffective in changing prescribing behavior. CME should be provided for all cadres of health worker including in the informal sector such as drug retailers. Often due to lack of public funds CME is heavily supported by the pharmaceutical sector and may thus be biased. Governments should therefore support efforts by university departments and national professional associations to give independent CME.

Supervision, Audit and Feedback

Supervision is essential to ensure good quality of care. Supervision that is supportive, educational and face to face, will be more effective and better accepted by prescribers than simple inspection and punishment. Effective forms of supervision include prescription audit and feedback, peer review and group processes such as self monitoring. Many industrialized countries have a strong supervisory infrastructure but resources are often lacking for this in low-income countries.

Independent Information on Medicines

Inadequate knowledge and lack of access to independent information about medicines significantly contribute to irrational use of medicines. Often, the only information that practitioners receive is provided by the pharmaceutical industry and may be biased. Provision of independent (unbiased) information is therefore essential. Drug information centres (DIC's) and drug bulletins are two useful ways to disseminate such information. Both may be run by government or a university teaching hospital or a non-governmental organization, under the supervision of a trained health professional.

Public Education about Medicines

It is essential that the general public have the skills and knowledge to make informed decisions about when and how to use medicines, and to understand their potential risks as well as benefits. Without such knowledge and skills, people will often not get the expected clinical outcomes and may suffer adverse effects. This is true for prescribed medicines, as well as medicines used without the advice of health professionals.

Governments have a responsibility to ensure both the quality of medicines and the quality of the information about medicines available to consumers. This will require:

- Ensuring that over the counter medicines are sold with adequate labeling and instructions that are accurate, legible, and easily understood by lay persons;
- Monitoring and regulating advertising, which may adversely influence both prescribers and consumers;
- Running targeted public education campaigns, which take into account cultural beliefs and the influence of social factors.

Avoidance of Perverse Financial Incentives

Financial incentives that encourage irrational use of medicines should be avoided. For example, prescribers who earn money from the sale of medicines (e.g. dispensing doctors) prescribe more medicines, and more expensive medicines, than prescribers who do not. The health system should therefore be organized to deter prescribers who dispense or sell medicines. Patients prefer to get 2 to 3 medicines rather than one if the total cost to them is the same regardless of the number of medicines. Flat prescription fees covering all medicines in whatever quantities within one prescription lead to over prescription. User charges should therefore be made per medicine, not per prescription. Insurance policies should provide reimbursement only for essential medicines, not non-essential ones.

Appropriate and Enforced Regulation

Regulation of the activities of all actors involved in the use of medicines is critical to ensuring rational use. Regulations only have an effect if they are enforced, and the regulatory authority sufficiently funded and backed up by the judiciary.

Sufficient Government Expenditure to Ensure Availability of Medicines and Staff

Irrational drug use is caused in part by the lack of essential medicines and the lack of appropriately trained personnel. Without sufficient competent personnel and finances, it is impossible to carry out any of the core components of a national programme to promote rational use of medicines. Poor clinical outcome, needless suffering and economic waste are sufficient reasons for large government investment.

Rational Use of Medicines: National Strategy¹⁴

Ensure therapeutically sound and cost effective use of medicines by health professionals and consumers. Improving the use of medicines by health workers and the general public is crucial both to reducing morbidity and mortality from communicable and non-communicable diseases, and to containing drug expenditure.

Ideally, therapeutically sound and cost effective use of medicines by health professionals and consumers is achieved at all levels of the health system, and in both the public and the private sectors. A sound rational drug use program in any country has three elements:

- *Rational use of medicines strategy and monitoring:* Advocating rational medicines use, identifying and promoting successful strategies, and securing responsible medicines promotion.

- *Rational use of medicines by health professionals:* Working with countries to develop and update their treatment guidelines, national essential medicines lists and formularies, and supporting training programs on rational use of medicines.
- *Rational use of medicines by consumers:* Supporting the creation of effective systems of medicines information, and empowering consumers to take responsible decisions regarding their treatment.

The above elements are formulated in such a way as to reflect the main responsibilities of a national essential medicines program.

Rational medicine use strategy and monitoring: Need for implementation of a national strategy to promote rational use of medicines by health professionals and consumers and provision of monitoring.

Rational medicine use by health professionals: Develop national standard treatment guidelines, essential medicine lists, educational program and other effective mechanisms to promote rational medicine use by health professionals.

Rational medicine use by consumers: Establishing effective medicines information systems to provide independent and unbiased medicine information—including on traditional medicine—to the general public and to improve medicine use by consumers.

Drug selection while treatment must be based on the following:¹⁵

- *Relevance to disease:* Indicated in the treatment of prevalent diseases.
- *Efficacy and safety:* Based on the objective results from adequate pharmacological studies including at least expanded phase (II) clinical trials and/or additional phase (III) studies.
- *Quality*
- *Cost*—of treatment regime (not just the unit cost).
- *Appropriateness* to the capability of medical personnel at different levels of health care—The level of expertise required to prescribe, administer and monitor safety and adverse effects of single drug or group of drugs in the therapeutic category must be considered. Consideration should be given to the competence of local personnel in making the correct diagnosis.
- *Local health problems:* The influence of concomitant, locally prevalent diseases or conditions on pharmacokinetic and pharmacodynamic parameters modifying therapeutic response have to be considered in making the selection, e.g. malnutrition, liver disease.
- *Benefits/risk ratio:* When several comparable drugs are available for the same therapeutic indication it is necessary to select the one which provides the most favorable benefit/risk ratio.
- *Preferential factors* for evaluating therapeutically equivalent drugs: When two or more drugs are therapeutically equivalent preference should be given to:
 - The drug most thoroughly investigated and therefore the best understood with respect to its beneficial properties and limitations.
 - The drug which is clinically appropriate for more than one disease.
 - The drug with the most favorable pharmacokinetic properties, e.g. to improve the compliance to minimize risk.
 - The drug that are in a dosage form that is easy for the health staff to dispense easily and safely administer to the patient.
 - The drugs that are easy for the patient to take or with the broadest acceptability.
 - The drugs, pharmaceutical products and dosage forms with favorable stability under anticipated local conditions for which storage facilities exist.
 - The drugs for which reliable local manufacturing facilities exist.
- In the majority of cases the drugs should be formulated as single compounds. Fixed ratio combination are only acceptable when:
 - The clinical value of simultaneous use of more than one dose is documented.
 - The therapeutic benefit of the combination is greater than the sum of each of the individual components.
 - The combination is safer than the use of an individual drug.
 - The cost of the combination product is less than or equal to the total cost of the individual products.
 - The compliance is improved.
 - The combination must be such that sufficient quantities to meet the needs of the majority of the population can be maintained.
- *Periodic review of drug list:* Yearly or whenever necessary to incorporate significant new therapeutic advances and selected drugs.
 - Generally new drugs should be introduced only if they offer distinct advantages over previously selected drugs.
 - If on the basis of new information, drug already on the list are found to no longer possess a favorable benefit/risk ratio, they should be replaced by drugs with the higher benefit/risk ratio.
- *International non-proprietary names* (INN; generic names) should be used for drugs.

CONCLUSION

Drug use is the end of the therapeutic consultation. Ensuring that the correct drug is given to the correct patient is a high priority for all health professionals. Improving the rational use of drugs is a challenge that can only be achieved by carefully

testing interventions to identify what works. Reporting both positive and negative results is most important to build up a body of knowledge that can be used by others to make choices about their programs. Means exist to measure drug use, to intervene to change drug use, and to evaluate these interventions. Health planners and prescribers need to use these tools to improve the quality of care provided to their patients.

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Modern Day Office Practice: Concepts and Critical Analysis

Devesh Aggarwal, Mahaveer Jain

A successful practice is about the doctor and patient succeeding together. There is no greater achievement for a doctor than a cured and satisfied patient. While the cure is totally dependent on our technical knowledge and its smooth execution, for which we are all well trained in the many years, we spend in the medical college, the satisfaction of the patient is a very different task. This is a skill which we all usually acquire after years of hard work but still sometimes find ourselves in a puzzling situation and often pondering.

“I have cured the patient in the best possible manner, why is he still so dissatisfied?”

A structured approach towards the patient goes a long way in helping us achieve our goal.

These factors are listed in Table 1.

DOCTOR’S ATTRIBUTES

Availability

Easy and ready access to the doctor is the cornerstone of any practice, this is the area of practice that the doctor has to manage very well, for otherwise everything else falls apart and nullifies all the efforts. To improve our accessibility to the patient we must keep a flexible schedule. While most of the patients can be seen during the normal office hours, we must also make room for our working patients. A chunk of our patients may find it difficult to leave their workplace during normal working hours. Such patients should be adjusted with early morning or late appointments to minimize attrition.

Behavior

Moods are infectious. A doctor with a “Happy Glow” is more likely to have a satisfied patient. A patient is likely to leave your chamber filled with satisfaction and with smiles if he is confident that you have listened to all his problems

with patience. You should appear patient, confident and in control of the whole situation. This way the patient leaves your office not just cured but happy also. If you have reached your clinic late, be sure to gracefully apologize to all the waiting patients before entering your chamber. Once in the chamber, as the patients enter your room greet everyone with a smile and direct them where to sit. Acknowledge everyone accompanying the patient so that they all feel involved in the visit. Make sure to establish an eye contact with the parents and the child, this helps in

Table 1: Factors which determine the success of an office practice

<i>Doctor attributes</i>	<ul style="list-style-type: none"> • Availability • Behavior • Competence • Communication skills • Attire • Managing referrals • Patience and good listener
<i>Office attributes</i>	<ul style="list-style-type: none"> • Location • Physical environment • Front desk • Trained manpower • Appointment management • Electronic health records • Mode of payment
<i>Patient attributes</i>	<ul style="list-style-type: none"> • Cultural and lifestyle diversity • Dissatisfied or angry • Language barrier • Faith and confidence

bonding. Avoid excessive stare-downs as this appears to be threatening and makes the patient uncomfortable. After finishing your job if you feel the patient may need a close watch or the parents are not fully satisfied while leaving the office, give the parents the permission to call you back in case they are in doubt about the child's condition or they find the progress unsatisfactory.

Competence

Years of rigorous training in the medical college has given us all the technical strength to practice. But, we must not forget that this is the age of information and knowledge. This is the age of internet and sizeable chunk of patients surf the net for their problems. We must keep ourselves abreast with the latest in our fields before the patient outgrows us. We must keep in touch with the latest literature (Journals and books), regularly attend CME's, plenty of websites, like those of Indian Pediatrics, AAP- Guidelines, WHO—Guidelines are available to guide and help us. In a difficult clinical situation do not be in a hurry to give the verdict. Refer to available resources and colleagues before taking a final decision.

Communication Skill

Do not forget the rule of the "Golden Minute". When the patient has entered your office and you have made him comfortable let him start with his history. Once the patient starts with his history do not interrupt him for at least the first minute. Doing so makes the patient feel that you are either not listening to all his problems and want to concentrate on only a few or that you are in a hurry and want him out quickly. While the patient is narrating his history, do maintain an eye contact. With lack of eye contact whether for history writing or for anything else, makes the patient feel that you are not listening anymore and already planning your treatment. This makes the patient unsure of the exactness of your prescription.

During conversation do make sure that the language of communication is to the patients and your comfort. Trying to use a language which is not comfortable for the patient is equivalent of non-communication. Your body movements should be slow and gentle. Rapid body movements convey hurry and aggression which no patient appreciates.

Attire

Contrary to what is popularly believed, children and patients appreciate their doctor in a white coat. A study from Dharwad, Karnataka¹ looked into the patient's perception as to what a doctor should wear. This included both urban and rural parents. Majority of the total assertive respondents preferred a formal traditional attire and appearance for the pediatrician. The respondents generally favored a white coat and nameplate on the

pediatrician, shoes and necktie for the male pediatrician and scarf for the female pediatrician. They did not approve clothes with jazzy designs, use of perfumes, long hair, T-shirts and jeans pants for the male pediatrician, chudidhar, lipstick and other make ups, costly jewellery and short hair for the female pediatrician. Similarly traits of nurse professionalism as perceived by the patient were highest in white uniform.

There is a lot of debate as to wearing of protective gear by the pediatrician to prevent themselves from infection. Unlike popular perception the use of face mask or face shield does not frighten the parents or the child (Figs 1A to D). However face shields may be a better option, as given a choice, both parents and children would prefer this.²

Managing Referrals

During our routine office practice we often need referral services. We should not hesitate from doing so. We must explain to the patient why we need the referral and must make a referral note for the referred physician detailing him about the patient and with the exact reason and requirements of the referrals. Instruct your front desk to assist the patient in fixing an appointment with the referred doctor. Insist on getting a feedback from the referred doctor and the patient to keep yourself in the loop of the entire medical management.

OFFICE ATTRIBUTES

Location

Those with an old established office practice realize the importance of the location of their office. When setting up a new practice the doctor must ensure that the location of the clinic does offer his clientele the advantage of easy



Figs 1A to D: Face mask and face shield for protection
(For color version see plate 18)

access. The downtown areas are sometimes so crowded that it is difficult for the patient to reach on time and often if he does so, he may face hardship in finding a parking space. This, however, may not be an important factor in an office practice where majority of the clientele is using a public transport. Similarly, the office should also not be uncomfortably away from the city. An ideal practice should be located midway of the two, to give the patients an easy and comfortable access.

Front Desk

This is where the action starts. It is the showcase of any practice. The front desk staff should always have a friendly and smiling face and have an attitude of “how a job can be done” and not “why it cannot be done”. The front desk should be an open desk where the patient should be directly able to see and speak with the staff. A desk which is closed in the front with a glass partition often fails to welcome the patients properly by acting as a barrier between them and the staff. Avoid using any excessive signages particularly if they sound authoritative (e.g. patients late for their appointment will be seen at last). Signages if any should be very neatly prepared on the computer and pasted in a plastic sleeve. This is cheap, aesthetically better and looks more professional. Cluttering on the front desk is an absolute no no, instruct and periodically check that the front desk staff is keeping the records and stationery well arranged on the counter and any eatables and beverages are not visible on the desk. Train the front desk staff that any conversation between them should be soft and not be loud enough for the waiting patients to hear. They should not indulge in conversations involving movies, TV shows, etc.

Physical Environment

Neatness is the key word. Depending on the kind of practice everything can vary but neatness cannot be compromised upon.

Basic important elements are:

- Clean and shining floor with no littering.
- Well placed furniture with no cuts exposing foam or any stuffing.
- Plants, if any, should be well maintained and not look neglected.
- Dustbin clearly visible to all patients.
- Easily accessible toilet.
- Television, if any, should be played softly and set to channels of children's interest. Strictly no filmy channels.
- Magazines should be carefully chosen and should relate to health issues, parenting, educational issues, etc. Avoid magazines concerning social or filmy gossip. These need to be periodically changed to discard old and messy magazines.

Trained Manpower

This is a great efficiency booster in a busy practice. A well-trained nursing staff may initially appear to be a financial burden but is very rewarding in a busy practice.

- A well-trained nurse can prime the patient that he/ she is the next to be seen.
- Help them arrange their documents beforehand, for many patients start looking for documents after coming into doctor's chamber.
- A well-trained nurse can do the anthropometry and plotting of growth charts.
- Trained nurse can often help the front desk during “Prime time Crisis”.

This way even a couple of minutes saved per patient will result in many more patients seen with greater efficiency during a day. This is both qualitative and quantitative enhancement to practice.

Appointment Management

To improve our accessibility to the patient we must understand our patient profile. Having a rigid appointment schedule can be patient unfriendly. While majority of the patients can be seen during main working hours,³ some patients find it difficult to leave their workplace during office hours. Such patients should be adjusted by either giving them early morning (Pre-Office) or week end appointments. This would decrease your patient attrition rate.

The appointments should be made out in such a manner, so as to place the clinic appointments as far apart as possible keeping ample space in between for patients with acute ailments.

Despite best planning, sometimes waiting does happen. If this happens because of your reaching late to the clinic a simple smile and an apology to the waiting patients usually offsets any resentment in the patient who has been waiting for you. In a study⁴ it was found that patients were OK with waiting time of 15–20 minutes but the satisfaction level dropped significantly with every minute spent in clinic after that (Fig. 2). If one is running late do not try to cut down on your consulting time per patient but try to reschedule the appointments. It has been seen that the more time spent in the consultation offsets patients dissatisfaction due to a longer waiting period (Fig. 3)

Due care needs to be taken of your patient needs while you are unavailable for personal reasons or during a vacation. These can be solved either by a group practices where your patients know whom to reach in case of your unavailability or with the help of an hospital attachment which offers round the clock coverage by a senior resident.

Website

A web-based appointment⁵ scheduling offers the patient a 24 X 7, service where he can book an appointment at

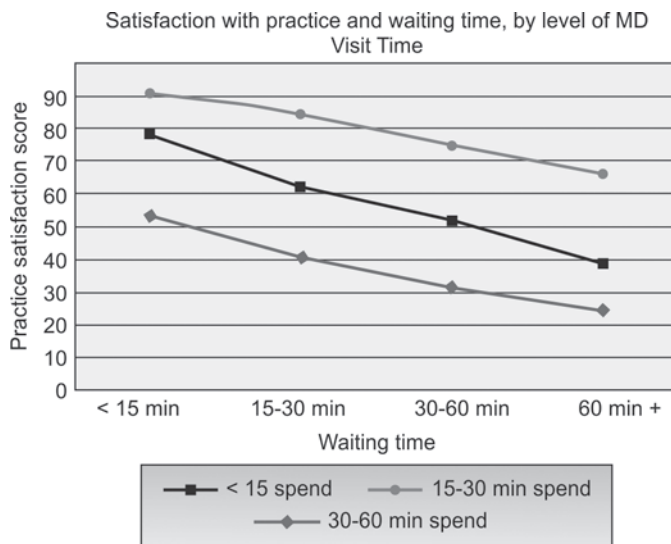


Fig. 2: Patient satisfaction and waiting time

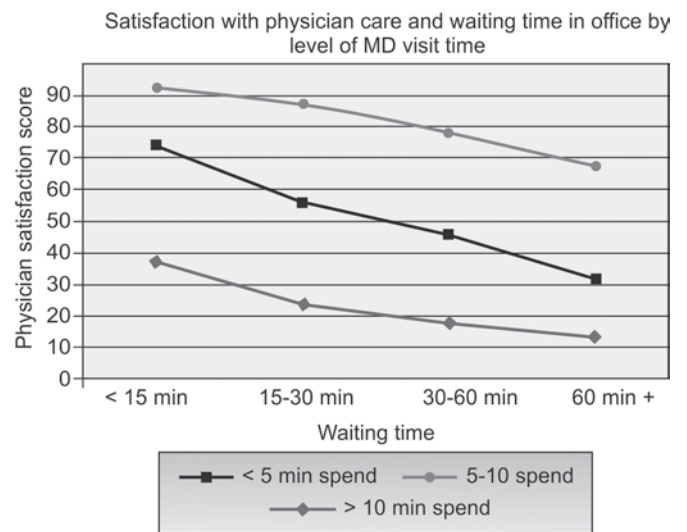


Fig. 3: Physician care and waiting time

an hour of his choice. This reduces the load on the front desk which is already burdened with OPD register, card machines and waiting patients.

Electronic Health Records

Several pediatric softwares are available in the market and are frequently advertised in Indian Pediatrics journal. These are useful in maintaining all your records, i.e. vaccination, growth, medical history and medication history. Patients appreciate this service in case they lose their records or forget to bring them to the clinic. Such software can often help remind your patients regarding their visit to the clinic.

Mode of Payment

Besides cash, it is advisable to make arrangements for other mode of payment like credit cards and debit cards. Besides offering convenience to the patients it also reduces balance payments and bad debts.

PATIENT ATTRIBUTES

Cultural Background and Lifestyle Diversity

It takes much more than a prescription to have a cured and satisfied patient. It is very important to know about his religious beliefs, dietary habits, family setup (Nuclear or joint), daily routine, i.e., how much time parents can devote to house and the child.

It is important that all advice given should conform to the patients, religious and personal sentiments, e.g., egg as a source of protein would be acceptable to one section of the society, but however, becomes a taboo for the other

section, where one may have to look for other viable and locally available options, knowing the family setup greatly affects the quality of child care. In a nuclear family we have to be more sympathetic towards the mother and give her a patient hearing when she looks forward towards early weaning. Similarly knowing about the daily routines helps us anticipate problems. A working professional mother e.g., is more likely to fall into the trap of bottle feeding. Such a mother would need constant encouragement and moral support to keep the looming danger of bottle feeding away from the baby.

Managing an Angry Patient

Despite all our efforts to have a cured and satisfied patient, we are sometimes going to face a dissatisfied or angry patient. This anger could be emanating from a number of causes which have already been discussed. The patient is often aware of his anger but not fully aware of the cause. It is never a good idea to deal sternly with the patient or not to address his anger and go on with your job. The following techniques are useful for dealing with an angry patient.

Diffusion

Sometimes it is important to tell the patient that he or she appears to be upset. This at least opens the door for a dialogue. The following discussion could help us understand our shortcoming or the patient misgiving. This usually clears the bad air following which a fruitful consultation could start. This decreases the patient attrition rate and leads to a better bonding between the doctor and the patient.

Table 2: Certain do's and dont's of office practice

<i>Do's</i>	<i>Dont's</i>
<ul style="list-style-type: none"> • Accommodating appointment schedule • Attentive and smiling (Happy Glow Look) • Respect your patient • Formal dressing • Clean, aesthetic office space—conforming to functional needs • Give the patient his golden minutes • Trained and adequate manpower • Continuous enhancement of skills and knowledge • Communicate in patient-friendly language • Prominently displayed consultation and other charges • Address the dissatisfaction of the patient 	<ul style="list-style-type: none"> • Rigid non-accommodating attitude • Grumpy under confident look • Forgetting basic manners and etiquettes • Flashy and trendy attire • Cluttered and unorganized office • Hurried approach • “I will do it all” approach • Relying solely on experience • Excessive and confusing medical jargon • Oblivious of the economically weak • Routine consultation—oblivious of the discontent

Redirection

Many times the patient is upset with an issue not pertaining to you but since he or she is upset, the anger gets directed towards you. A simple approach of helping the patient in identifying the cause of their discomfort can ease the situation for the doctor. The patient who has identified the cause can handle it at a later time and a fruitful consultation can ensue.

Separations

There may be those rare instances where you are unable to address and disentangle the patient's anger despite all your efforts. If this happens, it is best to end the relationship. Approach the situation with a constructive approach and not a punishing attitude. Gently explain to the patient that it would be in patient's interest to look for a new doctor to sort out the problem. However, if you feel that this is happening a little too often, kindly look into your emotional health too.

Language Barrier

It is of prime importance that we should be able to converse with the patient in a language with which, both the doctor and the patient, are comfortable. Mostly this is a non-issue as most of us usually chosen to practice in geographical areas close to our home town and are conversant with the local language and dialect. However, using tools like Google translator or anyother similar software available on the net saves the day for everyone. In every situation be sure to speak softly and slowly so that the patient understands every word of what you say.

SUMMARY

In the end it is important to understand that our profession needs empathy and compassion our offices area is the area of our livelihoods but at the same time they are not a business center. We should never forget the economically weaker section and to adjust to their needs will always contribute towards our social responsibility.

At the end of the day we must sit back and go through our experiences and try to understand what we did right, which will need to be further strengthened and what created unpleasant situations, which will need changes in our approach. A suggestion box placed in the clinic will greatly help us in our effort to improve our office practice.

“Pursue excellence, gains will follow”

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Facility Based Integrated Management of Neonatal and Childhood Illnesses

Rekha Harish, SS Slathia

Nearly half of the under five deaths (U5) occur during infancy and two thirds of infant deaths occur during neonatal period (41% of U5). The National Population Policy Goals aim at achieving an infant mortality rate (IMR) of 30/100,000 live births. The National Rural Health Mission (NRHM) launched in April 2005 reiterates this commitment. In order to achieve this goal, Government of India launched the integrated management of neonatal and childhood illnesses (IMNC) program which simplified and integrated the management of most common morbidities of children <5 years in a color coded stratification, helping the physician to first assess, then classify and finally treat the child. It also guided the physicians for the detection of danger signs which dictated the referral of sick children to the nearby health facility. Subsequently, it was realised that strengthening of available referral health facilities was also the need of the hour and it was essential to prepare standard guidelines keeping in view the available resources for managing these cases by both the medical officers as well as the staff nurses at the first referral units. This became one of the main objectives of RCH-II under NRHM.

Good quality prompt inpatient care for children is required at these facilities to increase the impact of appropriate interventions in reducing child mortality. According to the Bulletin on Rural Health Statistics 2007, the number of pediatricians in the country is only 898 as against the required number of 4045!!! Keeping in view the acute shortage of pediatricians at health facilities, it is imperative to build the skills of the health staff at these facilities to manage referred sick newborn and children. F-IMNCI is a facility based care for severely ill children, which is complementary to primary care for providing a continuum of care for severely ill children. Currently, it is the only comprehensive yet compact package which enhances the

skills of the health staff. It has been developed with inputs from various professional bodies such as Indian Academy of Pediatrics (IAP), National Neonatology Forum (NNF), WHO and UNICEF and field level experts. The introduction of F-IMNCI helps to build capacities of the health personnel at facility level to address newborn and childhood illnesses confidently, correctly and promptly to help in attaining the National goals despite acute shortage of specialists.

Facility based care chart booklet module explains the sequential process for managing sick young infants and children as soon as they arrive in the hospital. A brief review of this approach is covered in the following section:

FACILITY BASED INTEGRATED MANAGEMENT OF NEONATAL AND CHILDHOOD

Emergency Triage Assessment and Treatment

The guidelines for triage, emergency treatment and inpatient care of children including the newborns even at PHC level are illustrated vividly as shown in Flow chart 1. One learns how to carry out ETAT (emergency triage, assessment and treatment), which is the most important intervention in saving many critically ill children. The first step is triage—the process of rapid screening to decide to which of the following group(s) a sick child belongs to:

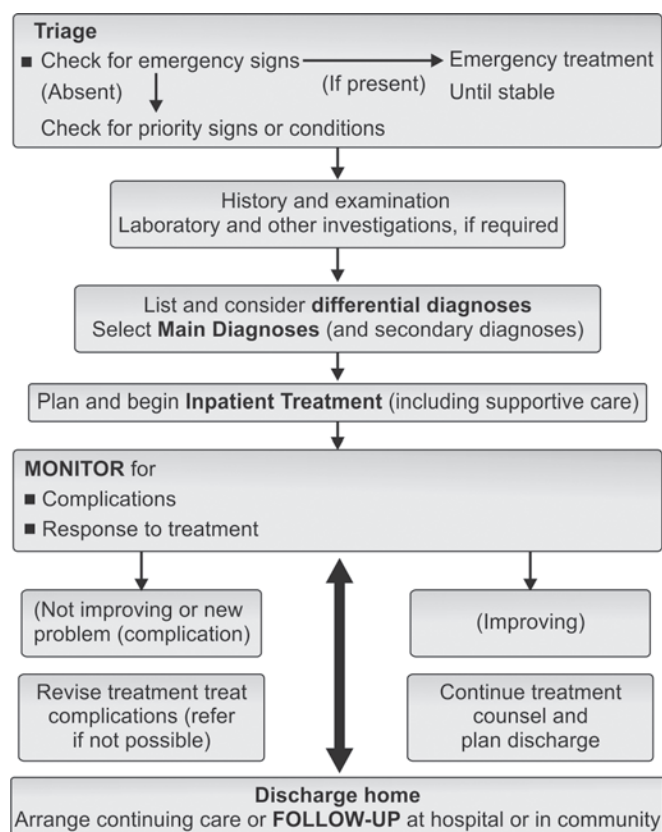
Those with emergency signs require immediate emergency treatment.

Those with priority signs need immediate assessment and treatment.

Children with no emergency or priority signs are treated as nonurgent cases.

After the child with emergency signs is stabilized, a detailed history is taken, examination and relevant laboratory investigations are performed.

Flow chart 1: Steps in the management of the sick child admitted to hospital: Summary key elements



TRIAGE OF ALL SICK CHILDREN

All sick children are assessed for airway, breathing, circulation, coma, convulsions and severe dehydration (ABCD) Flow chart 2. In view of the poor outcome in many small infants and severely malnourished children due to co-existent hypothermia and hypoglycemia, the management of these is detailed here before ABCD. Efforts are made to maintain euglycemia and euthermia while managing ABCD.

MAINTAINING TEMPERATURE

Maintaining temperature is an essential step in managing sick newborns and sick children, especially with shock or with severe acute malnutrition (SAM). As soon as a sick child is brought with temperature below 35.5°C or who is cold to touch (where thermometer is not available), maintain thermal environment as given below. Keep the infant dry and well wrapped. Cap, gloves and stockings are helpful to reduce heat loss. Keep the room warm (at least 25°C) making sure that there is no heat source directed straight at the newborn. Keep the baby under a radiant warmer and rewarm so as to bring the child's temperature to 36.5°C. Monitor temperature every half hourly for first 2 hours and then every 2 hourly.

TREATMENT OF HYPOGLYCEMIA

Check for blood glucose in all children presenting with emergency sign, those with severe acute malnutrition and all sick young infants:

If hypoglycemia is detected (defined as <45mg/dl for young infants and <54 mg/dl in older sick children beyond 2 months), give I/V bolus dose of 10 percent dextrose, in the dose of 2 ml/ kg for young infants, and 5 ml/ kg for older children. If blood glucose cannot be measured, give bolus dose as above.

Details of management of hypoglycemia in young infants are given subsequently.

MANAGEMENT OF AIRWAY AND BREATHING

The letters A and B in ABCD represent airway and breathing. If there is no problem with A and B look for C. The things to be looked are given in Flow chart 2.

If child is not breathing support breathing with bag and mask ventilation and continue as per basic life support (Flow chart 3): Basic life support for a young infant is different from that of an older child because of differences in anatomy and physiology.

MANAGEMENT OF AIRWAY IN A CHILD (>2 MONTHS) WITH GASPING OR WHO HAS JUST STOPPED BREATHING

Always ask and check for head or neck trauma before treating, as this will determine how much a child can be moved. If a child has trauma one must avoid further injury during assessment or treatment. It is also important to know the child's age because one will position an infant (under 12 months of age) differently from an older child.

HOW TO MANAGE THE AIRWAY NO NECK TRAUMA SUSPECTED (FIG. 1)

Child Conscious

- Inspect mouth and remove foreign body, if present.
- Clear secretions from throat.
- Let child assume position of maximal comfort.

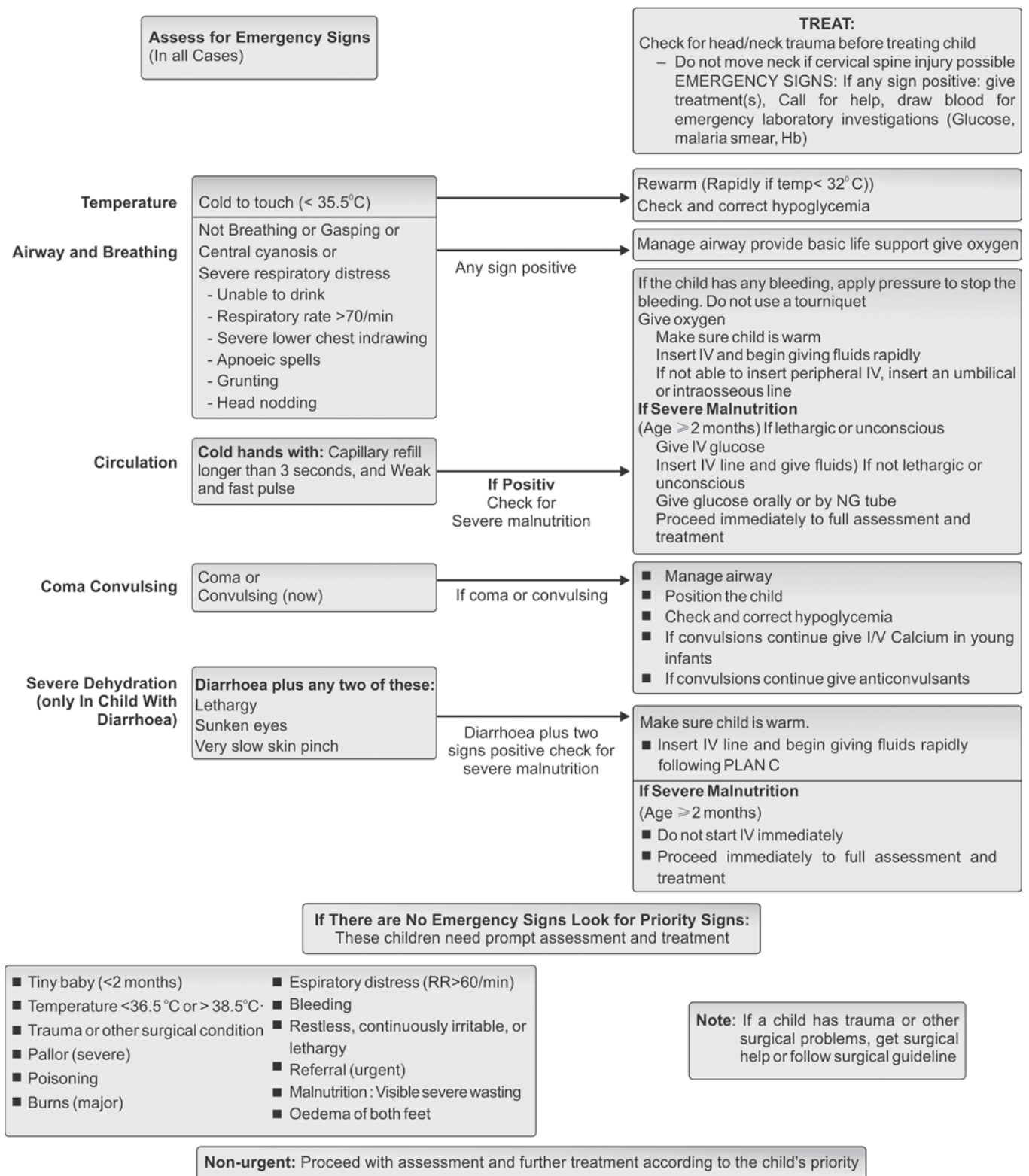
Child Unconscious

- Tilt the head as shown (Head tilt-chin lift maneuver).
- Inspect mouth and remove foreign body, if preclear secretions from throat.
- Check the airway by looking for chest movements, listening for breath sounds and feeling for breath.

Neck Trauma Suspected (Possible Cervical Spine Injury) (Fig. 2)

- Stabilize the neck. Inspect mouth and remove foreign body, if present.

Flow chart 2: Triage of all sick children



Flow chart 3: Providing basic life support

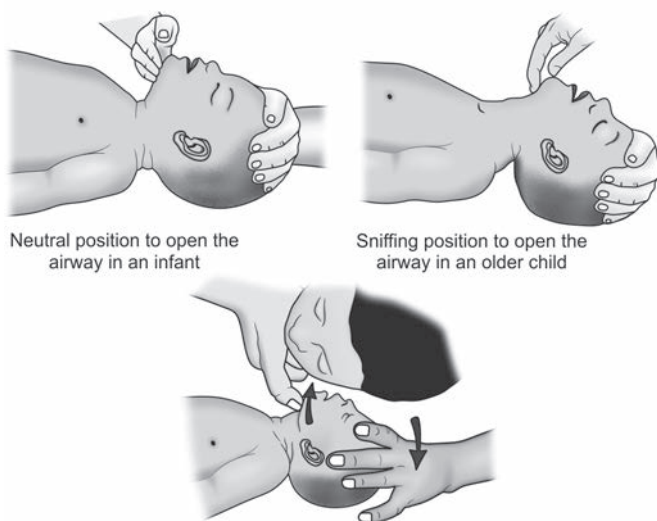
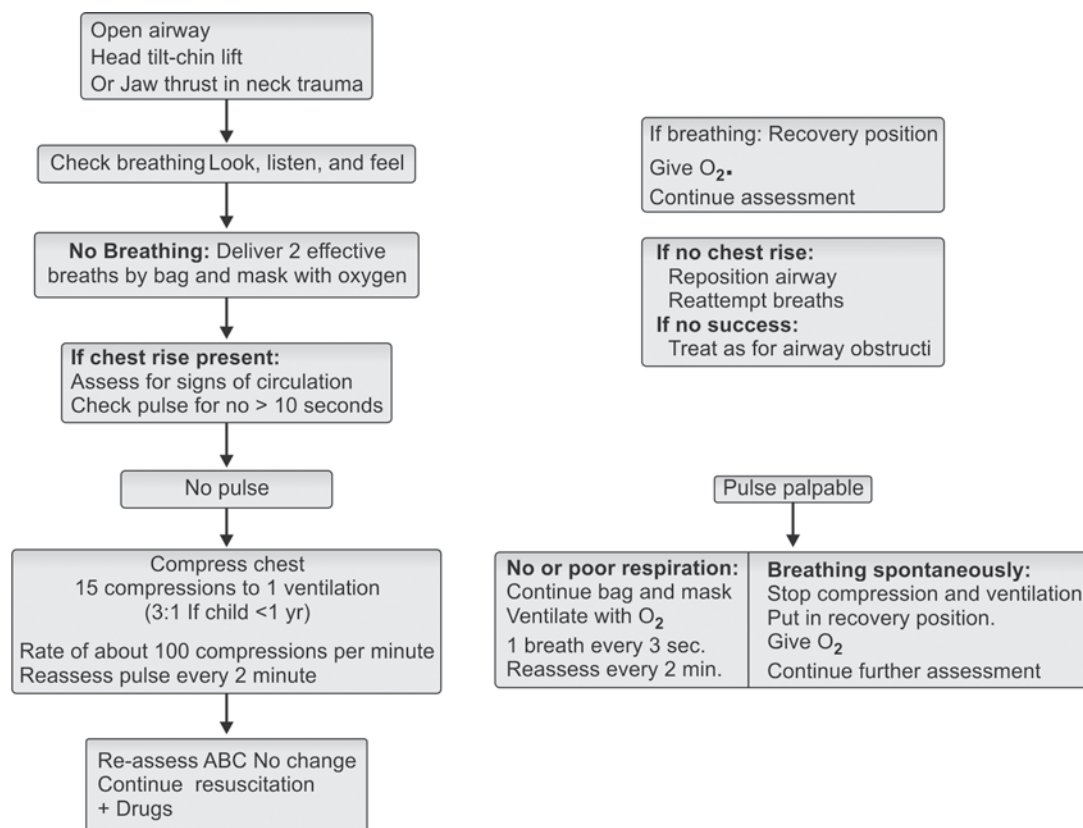


Fig. 1: No neck trauma suspected

- Clear secretions from throat.
- Check the airway by looking for chest movements, listening for breath sounds, and feeling for breath.

Use Jaw Thrust without Head Tilt

If after any of these maneuvers the child starts breathing, an oropharyngeal airway should be put and start oxygen.

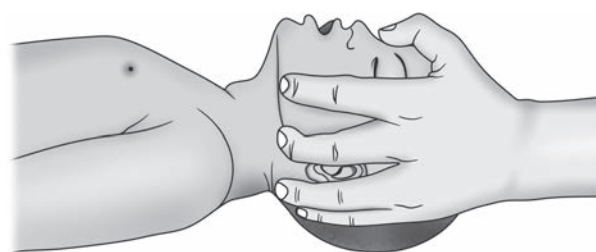


Fig. 2: Neck trauma suspected

Ventilate with Bag and Mask

If the child is not breathing even after the above maneuvers or spontaneous ventilation is inadequate (as judged by insufficient chest movements and inadequate breath sounds), ventilate with a self-inflating bag and mask. The bag is used together with a face mask.

Call for help in any child who needs bag and mask since some of these children may additionally need chest compression. After two effective ventilations, check the pulse (femoral, brachial or carotid) for no more than ten seconds. If pulse is absent, the second person should start chest compression by thumb technique where the 2 thumbs are used to depress the sternum, while the hands encircle the torso and the fingers support the spine. Therefore, the 2 activities must be coordinated, with one ventilation interposed after every third

compression, for a total of 30 breaths and 90 compressions per minute.

Adrenaline 0.1 ml/kg (1:10,000) intravenous can be used in a child who does not respond to initial ventilation and chest compressions and his pulses are absent. Two such doses can be used 3 to 5 minutes apart.

Giving Oxygen to a Child with Respiratory Distress

A child with cyanosis or severe respiratory distress should be allowed to take a comfortable position of his choice and should be given oxygen. In these children begin oxygenation with a head box (8 – 10 L/min) or a face mask (5–6 L/min). When the child improves, catheter/prongs can be used for oxygen delivery. There are two possible sources of oxygen: Oxygen concentrators and Oxygen-filled cylinders.

Give oxygen at a high-flow rate (5–10 liters/min). If breathing difficulty is so severe that the baby has central cyanosis even with high-flow oxygen, organize transfer and urgently refer the baby to a tertiary hospital or specialized center capable of assisted ventilation, if possible.

Continue giving oxygen continuously until the child is able to maintain a SaO₂ >92 percent in room air. When the child is stable and improving, take the child off oxygen

for a few minutes. If the SaO₂ remains above 92 percent, discontinue oxygen, but check again 1/2 hour later, and 3 hourly thereafter on the first day off oxygen to ensure the child is stable. Where pulse oximetry is not available, the duration of oxygen therapy is guided by clinical signs, which are less reliable.

Oxygen can be given by: 1. Nasal catheter or 2. Nasal prongs or 3. Head box and face mask.

Circulation

The letter C in “ABCD” stands for Circulation, Coma and Convulsions. We assess the circulation for signs of shock after the airway has been opened by below given methods:

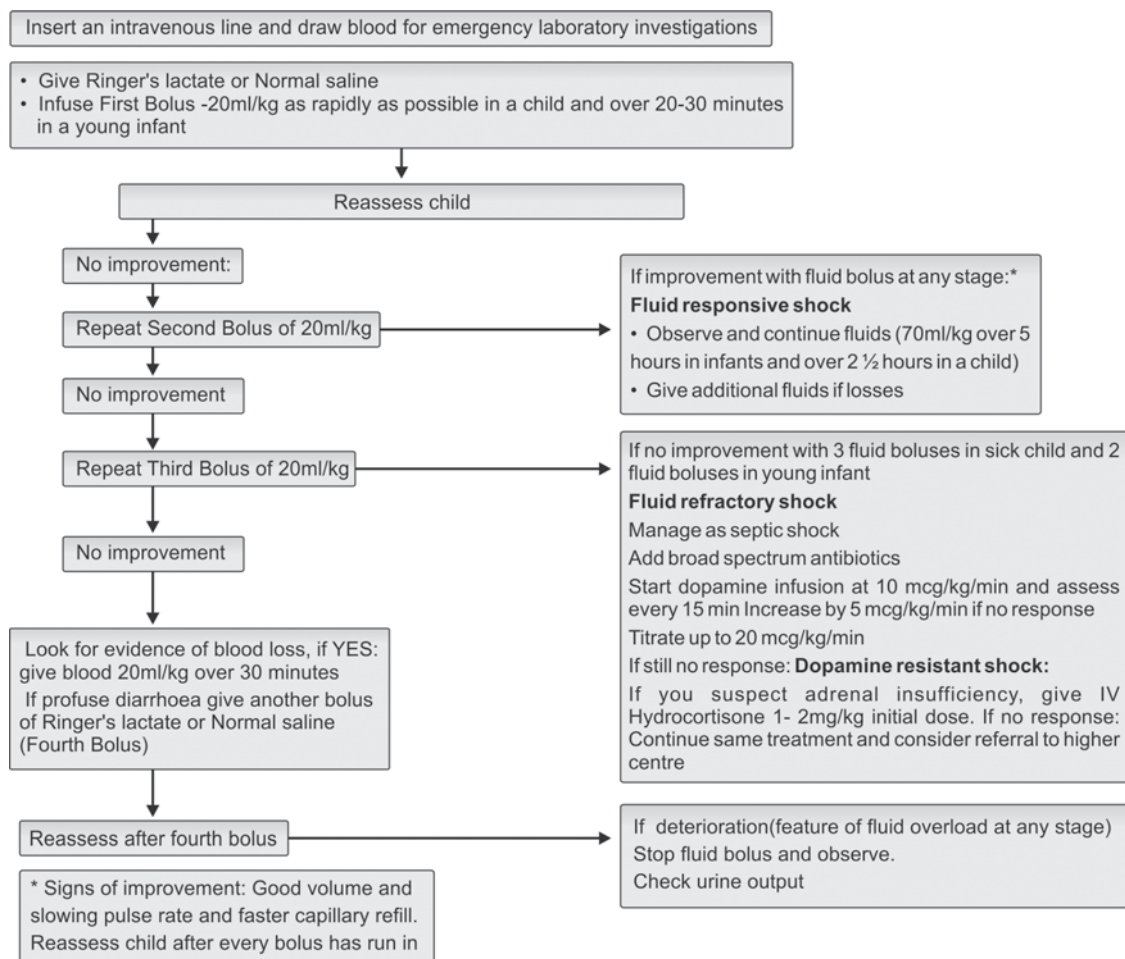
- Are the child's extremities warm?
- Is the capillary refill time longer than 3 Seconds?
- Is the pulse weak and fast?

SHOCK

Treatment of Shock: (Chart 4)

Treatment of shock requires teamwork. The following actions need to be started simultaneously:

Flow chart 4: Management of shock in a child without SAM



Note that blood pressure is not required for identifying shock because:

- Low blood pressure is a late sign in children and may not help identify treatable cases, and
- The correct size BP cuff necessary for children of different age groups may not be available.
 - Applying pressure to the nail bed for 3 seconds
 - Check the time to the return of the pink color after releasing the pressure.

Giving Fluids and Other Treatment for Shock

Young Infants

Fluid resuscitation: Infuse fluid bolus of 20 ml/kg of normal saline over 20 to 30 minutes. If no or partial improvement (i.e. tachycardia and CRT still prolonged), repeat a bolus of 20 ml/ kg of normal saline.

If the signs of poor perfusion persist despite 2 fluid boluses, start vasopressor support, except in infants with severe dehydration who should be treated as per Plan C of diarrhea management.

The most commonly used vasopressor in practice is dopamine. Usual starting dose is 5 to 10 µg/kg/min and if no improvement occurs, the dose can be increased by increments of 5 µg/kg/min every 20 to 30 minutes to a maximum of 20 µg/kg/min.

How to give Dopamine

- For giving 1 mcg/kg/minute of dopamine
- Amount of dopamine (mg) to be added = Weight in kg x6

- To convert this dose into amount to ml of dopamine divide by 40 (1 ml of dopamine = 40 mg of dopamine)
- Add this amount of dopamine (ml) to make 100 ml of total fluid
- 1ml/ hour of this fluid gives 1 mcg/ kg/ minute
- To give 10 mcg/ kg/ minute give 10ml/ hour or 10 microdrops/ minute (as 60 microdrops = 1ml)

Children Above 2 Months of Age

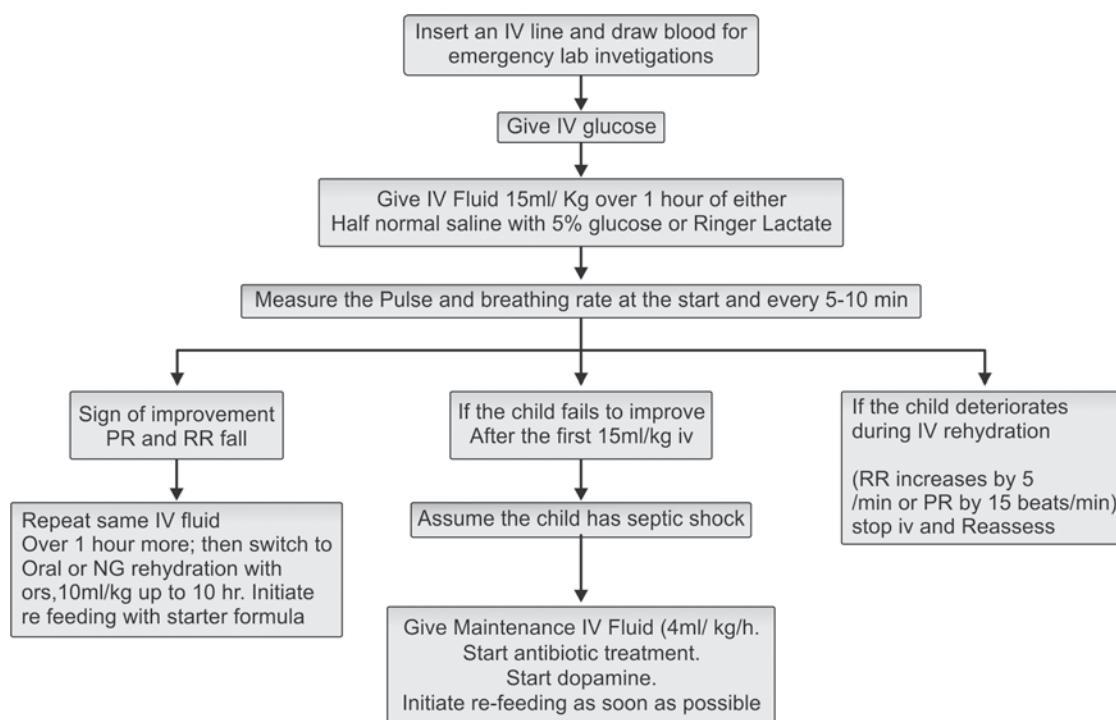
The recommended volumes of fluids to treat shock depending on the age/weight of child are shown in Chart 4.

If the child has severe malnutrition, you must use a different fluid and a different rate of administration and monitor the child very closely. Therefore a different regime is used for these children.

Management of Shock in a Child with Severe Acute Malnutrition (Chart 5)

If the child has severe malnutrition, you must use a different fluid and a different rate of administration and monitor the child very closely. Sometimes children with severe malnutrition have circulatory signs suggesting shock, but have sepsis rather than hypovolemia. It is important to follow the standard guidelines for caring for a child with severe malnutrition. If possible, avoid IV fluids—use a nasogastric (NG) tube or oral fluids. Only if the child is lethargic or unconscious and cannot swallow or tolerate an NG tube (e.g. vomiting), use ½-strength normal saline with 5 percent glucose or Ringer's Lactate at 15 ml/kg in 1 hour; but monitor carefully. Stay with the child and check

Flow chart 5: Management of shcoking a child with SAM



the pulse and breathing rate every 5 minutes. Discontinue the intravenous infusion if either of these increase (pulse by 15, respiratory rate by 5/min). If the child shows signs of improvement, give repeat IV 15 ml/kg over one hour and then switch to oral or nasogastric ORS. If the child fails to improve after the first 15 ml/kg IV, assume the child has septic shock.

Coma and Convulsions

C also represents “Coma and Convulsion”.

To help you assess the conscious level of a child is, a simple scale (AVPU) is used:

A Is the child Alert? If not,

V Is the child responding to Voice? If not,

P Is the child responding to Pain?

U The child who is unresponsive to voice (or being shaken) and to pain is unconscious.

A child who is not alert, but responds to voice, is lethargic. An unconscious child may or may not respond to pain. *A child with a coma scale of “P” or “U” will receive emergency treatment for coma as described below:*

Treatment of coma and convulsion

Treatment of coma and convulsions are similar and will be described together

Manage the Airway

Coma

Managing the airway is done in the same way as treating any child with an airway or breathing problem. This has been discussed earlier. Give oxygen for the emergency setting.

Convulsion

To manage the airway of a convulsing child gentle suction of oropharyngeal secretions should be done and child put in recovery position and oxygen started. Do not try to insert anything in the mouth to keep it open.

Put the Child in Recovery Position as Discussed Earlier

Insertion of an Oropharyngeal (Guedel) Airway

The oropharyngeal or Guedel airway can be used in an unconscious patient to improve airway opening.

How to Manage Convulsions?

Infant up to 2 Weeks of Age with Seizures

Secure IV access. If blood sugar <45 mg/dl, give 2 ml/kg 10 percent dextrose. If seizures continue: IV 10 percent Calcium gluconate 2 ml/kg over 10 minutes while monitoring heart rate (in young infants). If seizures continue: IV phenobarbitone 20 mg/kg over 20 minutes (Table 1). If no

control: Repeat phenobarbitone 10 mg/kg till a total of 40 mg/kg. If seizures continue: Give phenytoin 20 mg/kg over 20 minutes

Managing Convulsions Beyond 2 Weeks of Age

Diazepam is the first drug used to stop convulsions (anti-convulsant), if the child is convulsing. No drug should be given if the convulsion has stopped. Diazepam can be given by the rectal or intravenous route. Rectal diazepam acts within 2 to 4 minutes. In an emergency it is easier and quicker to give it rectally than intravenously, unless an intravenous line is already running. The dose is 0.5 mg/kg (0.1 ml/kg) rectally or 0.25 mg/kg (0.05 ml/kg)

Give 0.5 mg/kg diazepam injection solution per rectum by a syringe or a catheter. Hold the buttocks together for a few minutes. If you already have intravenous access, you can give the correct volume of drug directly, but slowly, in at least one full minute. Reassess the child after 10 minutes. If still convulsing, give a second dose of diazepam, rectally, (or diazepam intravenously slowly over 1 minute if an IV infusion is running). If convulsions do not stop after 10 minutes of second dose of diazepam, Injection Phenytoin can be given intravenously if access has been achieved. 15 to 20 mg/kg phenytoin is diluted in about 20 ml of saline and given slowly (not more than 1mg/ kg Phenytoin per minute). Alternatively phenobarbitone can be used in a dose of 15-20 mg/kg IV (in 20 ml 5% dextrose or saline) or IM. At this stage, seek help of a senior or more experienced person, if available. Diazepam can affect the child's breathing, so it is important to reassess the airway and breathing regularly.

DEHYDRATION

The letter *D* in the ABCD formula stands for Dehydration. Assessment and treatment of Severe dehydration (without severe acute malnutrition and with SAM) are given subsequently.

AGE First give 30 ml/ kg then give 70 ml/kg in ORS Solution per hour

If IV treatment not possible, give ORS 20ml/ kg/ hour for 6 hours (120 ml/kg) by NG tube.

Reassess an infant after 6 hours and a child after 3 hours. Classify dehydration. Then choose the appropriate plan (A, B, or C) to continue treatment as given in IMNCI.

Give oral antibiotic for cholera if child 2 years or older. If possible, observe the child for at least 6 hours after rehydration to be sure that the mother can maintain hydration by giving the child ORS solution by mouth.

Severe Dehydration with Severe Acute Malnutrition

This has been given in detail later in the section on SAM.

MANAGEMENT OF A SICK YOUNG INFANT

Give IV Fluids (Intravenous Fluids)

Type of fluid

- First 2 days: 10 percent dextrose in water.
- After 2 days: Use either commercially available pediatric maintenance fluid containing 25 mmol/L of sodium (e.g. Isolyte-P) otherwise prepare the fluid by adding 20 ml NS + 1 ml KCl + 79 ml of 10 percent dextrose to make 100 ml fluid. Monitor the IV infusion very carefully.
- Use a monitoring sheet.
- Calculate drip rate.
- Check drip rate and volume infused every hour.
- Check for edema/puffiness of eyes (could indicate volume overload).
- Weigh baby daily to detect excessive weight gain (excess fluid) or loss (insufficient fluid); adjust IV fluids appropriately.
- Adjust daily IV maintenance fluids appropriately if baby is receiving dopamine or any other infusions.

Introduce milk feeding by orogastric tube or breastfeeding as soon as it is safe to do so. Reduce the IV fluid rates as the volume of milk feeds increases in infants on orogastric feeds. Discontinue IV fluids once oral intake reaches 2/3rd total requirement. For babies who are able to breastfeed well, stop IV fluids.

HYPOGLYCEMIA

Check for blood glucose in all sick young infants.

- If hypoglycemia detected (defined as <45 mg/dl for young infants), give 2 ml/kg IV bolus dose of 10 percent dextrose.
- Start infusion of glucose at the daily maintenance volume according to the baby's age so as to provide 6 mg/kg/min of glucose in all cases of neonatal hypoglycemia.
- Recheck the blood glucose in 30 minutes. If it is still low, repeat the bolus of glucose (above) and increase infusion rate of glucose to 8 mg/kg/min. If blood sugar still remains low, then increase to 10 mg/kg/min. Once normal, monitor blood sugar every 4-6 hourly.
- Glucose infusion rates ≥ 10 mg/kg/min can result in glucose concentration >13 percent in the infused fluid. Under such circumstances infusion through peripheral veins is not recommended. It would require infusion through umbilical vein. If you cannot cannulate the umbilical vein refer the baby to a higher health facility.
- After the blood sugar has been stabilized step down the concentration of glucose by 2 mg/kg/min every 4 to 6 hourly ensuring that blood sugar remains normal. Allow the baby to begin breastfeeding. If the baby cannot be breastfed, give expressed breast milk using an alternative feeding method.

- As the baby's ability to feed improves, slowly decrease (over 6 – 12 hours) the volume of IV glucose if the baby remains euglycemic while increasing the volume of oral feeds. *Do not discontinue the glucose infusion abruptly to prevent rebound hypoglycemia.*
- If hypoglycemia is persisting at 10 mg/kg/min of glucose infusion, give one dose of Hydrocortisone: 5 mg/kg and refer to a higher health facility for further management of persistent hypoglycemia.

SEPTICEMIA

Common systemic bacterial infections in young infants include sepsis, pneumonia and meningitis and all these may present alike.

Signs of bacterial sepsis in a young infant are discussed in detail in IMNCI module.

More specific localizing signs of infection which indicate serious bacterial infection include:

- Painful joints, joint swelling, reduced movement, and irritability if these parts are handled.
- Many skin pustules/big boils (abscess).
- Umbilical redness extending to the periumbilical skin or umbilicus draining pus.

TREATMENT OF SEPTICEMIA

- Where blood cultures are available, obtain blood cultures before starting antibiotics.
- Provide supportive care and monitoring for the sick neonate.
- Start antibiotics; give injection ampicillin and gentamicin.
- Give cloxacillin (if available) instead of ampicillin if extensive skin pustules or abscesses as these might be signs of *Staphylococcus* infection.
- Most bacterial infections in neonates should be treated with antibiotics for at least 7 to 10 days except meningitis, arthritis, deep abscesses and staphylococcal infections which would require 2 to 3 weeks of therapy.
- If not improving in 2 to 3 days the antibiotic treatment may need to be changed, preferably as per microbial culture reports.

MENINGITIS

Suspect meningitis in an infant of septicemia if any one of the following signs are present:

- Drowsiness, lethargy or unconscious
- Persistent irritability
- High pitched cry
- Apneic episodes
- Convulsion
- Bulging fontanelle

To confirm the diagnosis of meningitis a lumbar puncture should be done immediately unless the young infant is convulsing actively or is hemodynamically unstable.

Treatment of Meningitis

Give Antibiotics

Give ampicillin and gentamicin or a combination of an aminoglycoside with third generation cephalosporin.

DIARRHEA

Diarrhea is uncommon in breastfed babies and is usually seen in babies who are not breastfed. The normally frequent or loose stools of a breastfed baby are not diarrhea. If the stools have changed from usual pattern and are many and watery, then it is to be labelled as diarrhea. Diarrhea may be a sign of systemic sepsis or UTI.

Assess for:

- Signs of dehydration
- Duration of diarrhea
- Blood in the stool

Approach to a Young Infant with Blood in Stool

Blood in stool in a young infant may be because of dysentery but is often due to surgical cause, necrotizing enterocolitis (NEC) or a bleeding diathesis.

Loose stools with blood:

- Active baby
- 1st week of age
- No signs of sepsis
- Manage as hemorrhagic disease of newborn. Give injection vitamin K 1 mg
- Signs of possible sepsis
- Manage as sepsis/NEC
- Abdominal mass
- Attacks of crying with pallor
- Urgent surgical referral.

Severe Persistent Diarrhea

If the young infant has diarrhea for 14 days or more, manage as case of severe persistent diarrhea.

Treat Severe Persistent Diarrhea

- Manage dehydration if present.
- Investigate and treat for sepsis: Start injection ampicillin and gentamicin.
- Encourage exclusive breastfeeding. Help mothers who are not breastfeeding to re-establish lactation. If only animal milk must be given, give a breast milk substitute that is low in lactose.
- Give supplemental vitamins and minerals for at least 2 weeks.

MANAGEMENT OF JAUNDICE

More than 50 percent of normal newborns and 80 percent of preterm infants have some jaundice. Jaundice can be physiological or pathological. If newborn is jaundiced, the

progression of skin staining is from head to toe and the level of bilirubin can be clinically assessed by extent of skin staining.

Check if

- Onset of jaundice is within 24 hours of life
 - *Clinical assessment:* Jaundice beyond abdomen
 - Baby is more than 14 days of age
- If anyone of the above is 'yes' then do the following investigations:
- Serum bilirubin (total/direct)
 - Hemoglobin/hematocrit
 - Blood groups of baby and mother
- (other investigations that may be required in some babies with suggestive history and relevant examination findings include sepsis screen, thyroid function test, LFTs, Ultrasonography of abdomen, etc.)

Treatment

Treatment of pathological jaundice is usually phototherapy or an exchange transfusion. (Refer for details to F-IMNCI participant manual)

NEONATAL TRANSPORT

Components of neonatal transport are: careful assessment of the baby, stabilization of the neonate, referral note, encouragement of mother to accompany baby, arrangement of a provider to accompany and warm transport.

Case Management of Children Presenting with Diarrhea

Diarrhea is common in children especially in those between 6 months and 2 years of age. 14 days of Acute diarrhea (14 days) causes dehydration and contributes to malnutrition.

Indications for hospitalization:

- Children with severe dehydration.
- Children with severe acute malnutrition.
- Children with associated comorbid conditions.

The assessment and classification of dehydration is described in Table 1.

Severe Dehydration (without Severe Acute Malnutrition)

Children with severe dehydration require rapid I/V rehydration with close monitoring, which is followed by oral rehydration once the child starts to improve sufficiently. In areas where cholera is endemic, give an antibiotic effective against cholera (Doxycycline is the first line recommended drug) to children above 2 years. The dose of doxycycline is 100 mg tab between 4 to 5 years and 50 mg (1/2 tab) between 2 to 4 years, single dose.

Management of severe dehydration with severe acute malnutrition is detailed later in section on SAM.

Table 1: Assessment and classification of dehydration

Classification	Signs or symptoms treatment
Severe dehydration Two or more of the following signs:	<ul style="list-style-type: none"> • Lethargy/unconsciousness • Sunken eyes • Unable to drink or drinks poorly • Skin pinch goes back very slowly • Give fluids for severe dehydration (Plan C)
Some dehydration Two or more of the following signs:	<ul style="list-style-type: none"> • Restlessness, irritability • Sunken eyes • Drinks eagerly, thirsty • Skin pinch goes back slowly • Give fluids for some dehydration (Plan B) • After rehydration, advise mother on home care
No dehydration Not enough signs to classify as some or severe dehydration	<ul style="list-style-type: none"> • Give fluids, zinc supplements and food and advise to continue ORS at home (Plan A)

Note: Ringer's lactate solution is the preferred I/V solution. If it is not available, normal saline can be used. Five percent dextrose solution is not effective and should not be used. In addition all patients should start to receive ORS solution at the rate of 5 ml/kg/hr when they can drink. This provides some base and potassium which may not be adequately supplied by I/V fluid.

Give 100 ml/kg Ringer's lactate solution (if not available, normal saline), divided as follows:

	30 ml/kg	70 ml/ kg
Infants (under 12 months)	1 hour*	5 hours
Children (12 months up to 5 years)	30 minutes*	2½ hours

* Repeat once if radial pulse is still very weak or not detectable.

- Reassess the child every 15 to 30 minutes. If hydration status is not improving, give the I/V drip more rapidly. Also give ORS (about 5 ml/kg/hr) as soon as the child can drink: usually after 3 to 4 hours (infants) or 1 to 2 hrs (children).
 - If I/V treatment not possible, give ORS 20 ml/kg/hr for 6 hrs (120 ml/kg) by NG tube.
- Assess an infant after 6 hours and a child after 3 hours. Classify dehydration again. Then choose the appropriate plan (A, B, or C) to continue treatment.
- Give oral antibiotic for cholera if child 2 years or older.
- If possible, observe the child for at least 6 hours after rehydration to be sure that the mother can maintain hydration by giving the child ORS solution by mouth.

DYSENTERY

Dysentery is diarrhea presenting with loose frequent stools containing visible blood. It is usually associated with fever, abdominal cramps and rectal pain. Most episodes in children are due to *Shigella* but can be caused by *Salmonella*, *E. coli*, *C. jejuni* and infrequently by *E. histolytica*.

Treatment of Dysentery

- In admitted children IM/IV Ceftriaxone (100 mg/ kg) once daily for 5 days may be used. For nonadmitted/discharged children give an oral antibiotic effective for *Shigella* (e.g. Ciprofloxacin, Cefixime).
- Prescribe a zinc supplement as done for children with watery diarrhea.

Provide Supportive Care

Supportive care includes the prevention or correction of dehydration (Assess the child for signs of dehydration and give fluids according to treatment Plan A, B or C.) and continued feeding. Never give drugs for symptomatic relief of abdominal pain and rectal pain, or to reduce the frequency of stools, as they can increase the severity of the illness.

MANAGE COMPLICATIONS

- Potassium depletion
- High fever
- Rectal prolapse
- Convulsions
- Hemolytic-uremic syndrome

Persistent Diarrhea

Persistent diarrhea (>14 days): Up to 20 percent of episodes of diarrhea become persistent. Persistent diarrhea often causes nutritional problems and contributes to deaths in children.

- Assess dehydration.
- *Screen for nonintestinal infections:* Pneumonia, UTI, Sepsis, Otitis media and Oral thrush.
- *Screen for intestinal infections:* Stool routine and culture if facility is available.
- In areas where HIV is highly prevalent, suspect HIV if there are other clinical signs or risk factors.

Treatment of Severe Persistent Diarrhea

Manage dehydration as Plan B or C and give antimicrobial therapy if:

- *Associated systemic infection:* Combination of parenteral Ampicillin and aminoglycosides is usually appropriate.
- *Associated severe malnutrition:* Use combination of Ampicillin and an aminoglycoside as for associated systemic

infection even if uncertain whether there is systemic infection.

- *Presence of gross blood in stools:* Give IM/IV Ceftriaxone (100 mg/kg) once daily or an oral antibiotic effective for *Shigella* (e.g. Ciprofloxacin) for 5 days.
- *Amoebiasis:* Give oral Metronidazole 10 mg/kg, 3 times a day for 5 days only if - Microscopic examination of fresh feces carried out in a reliable laboratory reveals trophozoites of *E. Histolytica* with red blood cells.
- *Giardiasis:* Give oral metronidazole 5 mg/kg, 3 times a day, for 5 days if trophozoites of *Giardia lamblia* are seen in the faeces.
- Give zinc supplements for 14 days (Tablet Zinc Sulphate 20 mg).

Zinc: Up to 6 months = 10 mg; >6 months = 20 mg

FEEDING

Children treated in hospital require special diets and the goal is to give a daily intake of at least 110 kcal/kg.

- Encourage exclusive breastfeeding. Help mothers who are not breastfeeding exclusively to do so.
- If child is not breastfeeding give a breast milk substitute that is low in lactose such as yoghurt or lactose free commercial formula. Use a spoon or cup; do not use a feeding bottle. Once the child improves, help the mother to re-establish lactation.

6 months or older feeding should be restarted as soon as the child can eat. Reduced lactose diet should be given 6 times a day to achieve a total intake of at least 110 calories/kg/day 6. Many sick children will eat poorly, until any serious infection has been treated for 24–48 hours. Such children may require nasogastric feeding initially.

Give supplementary multivitamins and minerals.

CASE MANAGEMENT OF CHILDREN PRESENTING WITH FEVER

Child Presenting with Fever

Three major categories of children presenting with fever are:

- Fever due to infection without localized signs (no rash).
- Fever due to infection with localized signs (no rash).
- Fever with rash.
 - Differential diagnosis of fever without localizing signs
 - Malaria, septicemia, typhoid, urinary tract infection
 - Fever due to infection with localized signs (no rash).
 - Meningitis, otitis media, mastoiditis, septic arthritis, pneumonia, viral upper respiratory tract infection.
 - Fever with rash.
 - Measles, viral infections, Meningococcal infection, dengue hemorrhagic fever.

SEVERE MALARIA

Presence of any of the following features in a child with microscopy or RDT positive for malaria indicates severe malaria:

- Altered consciousness
- Severe anemia (hematocrit <15% or hemoglobin <5g/dl)
- Hypoglycemia
- Respiratory distress
- Jaundice

Mortality may result in about 30 percent of such cases if timely treatment is not given.

Emergency Measures: to be taken within the First Hour

- Check and correct hypoglycemia. Treat convulsions. Manage shock, if present.
- If the child is unconscious, minimize the risk of aspiration pneumonia (insert a nasogastric tube and remove the gastric contents) treat severe anemia, if present. Antimalarial treatment provide supportive care if child is unconscious.

Also give treatment for bacterial meningitis if it cannot be excluded.

MONITOR THE CHILD

The child should be checked by nurses at least every 3 hours and by a doctor at least twice a day. Monitor temperature, pulse rate, respiratory rate and blood pressure every 6 hours, for at least the first 48 hours: Check blood sugar every 3 hourly until the child is conscious. Monitor the rate of I/V infusions. Fluid intake and output.

Meningitis (>2 Months Old)

Suspect meningitis if child has fever, vomiting, headache, irritability, inability to feed and seizures. Children with meningitis have neck stiffness with photophobia. Anterior fontanelle if open may be bulging. Early diagnosis is essential for effective treatment. The diagnosis is confirmed with a lumbar puncture and examination of the CSF. However, start the treatment immediately even if lumbar puncture is not possible or lumbar puncture cannot be done because the child has signs of raised intracranial pressure.

Treatment

Give antibiotics (for details refer to F-IMNCI participant Manual)

DENGUE FEVER

Dengue fever is suspected in an area of dengue risk if a child has fever lasting more than 2 days. Headache, pain behind the eyes, joint and muscle pains, abdominal pain, vomiting and/or a rash may occur but are not always present. It can be difficult to distinguish dengue from other common childhood infections.

Causative organism, dengue virus is an arthropode borne virus and has four serotypes (Den I, II, III and IV). *Aedes aegypti* a day time mosquito is the principal vector

in India, mostly seen in rainy season or in months following rainy season.

Diagnosis

Confirmation of diagnosis of dengue fever is based on demonstration of IgM antibody specific for dengue virus. Total leukocyte count is either normal or decreased. Platelet count is less than normal.

Treatment of Dengue Fever

Most children can be managed at home provided the parents have reasonable access to the hospital:

- Counsel the mother to bring the child back for daily follow-up but to return immediately if any of the following occur: severe abdominal pain; persistent vomiting; cold, clammy extremities; lethargy or restlessness; bleeding, e.g. black stools or coffee-ground vomit.
- Encourage oral fluid intake with clean water or ORS solution to replace losses from fever and vomiting.
- Give paracetamol for high fever if the child is uncomfortable. Do not give aspirin or ibuprofen as these drugs may aggravate bleeding.
- Follow-up the child daily until the temperature is normal. Check the hematocrit daily where possible. Check for signs of severe disease.
- Admit any child with signs of severe disease (mucosal or severe skin bleeding, shock, altered mental status, convulsions or jaundice) or with a rapid or marked rise in hematocrit.

SEVERE DENGUE

Severe dengue includes dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS).

Grading of Dengue Hemorrhagic Fever

DHF is classified into four grades of severity, where grades III and IV are considered to be DSS. The presence of thrombocytopenia with concurrent hemoconcentration differentiates grades I and II DHF from DF.

Grade I: Fever accompanied by nonspecific constitutional symptoms; the only hemorrhagic manifestation is a positive tourniquet test and/or easy bruising.

Grade II: Spontaneous bleeding in addition to the manifestations of Grade I patients, usually in the form of skin or other hemorrhages.

Grade III: Circulatory failure manifested by a rapid, weak pulse and narrowing of pulse pressure or hypotension, with the presence of cold, clammy skin and restlessness.

Grade IV: Profound shock with undetectable blood pressure or pulse.

Treatment of Severe Dengue as per Flow Chart 6 and 7

Most cases of DHF grade I can be managed on outpatient basis.

Indications for Hospitalization

Hospitalization for bolus intravenous fluid therapy may be necessary where significant dehydration has occurred and rapid volume expansion is needed because of reduced blood volume due to plasma leak. Signs in such cases include:

- Tachycardia
- Increased capillary refill time (>2 seconds)
- Cool, mottled or pale skin
- Diminished peripheral pulses
- Changes in mental status
- Oliguria
- Sudden rise in hematocrit or continuously elevated hematocrit despite administration of fluids
- Narrowing of pulse pressure (<20 mm Hg)
- Hypotension (a late finding representing uncorrected shock).

Manage Hemorrhagic Complications

- Mucosal bleeding may occur in any patient with dengue but is usually minor. It is due mainly to the low platelet count, and this usually improves rapidly during the second week of illness.
- If major bleeding occurs it is usually from the gastrointestinal tract, particularly in patients with very severe or prolonged shock. Internal bleeding may not become apparent for many hours until the first black stool is passed.

Consider this in children with shock who fail to improve clinically with fluid treatment, particularly if the hematocrit is stable or falling and the abdomen is distended and tender.

- In children with profound thrombocytopenia (<20,000 platelets/mm³), ensure strict bed rest and protection from trauma to reduce the risk of bleeding. Do not give IM injections.
- Transfusion is very rarely necessary. When indicated it should be given with extreme care because of the problem of fluid overload. If a major bleed is suspected, give 5 to 10 ml/kg fresh whole blood slowly over 2 to 4 hours and observe the clinical response. Consider repeating if there is a good clinical response and significant bleeding is confirmed.
- Platelet concentrates (if available) should only be given if there is severe bleeding. They are of no value for the treatment of thrombocytopenia without bleeding.

Provide Supportive Care

- Give paracetamol for high fever if the child is uncomfortable. Do not give aspirin or ibuprofen as this will aggravate the bleeding.

MONITORING

- In children with shock, monitor the vital signs hourly (particularly the pulse pressure, if possible) until the patient is stable, and check the hematocrit 3 to 4 times per day.
- Check the platelet count daily, where possible, in the acute phase.
- Keep a detailed record of all fluid intake and output.

Management of Typhoid Fever

Admitted patients are treated with ceftriaxone (80 mg/kg I/V or IM once daily). In ambulatory patients cefixime (20 mg/kg/day) can be used. In areas where sensitive strains have reemerged, use of chloramphenicol (25 mg/kg/dose, 8 hourly) is recommended. Duration of antibiotic treatment should be for 5 days after the child becomes afebrile or 10 to 14 days whichever is later. Other drugs used to treat typhoid fever include fluoroquinolones (ciprofloxacin 15 to 20 mg/kg/day in 2 divided doses, ofloxacin 10 to 20 mg/kg/day in 2 divided doses) and azithromycin (10 to 20 mg/kg/day).

The cases with typhoid fever should be closely monitored for complications like gastrointestinal hemorrhage, intestinal perforation, hypotension and shock. Antipyretics for fever and maintenance intravenous fluids may be required initially in cases who have poor oral intake.

MANAGEMENT OF CHILDREN WITH ANEMIA

Anemia is very common in children in developing countries. Severe anemia in a child is suggested by the presence of severe palmar pallor and may be associated with a fast pulse rate, difficulty in breathing, or confusion or restlessness. There may be signs of heart failure such as gallop rhythm, an enlarging liver and rarely pulmonary edema. Anemia/pallor should be looked for in each patient attending the health facility.

Nutritional anemia is the most common cause of anemia in children. Nutritional anemia results from deficiency of iron, folic acid and vitamin B₁₂. Iron deficiency anemia (IDA) commonly occurs in later part of infancy and preschool children particularly if they are not receiving adequate complementary feeding. Physical examination of children with IDA is usually unremarkable. They do not have significant hepatosplenomegaly or lymphadenopathy. Children having anemia due to folic acid and/or B₁₂ deficiency (megaloblastic anemia) may have hyperpigmentation of knuckles and occasionally bleeding manifestations due to thrombocytopenia.

Laboratory Diagnosis

Anemia in children less than 5 years is defined as Hemoglobin <11 gm/dl. Complete blood counts and examination of peripheral blood smear should be done in all anemic

children if possible. Blood films should be examined for malaria parasites particularly in high malaria risk areas. Stool examination for ova, cyst and occult blood. Blood counts should be performed using electronic cell counter if available. Children with IDA will have microcytic-hypochromic anemia. Usually leukocyte counts and platelet counts are normal. Children with folate and/or B₁₂ deficiency will have macrocytic anemia. These cases may have associated leucopenia and/or thrombocytopenia. Such cases should be referred for specialized investigation as in these cases other causes resulting in alterations in blood counts (bi/pancytopenia) and macrocytosis need to be excluded.

Treatment

IDA should be treated using oral iron 2 to 3mg/kg/day (dose of elemental iron). Older children who can take tablets can be given IFA tablets. Iron therapy should be continued 8 to 12 weeks after normal hemoglobin level is achieved. The children on iron therapy should be evaluated for response to treatment. Iron therapy results in prompt clinical response (return of appetite, decreased irritability). Check haemoglobin level after two weeks of therapy. Children not responding to treatment should be evaluated for compliance to treatment and adequacy of dose and presence of infections such as UTI and tuberculosis.

Blood transfusion is indicated in following situations:

- All children with Hb <4 gm/dl.
- Children with Hb 4 to 6 gm/dl with any of the following:
 - Dehydration
 - Shock
 - Impaired consciousness
 - Heart failure
 - Fast breathing
 - Very high parasitemia (>10% of RBC).

CASE MANAGEMENT OF CHILDREN WITH SEVERE ACUTE MALNUTRITION (SAM)

Malnutrition remains one of the most common causes of morbidity and mortality among children. The high case fatality rates among severely malnourished children can be reduced by using standardized and easily implementable protocols.

Criteria for Hospital Admission

- Weight for height/length <-3 z score of median of WHO child growth standards or
- Bipedal edema.

If weight-for-height or weight-for-length cannot be measured, use the clinical signs for visible severe wasting

Assessment of Severely Malnourished Child

A good history and physical examination is required for deciding the treatment but always start the emergency

treatment first. The details of history and examination can be recorded later.

Providing General Treatment for Malnutrition

The triage process and assessment of children with severe malnutrition and management of shock has already been discussed. Severe anemia, if present, will need urgent treatment.

There are 10 essential steps in two phases: an initial stabilization phase and a longer rehabilitation phase (Table 3). *Hypoglycemia and hypothermia are treated and prevented on urgent basis as these can kill the child.*

RECOGNIZE DEHYDRATION

Dehydration tends to be over diagnosed and its severity is overestimated in severely malnourished children. Many of the signs that are normally used to assess dehydration are unreliable in a child with severe malnutrition, making it difficult or impossible to detect dehydration reliably or determine its severity. Moreover, many signs of dehydration are also seen in septic shock.

Remember

A child with severe acute malnutrition may be dehydrated in the presence of oedema.

Treatment

Whenever possible, rehydrate a dehydrated child with severe malnutrition orally or through a nasogastric tube.

A severe acute malnourished child is at risk of hypokalemia due to reduced muscle mass. In addition to ORS start potassium supplements to prevent hypokalemia (syrup potassium chloride 15 ml of the syrup provides 20 meq of potassium).

Remember

Use IV rehydration only if the child has signs of shock and is lethargic or has lost consciousness.

Calculate Amount of ORS to Give

- Every 30 minutes for the first 2 hours 5ml/kg body weight
- Alternate hours for up to 10 hours 5- 10 ml/kg the amount offered in this range should be based on the child's willingness to drink and the amount of ongoing losses in the stool. Starter formula is given in alternate hours during this period until the child is rehydrated.
- If the child has already received IV fluids for shock and is switching to ORS, omit the first 2 hours treatment and start with the amount for the next period of up to 10 hours.

MONITOR THE CHILD WHO IS TAKING ORS

Signs of Overhydration

If you find signs of over hydration (increasing respiratory rate by 5/minutes and pulse rate by 15/minutes), stop ORS immediately and reassess after 1 hour.

Measures to prevent dehydration from continuing watery diarrhea are similar to those for well-nourished children.

- If the child is breastfed, continue breastfeeding.
- Give ORS between feeds to replace stool losses. As a guide, give 50 to 100 ml after each watery stool.

Shock in Severely Malnourished Children (See Flow chart 5)

Shock from dehydration and sepsis are likely to coexist in severely malnourished children. They are difficult to differentiate on clinical signs alone. Children with dehydration will respond to I/V fluids. Those with septic shock and no dehydration will not respond. The amount of fluid given is determined by the child's response. Overhydration must be avoided.

ELECTROLYTE IMBALANCE

- Give supplemental potassium at 3 to 4 meq/kg/day for at least 2 weeks. Potassium can be given as syrup potassium chloride; the most common preparation available has 20 meq/15 ml.
- On day 1, give 50 percent magnesium sulphate IM once (0.3 mL/kg up to a maximum of 2 ml), Thereafter, give extra magnesium (0.4–0.6 meq/kg daily) orally. If oral commercial preparation is not available you can give injection magnesium sulphate (50% which has 2 meq/ml) orally as magnesium supplements mixed with feeds for 2 weeks.
- Prepare food without adding salt to avoid sodium overload.

Table 3: The focus of initial management is to prevent death while stabilizing the child

	Stabilization Days 1-2	Days 3-7	Rehabilitation Weeks 2-6
• Hypoglycemia-----			
• Hypothermia-----			
• Dehydration-----			
• Electrolytes			
• Infection			
• Micronutrients No iron with iron---No iron with iron			
• Initiate feeding			
• Catch-up growth			
• Sensory stimulation			
• Prepare for follow-up			

INFECTION

Presume and Treat Infection

Assume all children with severe malnutrition admitted in a hospital have an infection and give broad spectrum Select antibiotics as shown in the Flow chart below.

All Admitted Cases

- Injection ampicillin 50 mg/kg/dose 6 hourly and injection gentamicin 7.5 mg/kg once a day for 7 days
- Add Injection cloxacillin 50 mg/kg/dose 6 hourly if staphylococcal infection is suspected
- Revise therapy based on sensitivity report.

For Septic Shock or Worsening/No Improvement in Initial Hours

- IV Cefotaxime 50 mg/kg/dose 6 hourly or injection ceftriaxone 50 mg/kg/dose
- 12 hourly plus injection amikacin 15 mg/kg/once a day

MENINGITIS

- IV Cefotaxime 50 mg/kg/dose 6 hourly or injection ceftriaxone 50 mg/kg/dose
- 12 hourly plus injection amikacin 15 mg/kg/once a day

DYSENTERY

- Injection ceftriaxone 100 mg/kg once a day for 5 days

Duration of Antibiotic Therapy Depends on the Diagnosis

- *Suspicion of clinical sepsis*: at least 7 days
- *Culture positive sepsis*: 10 to 14 days
- *Meningitis*: at least 14 to 21 days
- *Deep seated infections like arthritis and osteomyelitis*: at least 4 weeks.

Treat associated conditions: Malaria, HIV, tuberculosis, anemia, vit A deficiency, skin lesions, persistent diarrhoea etc.

MICRONUTRIENTS

Vitamin A, multivitamin supplement (should contain vitamin A, C, D, E and B₁₂ and not just vitamin B-complex), zinc, folic acid, copper and iron are added.

Initiate Feeding

- Give frequent and small nutrient rich feeds of low osmolarity and low lactose.
- Offer 130 ml/kg/day of liquids (100 ml/kg/day if child has severe edema), 80 to 100 Kcal/kg/day and 1 to 1.5 g/kg/day of proteins.
- Use nasogastric feeding till child takes orally 75 percent of all feeds.

- If child breastfed, continue breastfeeding but give the feed first.
- Ensure night feeds.

STARTER FORMULA

Starter formula is to be used during initial management. It is started as soon as possible and continued for 2 to 7 days until the child is stabilized. Severely malnourished children cannot tolerate usual amounts of proteins and sodium at this stage, or high amounts of fat. They may die if given too much protein or sodium. Starter formula is specially made to meet the child's needs without overwhelming the body's systems in the initial stage of treatment which provides 75 calories/ 100ml and 0.9 gm of protein/100 ml.

Feed the child starter formula orally, or by NG tube if necessary:

Oral Feeding

It is best to feed the child with a cup and spoon. Encourage the child to finish the feed. Encourage breastfeeding on demand between starter formula feeds.

Nasogastric Feeding

Use an NG tube if necessary, i.e. the child does not take 75 percent of the feed for 2 to 3 consecutive feeds.

Remove the NG tube when the child takes: 75 percent of the day's amount orally; or two consecutive feeds fully by mouth.

Record Intake and Output on a 24 Hours Food Intake Chart

Criteria for increasing volume/ decreasing frequency of feeds (Table 4):

- If there is vomiting, significant diarrhea, or poor appetite, continue 2-hrly feeds.
- If there is little or no vomiting, diarrhea is less than before, and most feeds are consumed, change to 3 hourly feeds.
- After a day on 3-hrly feeds: If there is no vomiting, occasional diarrhea, and most feeds are consumed, change to 4 hourly.
- The initial cereal based low lactose (low osmolarity) diet is recommended for those with persistent diarrhea (Table 5).

Table 4: Recommended schedule with gradual increase in feed volume

Days	Freq	Vol/Kg/feed	Vol/Kg/day
1–2	2 hourly	11 ml	130 ml
3–5	3 hourly	16 ml	130 ml
6 onwards	4 hourly	22 ml	130 ml

Table 5: Initial diets recommended in severe malnutrition: Starter formula

<i>Diets contents (per 100 ml)</i>	<i>Starter formula</i>	<i>Starter formula (Cereal based) Ex: 1</i>	<i>Starter formula (Cereal based) Ex: 2</i>
Fresh cow's milk or equivalent (ml)* (Approximate measure of one cup)	30 (1/3)	30 (1/3)	25 (1/4)
Sugar (g) (Approximate measure of 1 teaspoon)	9 (1 + 1/2)	6 (1)	3 (1/2)
Cereal flour: Powdered puffed rice (g) (Approximate measure of 1 level teaspoon)	— —	2.5 (3/4)	6 (2)
Vegetable oil (g) (Approx. measure of 1 level teaspoon)	2 (1/2)	2.5 (1/2+)	3 (3/4)
Water: make up to (ml)	100	100	100
Energy (kcal)	75	75	75
Protein (g)	0.9	1.1	1.2
Lactose (g)	1.2	1.2	1.0

*Can replace fresh milk 30 ml with 3.5 gm whole dried milk

MONITORING

- Amounts of feed offered and left over
- Stool frequency and consistency
- Vomiting
- Daily body weight.

CATCH-UP GROWTH

Recognize Readiness for Transition

Signs that a child has reached this phase are:

- Return of appetite (easily finishes 4 hourly feeds of starter formula)
- Most/all of the edema has gone.

Begin Giving Catch-up Formula Slowly and Gradually

Make a gradual transition from starter to catch-up formula.

Catch-up Formula

Catch-up formula is used to rebuild wasted tissues. It contains more calories and protein.

- Replace the starter formula with an equal amount of catch-up formula for 2 days. Give a milk-based formula, such as catch-up formula which contains 100 kcal/100ml and 2.9 g of protein per 100 ml.
- *Then on the 3rd day:* Increase each successive feed by 10 ml as long as child is finishing feeds. Continue increasing the amount until some feed remains uneaten. The point when some of the feed remains unconsumed is likely to occur when intakes reach about 200 ml/kg/day. After a gradual transition, give:

- Frequent feeds, unlimited amounts
- 150 to 220 kcal/kg/day
- 4 to 6 g of protein/kg/day.

If the child is breastfed, continue to breastfeed between feeds. However, breast milk does not have sufficient energy and protein to support rapid catch-up growth, so give catch up formula as indicated.

SENSORY STIMULATION

During rehabilitation provide:

- Tender loving care.
- A cheerful stimulating environment.
- Structured play therapy for 15 to 30 minutes a day.
- Physical activity as soon as child is well.
- Maternal involvement as much as possible (e.g. comforting, feeding, play).

Failure to Respond to Treatment (Table 6)

- Whether this occurred in all cases being treated (if so, a major review of case management is required).
- Whether this occurred in specific cases (reassess these children as if they were new admissions).

INADEQUATE FEEDING

Check

- That night feeds are given.
- That target energy and protein intakes are achieved. Is the actual intake (i.e. what was offered minus what was left over) correctly recorded? Is the quantity of feed

Table 6: Criteria for failure to respond to treatment

<i>Criteria after admission</i>	<i>Time</i>
Primary failure	
• Failure to regain appetite	Day 4
• Failure to start to lose oedema	Day 4
• Oedema still present	Day 10
• Failure to gain at least 5 gm/kg of body weight per day	Day 10
Secondary Failure	
Failure to gain at least 5 gm/ kg of body weight per day during rehabilitation for 3 successive days	
If the weight gain is <5g/ kg/ day, determine:	

recalculated as the child gains weight? Is the child vomiting or ruminating?

- Feeding technique: is the child fed frequent feeds, unlimited amounts?
- Quality of care: are staff motivated/gentle/loving/ patient?
- All aspects of feed preparation: scales, measurement of ingredients, mixing, taste, hygienic storage, adequate stirring.
- Whether complementary foods given to the child are energy dense.
- Vitamins and mineral supplements are given appropriately.

Look for Untreated Infection

If feeding is adequate and there is no malabsorption, suspect a hidden infection. The following are easily overlooked: urinary tract infections, otitis media, tuberculosis and giardiasis. In such a case:

- Re-examine carefully.
- Repeat urine microscopy for white blood cells.
- Examine the stool.
- If possible, take a chest X-ray.

PSYCHOLOGICAL PROBLEMS

Check for abnormal behavior such as stereotyped movements (rocking), rumination (i.e. self-stimulation through regurgitation), and attention seeking. Treat by giving the child special love and attention. For the child who ruminates, firmness, with affection, can assist. Encourage the mother to spend time playing with the child.

Monitoring Progress During Treatment

- If good weight gain, i.e. >10 g/kg/d, continue with the same treatment
- If moderate weight gain, i.e. 5 to 10 g/kg/day, check whether intake targets are being met or if infection has been overlooked
- If poor weight gain, i.e. <5g/kg/d, make a full assessment, particularly for:
 - Inadequate feeding

Table 7: Criteria for discharge from hospital care

<i>Criteria</i>	
Child	<ul style="list-style-type: none"> • Weight for height reached -1SD of median of WHO standards • Eating adequate amount of nutritious food that mother can prepare
	At home
	<ul style="list-style-type: none"> • Consistent weight gain • All vitamin and mineral deficiencies have been treated • All infections and other conditions have been treated or are being treated like anaemia, diarrhoea, malaria, tuberculosis • Full immunization programme started
Mother caretaker	or
	<ul style="list-style-type: none"> • Able to take care of the child • Able to prepare appropriate foods and feed the child • Has been trained to give structured play therapy and sensory stimulation • Knows how to give home treatment for common problems and recognizes danger signs warranting immediate medical assistance

- Untreated infection
- HIV infection
- Psychological problems
- Child is considered to have recovered when he reaches a weight for height 1 z score of median of WHO child growth standards.

Discharge and Prepare for Follow-up (Table 7)

Appropriate mixed diets are same as those recommended for a healthy child given at least 5 times a day providing 100 to 120 kcal/kg/day. Continue breast feeding. Every attempt should be made to manage the child till recovery and to avoid relapse and death after discharge. Follow-up regularly at 1, 2, 4 weeks, then monthly for 6 months and subsequently every 6 months for 2 years.

To conclude, with our own experience as a pediatrician we have not come across a presentation which is so exhaustive on pediatric management guidelines in such a compact form. It not only gives theoretical knowledge and reasoning but also imparts hands on training in a very friendly manner. Feedback reveals that the training is equally appreciated by all, including pediatricians, medical officers and paramedicals as despite being 'so much yet it is so easy to grasp'. The trained participants feel very confident in their ability to deal with neonates and children effectively. We take this opportunity to mention that time required to acquire skills, if extended to at least 30 days and made residential it would equip the participants with better practical skills particularly in learning procedures like IV lines without which they will not be confident and cannot render the services in desired manner. If implemented in letter and spirit we are very confident and hopeful that F-IMNCI strategy would definitely make a dent in NMR IMR and U5 mortality.

Recent Advances in the Management of Juvenile Idiopathic Arthritis

Sujata Sawhney

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is the umbrella term that encompasses a heterogeneous group of chronic childhood arthritides of unknown cause. The clinical spectrum of disease in this group is variable: the child may have one or two swollen joints, or be ravaged by persistent fevers and aggressive polyarthritis. It is a chronic disease with an unpredictable course, marked by exacerbations and remissions.¹

The incidence of JIA ranges from 10 to 50 per 100000, which suggests that it is relatively uncommon in childhood, but the prevalence, is significant at 1:1000, suggesting that it is chronic in nature.²

The medical advances available across the globe are meaningless if their application is late. The single most important prognostic indicator is “early, appropriate treatment”. It is important to realize that diseases like JIA have two components: disease activity and disease related damage such as- contractures and deformities including joint erosions and leg length discrepancy. The latter have the potential to be permanent and disabling, but can be prevented in many patients with early appropriate treatment. Thus optimal therapy must be in the context of early referral to specialist centers.

It is now realized that the more rapidly inflammation can be controlled, the less likely it is that there will be permanent sequel. An adequate response is no longer acceptable. The possibility of absolute control of inflammation is a goal that should be pursued.

Increasingly, the aim of treatment is remission not improvement. Medically, though the major focus is on arthritis, other extra articular complications need consideration e.g. uveitis, serositis, growth retardation, and osteopenia.²

The issues discussed in this chapter are:

- General principles of management.
- Aims of management.

- Psychosocial issues in the care of these children
- Recent advances in the management of JIA
- Treatment for different subtypes of JIA
- Generic issues that arise in the care of children with JIA
- Current outcome studies and conclusion.

GENERAL PRINCIPLES OF MANAGEMENT

- Objective analysis of the disease activity in children with juvenile idiopathic arthritis is very important to guide therapy and assess improvement when the therapy is changed. In adult patients the disease activity score (DAS 28) score has been validated and is an excellent tool that can be conveniently used in an outpatient setting. Though no such numeric tool is available for children with juvenile arthritis, the American College of Rheumatology (ACR) pediatric 30 outcome measures are useful in clinical practice. Recently, definitions for inactive disease, clinical remission on medication and clinical remission off medication have been published for some subtypes of JIA and in fact the “Wallace criteria” as they are known are used to assess outcomes in newer trials and in daily clinical practice.⁴ A new multidimensional questionnaire for assessment of children with juvenile idiopathic arthritis (JIA) in standard clinical care has been recently developed. This is called the Juvenile Arthritis Multidimensional Assessment Report (JAMAR). It includes 15 parent or patient-centered measures or items that assess well-being, pain, functional status, health-related quality of life, morning stiffness, disease activity, disease status and course, joint disease, extra-articular symptoms, side effects of medications, therapeutic compliance, and satisfaction with illness outcome. In a study of 618 JIA patients the JAMAR was found to be feasible and to possess face and content validity.⁵

- Child centric team approach should be available for all children. A pediatric rheumatologist, a nurse specialist, physical and occupational therapist, a child psychologist and a social worker all work with the child's primary care pediatrician. Consultations with an orthopedic surgeon, dietician, and dentist should be available when required.
- Care is delivered by "shared care" which is extensively practiced in the western world: The tertiary pediatric rheumatology team guides specific therapy based on expertise and experience, while the local primary pediatrician offers routine care, growth monitoring, vaccination, drug monitoring and liaises closely both with the tertiary level team and community resources such as the school. This approach is well suited to deliver comprehensive care to the child with a chronic disease.
- Prognostication is not possible early on in the disease. Therefore, the initial approach must be vigorous in all children. This is very important, as it is now clear that radiologic joint damage occurs in most patients with systemic arthritis and polyarthritis within two years and in oligoarthritis within five years.⁶ There are some prognostic factors for different categories of JIA, but none that can give an accurate prognosis at the time of disease diagnosis.
 - *Systemic onset JIA*: A poor outcome in the systemic form correlates with markers of disease activity, such as fever and polyarticular involvement, within the first 6 months. Secondary amyloidosis is observed mainly in children with systemic JIA
 - *Oligo JIA*: The risk of joint destruction in this category is proportional to the severity of arthritis within the first 2 years. Chronic uveitis is a complication of JIA observed mainly in patients with oligoarthritis associated with positive antinuclear antibodies in serum.
 - Polyarthritis with a positive rheumatoid factor is associated with marked disability in adulthood.
 - *Psoriatic patients*: The risk of developing sacroiliitis is higher in male and HLA-B27-positive patients.
 - Enthesitis-related arthritis patients with lower limb, knee, and tarsal involvement also are at greater risk of developing sacroiliitis.⁷

THE AIMS OF TREATMENT OF JIA (TABLE 1)

These are conveniently divided into immediate and long term:

The immediate aims are

- To control inflammation
- Preserve vision (by screening and treating silent uveitis that is associated with ANA positive oligoarticular patients)

Table 1: Validated outcome measures for juvenile idiopathic arthritis trials

Active joint count (joints with swelling or with limitation of motion and tenderness/pain on motion)
Joints with limited range of motion
Parent/patient global assessment (measured on 0-10 visual analog scale)
Physician global assessment (measured on 0-10 visual analog scale)
Laboratory measure of inflammation (erythrocyte sedimentation rate, C-reactive protein)
Functional assessment (childhood health assessment questionnaire)
<i>A patient is considered to have responded if there has been an improvement in at least 3 variables by at least 30% and worsening in not more than one variable by more than 30%.</i>

- Relieve pain and discomfort
- Prevent deformities
- Preserve function

The longterm goals are to

- Minimize side effects of the disease and drugs
- Promote normal growth and development of the child
- Minimize impact of the chronic disease on the family
- Educate the child and family
- Finally rehabilitate the child.

PSYCHOSOCIAL AND EDUCATIONAL MANAGEMENT OF CHRONIC ARTHRITIS IN CHILDHOOD

This is as important as the medical care. Important issues while looking after this area are:

- The child should be strongly encouraged to attend school regularly.
- Children should determine their own level on activity.
- Participation in recreational activities and camps with other children with arthritis is very beneficial.
- Vocational evaluation is very important for the adolescent with arthritis.

RECENT ADVANCES IN THE MANAGEMENT OF JIA

Six important developments/advances have taken place in the last decade:

1. Appropriate use of NSAID's has been understood.
2. Intra-articular steroids have proved to be effective in treating joint disease.
3. Methotrexate is safe and effective.
4. Leflunamide is safe and effective as an alternative to methotrexate.
5. Biologic reaction modifiers (BRM's)—Etanercept and infliximab promise even further improvement in the risk benefit ratio.

6. High dose immunotherapy with transplantation is available in select centers.

Nonsteroidal Anti-inflammatory Drugs

The choice of NSAID's is empiric; clinical trials of NSAID's by the PRCSG (Pediatric Rheumatology Collaborative Study Group) in the USA concluded that 65 percent of the children who were going to respond would do so in the first 4 weeks. If a child does not respond it is logical to use an NSAID from a chemical class different to the one used earlier. Twenty five to thirty three percent of patients with oligoarthritis show a significant response to NSAID's alone. Aspirin is not used commonly any longer for the following reasons – the need for frequent dosing, greater frequency of liver enzyme abnormality, and the association of REYES syndrome.^{8,9}

Details of commonly used NSAID's are detailed in Table 2.

Cox 2 inhibitors have been shown to be effective in adults with significant reduction of gastrointestinal side effects. Rofecoxib has been recently withdrawn from the market due to cardiovascular adverse effects in adults. Though it was recently licensed for use in children, the use is now controversial.¹⁰ In the vast majority of children who tolerate non selective cox inhibitors well, there is no added advantage of using a cox 2 inhibitor.

Intra-articular Steroid Injections

Triamcinalone hexacetonide is the preferred steroid preparation due to the long-term and predominantly local effects, with a reported median duration of improvement for a period of 74 weeks. In 60 percent of patients the response persists for at least 6 months, in 45 percent there is no inflammation for at least one year. Accelerated linear growth of the involved leg is typical in this disease as the knee and ankle joints are the most commonly involved and the arthritis is frequently asymmetric. Early and continued use of IA steroid has been recently shown to be associated with less leg length discrepancy in young children with oligoarticular JIA.^{11,12} This agent is not available in India, where we use triamcinalone acetone.

Side effects of intra-articular steroids are very few. It is a very safe procedure that may need appropriate sedation in a child under 7 or 8 years of age. Problems after a joint injection are:

- Periarticular subcutaneous atrophy.
- Asymptomatic calcification.

There is no report of it being associated with any joint or cartilage damage^{13,14}

Methotrexate

Methotrexate is the sheet anchor for the treatment of polyarticular disease. There is evidence for the safety and efficacy of once weekly methotrexate in JIA. There are two methods of giving methotrexate either oral or injectable. The injectable route has many advantages over oral administration - it is well absorbed even at higher doses and is better tolerated. Nausea and gastrointestinal side effects are less when methotrexate is given parentally. Methotrexate is started at a dose of 15 mg/m²/week and built up as needed. Children require and tolerate larger doses than adults, sometimes at 1 mg/kg/week. Doses of 20 to 25 mg are therefore commonly used in children under six years. Thereafter children's requirement and tolerance both fall such that doses above 25 to 30 mg are unusual. An open randomized trial has recently shown that there is no advantage of giving methotrexate at doses of 30 mg/m².¹⁵ Most clinicians would switch to the subcutaneous route at doses greater than 0.5 mg/kg/week. Patients respond within three months, very occasionally is the response delayed beyond three months. The poorest response with methotrexate is in patients with systemic onset JIA (SOJIA). Folic acid at a dose of 1mg/day is often given to children receiving methotrexate and appears to lessen the toxicity and increase the tolerability of the drug. Precautions to be exercised while the patient is on methotrexate are as follows: no live vaccination, avoidance of alcohol, and no pregnancy while on the drug. Regular monitoring of hemoglobin, white cell count, platelets and liver function tests every 4-6 weeks is mandatory.^{16,17}

Leflunamide

It is a DMARD licensed for the treatment of adults with active rheumatoid arthritis (RA). It is converted to an active metabolite that inhibits *de novo* synthesis of pyrimidine and prevents activation of T lymphocytes that are involved in the pathogenesis of RA. Blinded trials in adult patients have well proven the efficacy of this drug. At the doses used, some clinical benefit of methotrexate over

Table 2: Nonsteroidal anti-inflammatory drugs

NSAID	Total daily dose	Maximum daily dose	No. of doses/day	Side effects
Naproxen	10-20 mg/kg/day	1000 mg	2	Cutaneous pseudoporphyria
Ibuprofen	40-60 mg/kg/day	3200 mg	3 or 4	Well tolerated
Diclofenac	2.5 mg/kg/day	125 mg	2	Gastritis
Indomethacin	1.5-3 mg/kg/day	200 mg	2	Headache
Piroxicam	0.25-0.4 mg/kg/day	20 mg	4	Gastritis

leflunomide was observed in the first year of treatment¹⁸ A recent trial that recruited 94 children has shown that leflunomide is safe in children with polyarticular disease and has an efficacy similar to methotrexate.¹⁹

BIOLOGIC REACTION MODIFIERS (BRM)

Introduction

There are many cellular and molecular mechanisms that participate in inflammation in patients with juvenile arthritis. Specific biologic agents have been developed that can target one or more steps involved in the immune response.²⁰

Strategies for Intervention are

- *Interference with cytokines:* The biologic effects of T-cell derived and monocyte derived cytokines are responsible for clinical features seen in JIA such as arthritis, enthesitis, and systemic features such as fever. Cytokines are thus important targets for therapeutic manipulation. Evidence supports the role of TNF alpha in both the initiation and perpetuation of the rheumatoid process. Agents that block TNF alpha are excellent tools to reduce disease activity, improve function and even retard or reverse structural damage. Three anti-TNF agents available are etanercept, infliximab, and adalimumab. The other cytokines that can be manipulated are IL-1 and IL-6. Data is available for these agents and will be discussed in detail.
- *Tolerance induction:* Trials of oral type II collagen have been tried in adults and children, as there is documented auto immunity to type II collagen in both adult and juvenile arthritis. Studies in humans have shown variable results, but with advances in other areas this has not been further studied. Another agent called IJP-394 has been studied to induce B-cell tolerance in patients with lupus. It is not currently widely used.
- *Inhibition of MHC/antigen/T-cell receptor (TCR) interaction:* This is also called the trimolecular complex. If the initiating antigen was known, an immunization program could be developed to prevent disease. Another possible route of attack is to block the MHC sides by antiMHC antibodies. This is currently under study.
- *Inhibition of cellular function and cell to cell interaction:* T-cells are critical in initiating the rheumatoid process in both children and adults. They may however not be critical for perpetuation of synovitis. Trials using anti CD7 monoclonal antibodies, the use of CAM-PATH, and Anti CD 4 monoclonal antibodies has been disappointing. There is no trial as yet that has studied blocking cell to cell interaction for example interaction between T-cells and antigen presenting cells. Another promising approach has been to block co-stimulatory interactions between T and B cells, for example by inhibiting the CD40-CD40 ligand pathway

with anti-CD40 ligand monoclonal antibody or the B7 pathway with CTLA-4Ig. Initial results in adult patients look promising.

- *Apoptosis:* Strategies to correct defective apoptosis include using monoclonal anti-Fas antibodies and are currently experimental.

ANTI-TNF AGENTS

- Etanercept
- Infliximab
- Adalimumab

Double blind, randomized controlled studies have shown all three agents to be an effective therapy in patients with juvenile idiopathic arthritis (JIA). Currently these drugs are given to patients who do not respond to an adequate trial with methotrexate. Studies are underway in children to determine whether administration of anti-TNF agents early on in the course of the disease may induce remission.²¹⁻²⁴ Long term data is now available for treatment with etanercept: 8 years follow up of 26 patients on this medication showed that the drug had a prolonged efficacy, the overall exposure-adjusted rates of serious adverse events (SAEs) remained stable (0.12 per patient-year), and the rate of medically important infections (MIIs) remained low at 0.03 per patient-year.²⁵

Generic Issues with Anti-TNF agents

- Safety issues are a concern because of the ubiquitous role of TNF. To date the only consistent adverse event seen with etanercept has been injection site reactions. There should be caution, however, with using etanercept in patients with a serious infection, or recurrent infections or patients with untreated or latent tuberculosis. As of yet there has not been seen an increase of malignancies. Rare neurological and hematological events have been noted. Etanercept has been a significant addition to the armamentarium of medications for the treatment of RA, juvenile and psoriatic arthritis.
- Active tuberculosis may develop soon after the initiation of treatment with infliximab. Thus before prescribing the drug, physicians should screen patients for latent tuberculosis infection or disease. The risk of tuberculosis is more with infliximab than etanercept because as opposed to etanercept, it binds not only to soluble TNF-alpha but also to membrane TNF-alpha. It is however mandatory to screen all patients for latent tuberculosis prior to using any biologic agent. This is with a PPD test and chest X-Ray/CT scan of chest in doubtful cases.^{26,27}
- Infliximab is mouse chimeric antibody, is known to give infusion reactions and must be given in a hospital setting with adequate monitoring facilities.

- Though in the western world their use is open ended, in India these agents are prohibitively expensive and are used to reduce disease burden and are very seldom continued for years on end. The rough cost of etanercept therapy for a 30 kg child is 4.16 lakh rupees for one year; for infliximab it is 3.24 lakh rupees per year + incidental hospital charges for nine admissions in the first year. Adalimumab is not yet available in India.
- *Cancers and TNF blockers*: Recent reports have generated some concern about the risk of cancers in patients on TNF inhibition. This issue has been discussed by Cron in a recent paper.²⁸ There is a specific risk of developing hepatosplenic T cell lymphomas in children with inflammatory bowel disease (IBD) treated with a combination of azathioprine or 6-mercaptopurine (6-MP), and a monoclonal antibody (mAb) directed against TNF (e.g. infliximab or adalimumab). These combinations should therefore not be used. The absolute risks of malignancies in JIA patients on biologics are difficult to ascertain as JIA patients who are naïve to biologic agents may be at an increased risk of malignancies *per se*.²⁹

The three anti TNF agents are summarized in Table 3.

OTHER BRM'S

Anakinra

This is interleukin-1 receptor antagonist (IL-1Ra). It is a naturally occurring acute phase anti-inflammatory protein part of the IL-1 super gene family. It is an important physiologic regulator of IL-1 induced inflammatory activity. Anakinra is a human recombinant form of IL-1 Ra that is produced by recombinant technology in *E.Coli*. It is given daily by subcutaneous injection. In pediatrics it

is used in a dose of 0.1 mg/kg/day and it has been shown to be effective in etanercept resistant SOJIA patients.³⁰ A recently published paper evaluated the use of this drug in TNF naïve patients with SOJIA. This study, called the ANAJIS trial has shown that anakinra treatment is effective in SJIA, at least in the short term. It was also associated with normalization of blood gene expression profiles in clinical responders and induced a *de novo* IFN signature.³¹ To date, this molecule is unavailable in India.

Anti IL-6 Receptor Antibody/Actemra

There is evidence that IL-6 is important in the clinical features of SOJIA. Anti IL-6 receptor antibody MRA is a genetically engineered humanized monoclonal antibody that is produced by grafting the complementarity-determining region of mouse anti-human IL-6 receptor to human IgG₁. MRA has been used in a study on SOJIA patients in Japan where the results were dramatic with 70 percent JIA core set response in 100 percent of patients receiving 8 mg/kg/week. This was a preliminary study with only 11 children. An international multicenter trial is currently underway.³² A recently concluded randomized controlled study by Japanese workers showed that actemra was highly effective in children with poly JIA.³³ The drug has been shown to be effective in SJIA patients as well in the recent EULAR 2011 congress where the data from the TENDER study (OP006) was presented. The drug has now received US FDA approval for children with systemic onset JIA.

Stem Cell Transplantation in JIA

Autologous hemopoietic stem-cell transplantation (AHSCT) has been described as a possible treatment for severe

Table 3: Anti-TNF agents for JIA

Name	<i>Etanercept</i>	<i>Infliximab</i>	<i>Adalimumab</i>
Chemical content	Fully humanized	Mouse chimeric	Fully humanized
Chemical structure	P-75 soluble TNF receptor protein fused to human Fc region of human IgG ₁	Chimeric IgG ₁ Anti-TNF alpha antibodies—mouse antibodies and constant region of human antibody.	Recombinant human IgG ₁ monoclonal antibody
Binds to	Soluble TNF alpha	Soluble TNF alpha and membrane bound TNF alpha	Soluble TNF alpha and membrane bound TNF alpha
Half life	4 days	Weeks	2 weeks
Route	Subcutaneous	Intravenous (IV)	Subcutaneous
Dose	0.4 mg/kg/dose/twice weekly or 0.8 mg/kg once weekly	3-6 mg/kg/dose	24 mg/m ²
Frequency	By weekly or weekly	As 0, 2, 6 weeks and then every eight weeks	Every 2 weeks
Methotrexate use	Optional	Recommended (to prevent anti infliximab antibodies)	Optional
Risk of tuberculosis	+	++	++

autoimmune disease refractory to conventional treatment. The first four children with severe forms of juvenile idiopathic arthritis to receive AH SCT were reported in 1999. Collaborative European trials with strict entry criteria and pre transplant conditioning are ongoing. Patient selection is critical prior to undertaking this modality of treatment where the mortality has now come down from 14 percent to 5 percent.^{20,34}

Specific Treatment Modalities for Each Subtypes of JIA

Oligoarticular JIA

Intra-articular (IA) injections and appropriate use of Non steroidal anti-inflammatory drugs (NSAID's) is the mainstay of treatment for this subtype of JIA. If the child with oligoarthritis has persistent joint inflammation in spite of an NSAID for 2-6 weeks the joint must be injected to prevent leg length discrepancy and the attendant long-term morbidity. In the persistent oligoarticular group this is all that is required. Disease modifying antirheumatic drugs (DMARD's) are generally not recommended for this group, although occasionally methotrexate may be useful for difficult to control uveitis or when damage to a critical joint threatens function (wrist/hip). If the disease extends, methotrexate should be considered for the treatment.

A recent editorial in the pediatric rheumatology online journal has suggested that oligoarticular JIA is not always benign. Persistent elevation of ESR, long standing anemia, or difficult to control arthritis and/or uveitis are all indications for aggressive treatment/DMARD use.³⁵

Polyarthritis

Standard Treatment

- NSAID either alone for the very mild disease or in combination with methotrexate is the initial treatment regimen.
- Early introduction of DMARD's—usually methotrexate
- Rapid disease control with intravenous methyl prednisolone boluses, or oral steroids.

Other Strategies

- Data also supports the use of sulphasalazine in the treatment of polyarticular JIA, though tolerability is poor in one-third of patients.^{36,37}
- A double blind control trial recently concluded that leflunomide is a safe alternative to methotrexate.¹⁹
- Currently TNF blockers are reserved for patients resistant to methotrexate alone.²²

Systemic Onset JIA

Drug management of systemic onset JIA aims to alleviate both the systemic features and the arthritis. Some mild cases clear up spontaneously. The fever may be treated with ibuprofen 40-50 mg/kg/day, or naprosyn at a dose

of 20 mg/kg/day. In the more severe case steroids may be needed at a dose of 1 to 2 mg/kg/day. IV methylprednisolone is also used to induce remission at a dose of 30 mg/kg/day (maximum 500 mg) for three consecutive days, and may be repeated after one week. Methotrexate remains the DMARD of choice for the children who have arthritis. For the more severe cases management is challenging, and may need DMARD combination and/or repeated pulsing with methylprednisolone. Recently thalidomide has been shown to be effective for both the systemic and articular components of the disease. The first report of its usefulness came in 2002 and was followed up by a multicenter trial in 2004. The dose of thalidomide is between 3 and 5mg/kg/day. The patients need to be monitored for sensory neuropathy.^{38,39} The biologic agents used in this subcategory are TNF blockers, anakinra and MRA (anti IL-6).^{21,24,30,32}

Untreated, systemic onset JIA can be complicated by macrophage activation syndrome (also known as hemophagocytic syndrome) which presents with persistent fevers, drop in the platelet count, lowering of the ESR, and liver function abnormalities with coagulopathy. This condition has a high mortality and is best treated with IV methylprednisolone and cyclosporin.^{40,41}

Enthesitis Related Arthritis

This group is believed to represent the adult equivalent of ankylosing spondylitis and reactive arthritis. The difference is that peripheral arthritis and not sacroiliitis is the main clinical feature. The treatment of choice for the peripheral arthritis in this group is sulphasalazine at 25-50 mg per kg per day, using doses as high as 2 gm/day. The NSAID of choice in this group is indomethacin. With significant systemic manifestations of the disease methotrexate is often added. Biologics have a role to play in management of all components of the disease: peripheral arthritis, enthesitis, uveitis and sacroiliitis.^{41,42}

Psoriatic Arthritis

Asymmetric involvement of small joints especially the DIP joints and dactylitis is characteristic of psoriatic arthritis. Significant nail pitting often precedes arthritis. The skin and joint disease may not always follow the same course. In addition to local skin treatment NSAIDs/IA steroids are used for localized disease involving a few joints, and methotrexate is used for aggressive disease involving multiple joints.^{41,42}

American College of Rheumatology 2011 Guidelines for Management of JIA⁴³

These recently published recommendations cover the initiation and safety monitoring of therapeutic agents in the treatment of JIA and include

- Nonsteroidal anti-inflammatory drugs

- Intra-articular glucocorticoid injections
- Non-biologic disease modifying anti-rheumatic drugs
- Biologic DMARDs.
- Systemic glucocorticoids for the treatment of the systemic features of systemic arthritis.

Of note, these recommendations divide JIA into 'treatment groups' instead of the JIA categories set forth by International League of Associations for Rheumatology.

The recommendations are focused on early use of TNF blockade and anakinra in children (which are prohibitively expensive), there is no role of steroids to induce remission and the categories of prognosis in each subtype are complex to follow. A treatment pathway for a subset of children with SOJIA and poor prognostic markers even suggests use of upfront anakinra. For these reasons the suggestions are not directly applicable in India.

Generic Issues in the Management of JIA

Uveitis

Standard treatment of uveitis is the use of topical methyl prednisolone and mydriatics to prevent synechiae. Methotrexate and other DMARDs have been tried, but there is no clear evidence that they are especially useful in uveitis resistant to steroid treatment. The benefit seen with methotrexate is evident at higher doses, when used subcutaneously or intravenously. Uveitis in JIA is silent and painless except in children with enthesitis related arthritis that have acute painful anterior uveitis. Thus, it is mandatory that patients with JIA be electively screened for uveitis at regular intervals, as untreated uveitis is known to cause visual loss and morbidity.^{12,40,44}

When should Methotrexate be Stopped?

Up until recently there has been paucity of published data to support evidence-based decisions in this area. Most authors had suggested that discontinuation of methotrexate when treatment induced remission had persisted for less than 1 year frequently resulted in return of arthritis within 6 months of drug discontinuation.^{17,45} NSAIDs and other medications are discontinued prior to attempting withdrawal of methotrexate. This thought has been recently questioned with the publication of an article that looked systematically at methotrexate withdrawal from 364 children with JIA when they entered remission. This trial randomized the children into two groups: one group continued the treatment for a further 6 months and the other for 12 months. Twelve month withdrawal of methotrexate compared with a 6-month withdrawal did not reduce the relapse rate in patients with JIA in remission. The second aspect of this study was to look at myeloid related protein (MRP) 8/14 concentrations in the serum of these patients. MRP is a protein that is secreted by activated phagocytes and increases with inflammation. It is postulated that an increased MRP suggest ongoing disease at the local level

which cannot be picked up clinically or by markers used such as ESR and CRP. A level of 690 nanograms/ml was detected to be a cut off, suggesting that an increased level of MRP 8/14 in clinically normal children who have normal acute phase responses are at a risk of flare when the methotrexate is discontinued.⁴⁶

Combination DMARD Therapy

Combination therapy is the rule rather than the exception in treating adult rheumatoid arthritis (RA), where use of weekly methotrexate along with daily hydroxychloroquine and sulphasalazine appears to give good results without any increase in toxicity.⁴⁷ This approach is reserved for the difficult to control JIA patient who does not respond adequately to subcutaneous methotrexate at a dose of up to 30 mg/ m². Failure to respond adequately or poor tolerability can occur in approximately a quarter of these children. In addition to the combination suggested above

- Etanercept/other BRMs and/or leflunamide may be used.
- Cyclosporin may be combined with methotrexate.
- Pulsed methylprednisolone may be used at regular intervals.
- Cyclophosphamide may be tried^{22,24,48}

There are no controlled studies of combination DMARD therapy in JIA.

Care of the Adolescence, Transition Issues, and Compliance

JIA is a chronic disease, with a third of patients carrying the disease into their adult years. Delayed adolescence both physically and emotionally is being recognized more widely and adolescent centered services to aid transition to adulthood have a major role to play in the long term care of the patient with JIA. Transition to adult care is a process that begins in the adolescent age. Attention to vocational skills, independent living skills, and self-advocacy warrant careful care and planning. Compliance with the treatment regime including medication, blood monitoring, exercises, splint usage and regular visits to health professionals are demanding on the child and family. Multidisciplinary teams under one roof are ideally suited to deliver this care. Patient and parent education and incorporation of the needs of the child and family members in planning care are essential to ensure that the patient adheres to the plan.^{49,50}

Physiotherapy and Occupational Therapy

The therapists are the key personnel to restore function and strength of affected joints and musculature. Together they plan a treatment program that incorporates a range of exercises, stretches for the joints, and activities of daily living. The occupational therapist has two important roles: to provide custom made splints to maintain joint position especially for the wrist and the knee joint,

and assist children whose disability requires modification of the environment. Children and adolescents both can improve aerobic endurance through participation in weight bearing physical conditioning programs without any disease exacerbation or increased pain. They can also achieve decreased joint signs and symptoms through increased physical activity. Lastly the therapist is usually the key person to educate the parents, and school personnel to ensure integration of therapy goals into the child's daily routine.⁵¹

Osteoporosis and Growth Retardation

There are many factors that adversely affect bone mass in children with JIA. Active arthritis has a well-known osteopenic effect around joints (periarticular osteopenia) and often systemically. Medications used in arthritis, especially steroids also have a known osteopenic effect. Decreased physical fitness and participation in organized sport, in addition to poor vitamin D and calcium intake contribute to the low bone mineral density (BMD). Interventional studies are lacking, and until sound evidence is available the following strategies are generally employed to optimize bone mass in children with JIA: aggressive control of disease activity, avoidance of corticosteroid use, and optimizing physical activity and calcium intake.

Bisphosphonates—alendronate has been recently shown to be effective in treating secondary osteoporosis in juvenile idiopathic arthritis. This drug crosses the placenta and is highly teratogenic. It is thus mandatory for patients to avoid pregnancy during the duration of treatment and for up to six months after discontinuation. Finally, growth hormone also improves the growth retardation and osteoporosis, particularly where the disease is stable but not in remission.

The best strategy to maximize growth is aggressive disease control, nutritional support and judicious yet minimal use of steroids.⁵²⁻⁵⁴

Can We Do Better?

One-third of children with JIA will have significant active disease well into their adult years and 50 to 60 percent have some form of disability or deformity in adulthood. Major disabilities occur in 10 percent of patients. This is data from the western world where a referral system is very well established, and where intervention is directed by multidisciplinary teams in tertiary level academic centers.^{1,50,55} Data from India suggests that after a median followup of 10 years up to 60 percent of patients have active disease. Certainly a major contributor here is delayed referral and delayed institution of disease modifying agents.⁵⁶

Development of new therapies has dramatically increased our ability to treat children with JIA, and hopefully induce remission in many children. There is though,

lack of evidence based treatment for some JIA subtypes. Effect of early aggressive therapy on the disease, early use of BRMs and potential of combination induction therapy needs to be studied. Multicenter control trials will provide this much needed evidence in the near future.⁵⁷

It is important for pediatric rheumatologists in turn to objectively assess patients, look at the core set criteria in these patients at set points in time,³ and guide therapy with the aim to achieve remission as per standard definitions recently validated for use for JIA patients.⁵³

Strategies likely to help children with JIA in our country are:

- Formal inclusion of pediatric rheumatology core curriculum both at the graduate and postgraduate levels in medical schools in India.
- Increased awareness amongst general pediatricians and orthopedic surgeons about the prevalence of JIA in India and the urgency of early referral of these patients to specialist centers.

Establishment of several tertiary level centers with good skill and expertise to direct care for these children.

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Approach to a Child with Arthritis

Manjari Agarwal, Sujata Sawhney

INTRODUCTION

A child with complains of pain and/or swelling in joints is the most common cause of referral to a pediatric rheumatology clinic. These patients pose a diagnostic challenge due to an extremely broad differential diagnosis that needs to be considered.

The approach to a child with arthritis needs the following parameters to be carefully addressed:

- *The onset type:* Acute or chronic (the acute arthritis is one seen within 6 weeks of onset, whereas arthritis of more than 6 weeks duration is considered chronic)
- *The number of joints involved:* Single/more than one joint
- The type of joint involved
 - Small or large
 - Symmetrical or asymmetrical
 - Upper or lower segment
- Associated systemic features
 - Rash
 - Fever
 - Systems review
 - Uveitis
 - The lab markers
 - Family history.

This chapter will address the clinical approach to a child with joint pains.

CLINICAL PEARLS

The following clinical pearls should be kept in mind when these patients are evaluated:

Pain: It is not always present, many children with oligo JIA have a relatively asymptomatic swollen knee joint. Severe pain is seen in sepsis, trauma or bleed. Referred pain is also an important cause of a limp and needs to be differentiated from a swollen joint. Pain can be referred from the back (diskitis)¹ or from the hip to the thigh and

down the knee when the child can point towards the knee as the affected part.

Arthritis vs arthralgia

Arthralgia is a symptom or a complaint of pain in the joint made by the patient. It is not associated with a swelling or tenderness. Arthritis is a sign demonstrated on clinical examination and is defined as an intra-articular swelling or the presence of 2 or more of the following signs: limitation in range of motion, tenderness or pain on motion, and increased heat or erythema.²

JIA or Not?

By definition, juvenile idiopathic arthritis (JIA) is arthritis present for at least 6 weeks commencing in a child before the 16th birthday, with other known diagnoses excluded.³

Diagnosing juvenile idiopathic arthritis in a child poses special difficulties due to a number of reasons:

- Paucity of symptoms
- Requirement of a clinical skill set to examine a young uncooperative toddler who is not weight-bearing
- Lack of a diagnostic test
- It remains a diagnosis of exclusion and excluding a multitude of conditions is difficult.

The following approach towards the history, examination and investigations helps to recognize the pattern of the joint involvement in a child and is helpful in reaching the correct diagnosis.

History: A systematic and detailed history gives 85 percent clue to the diagnosis. Onset of arthritis can be acute or chronic. An acute presentation of arthritis within few minutes to hours is suggestive of an acute bleed inside a joint as in hemarthrosis, post-traumatic or in infections. It could occur occasionally in a child with reactive arthritis. A history of trauma is often given as this brings a previously quiet joint to the attention of the parents.

Trauma is considered significant if it causes non-weight-bearing immediately after the event. Pain/swelling occurring days after trauma is often of no consequence except if it causes mechanical derangements. A history of a preceding infection of the gastrointestinal tract or the upper respiratory tract would point towards a postdysenteric reactive arthritis or acute rheumatic fever.

Detailed history regarding the site, localization of pain is to be elicited. The number of joints involved is also important as it provides a clue to the type of arthritis (oligoarticular vs polyarticular).

History of associated systemic features like fever, rash, acutely swollen lymph nodes in the neck or axilla are a pointer towards systemic arthritis or can also point towards a malignancy.

History of pain in detail helps differentiate between mechanical, inflammatory and sinister pain (Table 1). Site of involvement can also give certain clues in regards to the diagnosis (Table 2).

The three clinical presentations of a child with arthritis are as follows:

- Acute monoarthritis
 - Sick child with or without fever
 - Well child with or without history of significant trauma
- Chronic monoarthritis
 - Sick child
 - Well child
- Polyarthritis
 - With fever
 - Without fever.

Approach to Acute Monoarticular Arthritis (Flow Chart 1)

An acutely painful joint is an emergency and needs to be diagnosed at the earliest not only to alleviate pain but also to prevent damage to the joint. Septic arthritis needs to be ruled out at the earliest.⁴⁻⁶

A detailed history and thorough clinical examination go a long way in narrowing down the diagnosis. Radiography along with laboratory support helps in the confirmation of the diagnosis.

Table 2: Site of involvement

Hip

An infant screams with nappy change.
The child may drag leg or rotate entire leg outwards.
Referred pain from hip to thigh or knee is common (usually anterior or sometimes medially).
Look for wasting of buttock and thigh
Check for Trendelenburg gait.

Knee

Knee will usually be held flexed when painful.
Look for wasting of thigh, calf.
If knee is held straight, consider psychosomatic problems.

Ankle

Look for wasting of calf. This often means ankle pathology.
A swollen ankle may be easier to detect from behind, especially in a smaller child.

Infected toe/ foot

Check for enlarged lymph gland in groin.

History

The age of the patient, the type of onset and the presence or absence of constitutional features help in narrowing down the wide differential in these children.

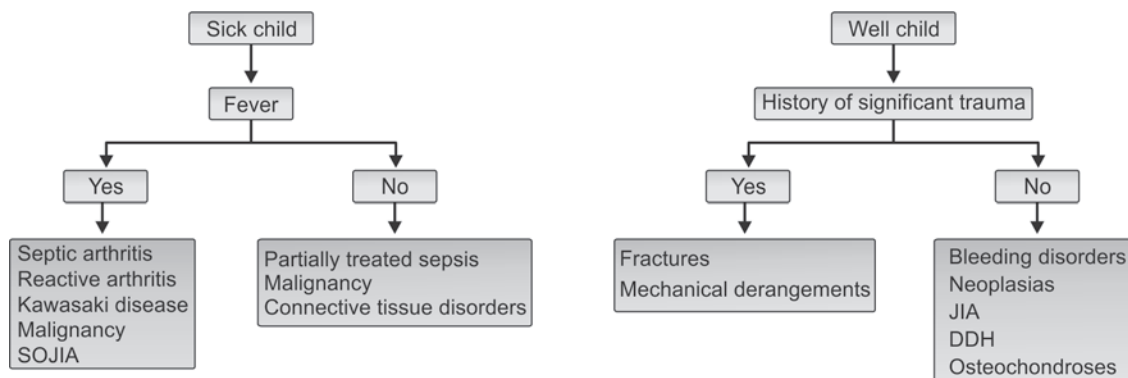
Age

- *Neonates*: A neonate presenting with an acutely swollen joint can have septic arthritis, NOMID (Neonatal onset multi inflammatory disease), developmental dysplasia of hip.
- *Infants*: Septic arthritis, Hemarthrosis due to bleeding disorders like hemophilia presents in infancy especially when the child is weight-bearing, developmental dysplasia of hip mild variant.
- *Childhood*: Septic arthritis, trauma, mechanical derangements, hypermobility, infiltrative disorders, reactive arthritis, juvenile idiopathic arthritis, skeletal dysplasia, etc. usually present in childhood.

Table 1: Types of joint pain

History	Inflammatory	Mechanical	Sinister
Onset	Insidious	Sudden/subacute	Insidious
Course	Fluctuant	Persistent	Persistent
Relation to time	More in morning	No relation	No relation
Relation to activity	Improves	Worsens	Worsens
Examples	Juvenile idiopathic arthritis	Slipped capital femoral epiphysis	Malignancy

Flow chart 1: Algorithm for acute monoarthritis



Onset

- *Sudden*: Sudden onset swelling and pain developing over minutes to hours is usually indicative of trauma causing fracture or soft tissue injury
- *Acute*: Pain and swelling of a joint over hours to days is suggestive of septic joint, reactive arthritis, hemarthrosis, acute rheumatic fever, etc.

Constitutional Features

Presence of fever, sore throat, weight loss, loss of appetite, diarrhea, dysentery, urethral discharge, history suggestive of uveitis, oral mucosal ulcers, hair fall, rash over skin, etc. is to be inquired into.

Nature of pain

- Is the pain severe enough to disturb the sleep of the child? (Osteomas)⁷
- Is there any early morning stiffness? (Inflammatory)
- Does the pain worsen after movement or does it get worse with exercise? (Inflammatory vs Mechanical)

Site and Distribution of Pain

In childhood arthritis recognition of the pattern of pain is very important as majority of the illnesses follow a pattern of joint involvement which aids in the diagnosis.

To interpret the pattern correctly it is necessary to know the following:

- Where did the pain start from?
- Which joints are involved?
- Upper limb joints/lower limb joints
- What is order of involvement?
- Whether arthritis is migratory or nonmigratory?
- Is the joint involvement symmetrical or asymmetrical?
- Is joint pain part of a systemic illness?

Associated Medical Illnesses

Psoriasis, inflammatory bowel disease, tuberculosis, etc.

Drug History

Long-term steroids can cause avascular necrosis, retinoids, anticonvulsants can unmask or exacerbate the articular manifestations of lupus.

Family History

History of arthritis, psoriasis.

Examination

General Examination

Complete head to toe examination is required.

Weight and height should be taken and growth charted if previous records available.

Look for alopecia, pallor, redness of eyes, cataract, icterus, rash, lymphadenopathy, nail pitting, thickening of skin, pigmentation, psoriasis, oral ulcers, nodules, Raynaud's phenomenon, etc.

Systemic Examination

CVS: Heart rate, murmurs

Abdominal examination: Visceromegaly

Respiratory System: Dyspnea, intercostal retractions

CNS: Headaches, neuropsychiatric manifestations (pointing towards SLE) need to be ruled out

Local Examination

Inspection: Warmth, Swelling, Redness

Look for soft tissue swelling

Examination: Movements of the joint

Ascertain whether the swelling is articular or periarticular

Enthesitis is to be ruled out by examination of the entheses especially the Tendo-Achilles.

Laboratory Markers

- Complete blood count, ESR, CRP, Blood culture, ANA, ASO titre, throat swab

- Ancillary investigations for specific diagnosis like Hb electrophoresis for sickle cell disease, factor VIII and factor IX estimation for hemophilia.
- *Synovial fluid examination: (Synovial fluid aspiration):* Most important investigation should be done by an experienced person with all aseptic precautions. On the basis of synovial fluid aspiration the diagnosis can be divided into three broad categories, first the fluid can be hemorrhagic and the diagnosis is either hemarthrosis or pigmented villous nodular synovitis. If the cell count in the synovial fluid is between 1500 cells/mm³ to <50,000 cells/mm³, it is suggestive of inflammatory/reactive arthritis. If the cell count is more than 50,000 cells/mm³ it is indicative of septic arthritis.⁸ Synovial fluid culture can help identify the specific organism and the sensitive antibiotic can be given.
- *Radiography:* X-ray of the joint affected, MRI, bone scan. CT scan or MRI are increasingly being used to identify the cause of an acute monoarthritis specially after history of trauma or where the pattern of joint involvement is suggestive of JIA, e.g. an eight-year-old male patient presenting with knee effusion and Tendo-Achilles swelling, where MRI becomes the investigation of choice to document tendinitis for the diagnosis of Enthesitis related arthritis. MRI is also helpful in the early diagnosis as it picks up bone edema early on in the disease course which is a sensitive marker for an inflammatory process.

Approach to Chronic Monoarthritis (Flow Chart 2)

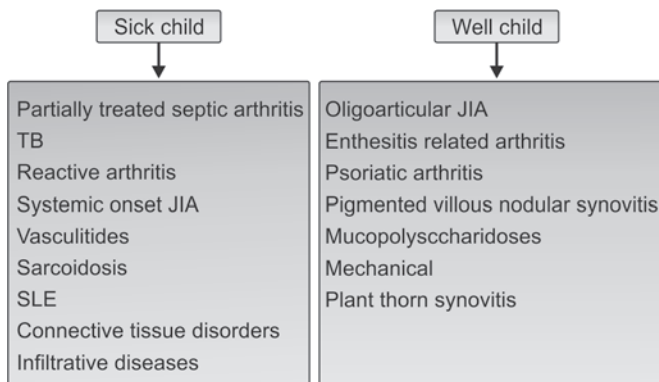
Arthritis for more than 6 weeks is termed as chronic.

History

Onset

Usually insidious, sometimes a partially treated acute septic joint can present as a chronic arthritis.

Flow chart 2: Algorithm for chronic monoarthritis



Pattern

In chronic monoarthritis recognition of the pattern of joint involvement is very important, e.g. in oligoarticular JIA, patient presents with few or absent constitutional symptoms and swelling or limitation of movement is often noted by parents. It is usually asymmetrical. A bilaterally symmetrical joint involvement is less common and is more in favor of a reactive arthritis.⁹

Constitutional Symptoms

Fever, rash, lymphadenopathy are present in systemic onset JIA, SLE and other connective tissue disorders. Arthritis in a child with juvenile dermatomyositis is associated with proximal myopathy and rash.

Nature of Pain

Migratory as in acute rheumatic fever¹⁰ relapsing as in hemarthrosis.¹¹

Duration

In chronic arthritis, duration of joint swelling is important as most diseases have a vertical presentation in children. The time period for classification of JIA and reactive arthritis is 6 weeks. If a child is suspected to be having oligoarticular JIA then a time period of 6 weeks should elapse before labelling the disease as other differentials like poststreptococcal reactive arthritis would usually subside by 6 to 8 weeks.

Past History

History of a joint swelling or of any illness like sore throat, diarrhea, dysentery recently (8 weeks), old trauma leading to mechanical derangement needs to be inquired about.

Examination

Similar as that of acute monoarthritis.

Investigations

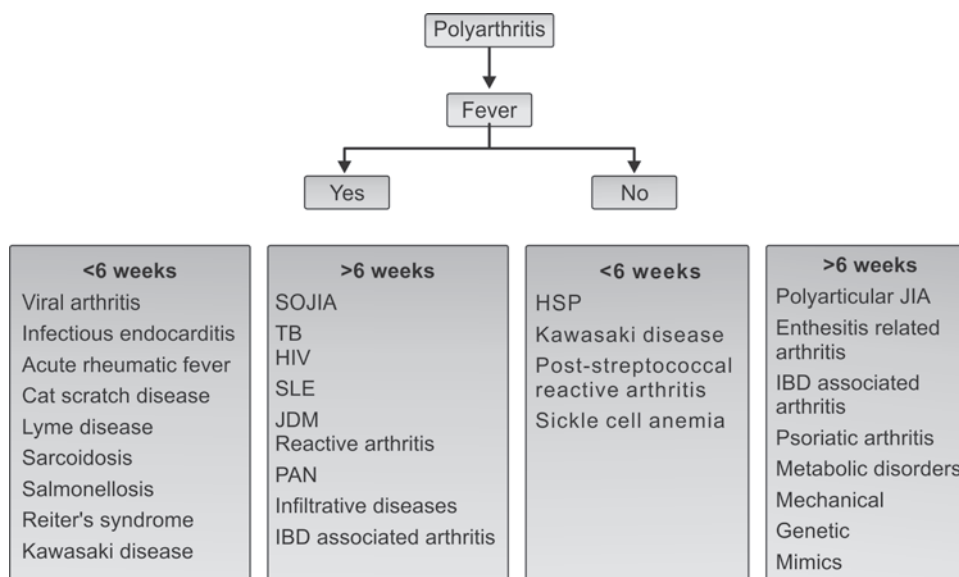
Laboratory Tests

Complete blood count, ESR, CRP, blood culture, quantiferon test, Mantoux test, screen for celiac disease if suspected, PT, aPTT, according to the clinical diagnosis.

Imaging

Forms the backbone of the diagnosis. Plain X-ray of the affected joint with the contralateral joint as control usually gives the clue to the diagnosis. MRI is superior to CT scan for the diagnosis as bone edema can be picked up earlier.

Flow chart 3: Algorithm for polyarthritis



Sometimes a bone scan is required to identify osteomyelitis, nonbacterial osteitis or bone infiltration.¹²⁻¹⁴

Approach to Polyarthritis (With and without fever) (Flow Chart 3)

Joint involvement lasting less than 6 weeks is termed as acute polyarthritis.

Joint involvement lasting beyond 6 weeks is chronic polyarthritis.

History

Onset

Polyarthritis can present with joint pains preceding constitutional symptoms or more commonly with fever and other constitutional symptoms presenting prior to onset of joint involvement.

Pattern

Recognition of joint involvement is imperative for the diagnosis, e.g. migratory or fleeting joint pain with fever preceded by sore throat is suggestive of acute rheumatic fever; additive pattern where some joints are involved at first and persist with recruitment of more joints later, e.g. polyarticular SLE.

Inflammatory vs noninflammatory: Pain in various joints due to hypermobility is noninflammatory as it appears at any time of day, (usually in the evenings after a day of hectic activity), is not associated with early morning stiffness and worsens with activity. Hypermobility should be considered in older child or adolescent with musculoskeletal pain principally confined to the lower limbs and back who lack objective evidence of joint swelling. A hypermobility

index called the Beighton score has been validated in Dutch children, although the cut off point differs for children depending on whether they are 10 years of age or older.¹⁵

On the contrary, inflammatory polyarthritis is worse in morning and improves with gentle activity.

Constitutional symptoms

History of irritable bowel, fever, redness of eyes, sore throat, rash, photosensitivity, early morning stiffness, oral ulcers, alopecia, etc. is to be inquired for by direct questioning.

Examination

Same as for monoarthritis.

Investigations

Infections need to be ruled out as per the clinical suspicion by ordering appropriate serology. ASO titre and throat swab can help in diagnosing acute streptococcal sore throat. Rheumatoid factor, Anti nuclear antibody, HLA B 27, etc. all help to confirm the diagnosis of various JIA subcategories.

Conclusion

In summary, a child who presents with arthritis needs a careful and detailed clinical evaluation. Acute conditions need to be identified at the earliest, specifically to diagnose septic arthritis that can destroy the joint in a few hours chronic polyarthritis needs to be identified and treated within a few weeks to prevent disease associated damage like joint contractures and leg length discrepancy. A systematic and

detailed history, careful clinical examination and few appropriate laboratory tests are all that is needed.

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Approach to a Child with Connective Tissue Disease

Mehul P Jariwala, Sujata Sawhney

INTRODUCTION

Connective tissue diseases of children include a wide range of multisystem disorders, most of which may present as multiple and varying symptoms. The classic autoimmune CTDs include systemic lupus erythematosus (SLE), juvenile dermatomyositis/polymyositis (JDM/PM), systemic sclerosis (SSc), Sjögren's syndrome (SS), undifferentiated CTD (UTCD) and overlap syndromes, e.g. mixed CTD (MCTD).

Although some of these diseases have parallel conditions in adults (e.g. SLE and DM), they also differ from their adult counterparts in presentation, course, subtypes, responses to therapy, and morbidities. Additionally, it is well recognized that in childhood these conditions may “evolve”, with new features appearing over time, which may be more typical of a separate disease. For example, children with arthritis may develop lupus-like features. These areas of overlap between connective tissue disorders mean that each child needs to be carefully assessed and re-examined on a regular basis.¹

These disorders are characterized by abnormalities in the protein matrix within the connective tissue. They are defined as those syndromes which manifest as multiple organ system involvement. The pathogenesis of these diseases is heavily dependent on self-directed immune mechanisms. These diseases are grouped together as:

- They affect the body as a whole
- The disease usually has an immune activation
- They share a similar response to immunosuppression.
- Immune dysregulation leading to formation of antibodies and autoreactive T cells are the main basic abnormalities behind the causation of these diseases.

Children with connective tissue diseases are often difficult to diagnose as they present with multisystem involvement together with an array of diverse clinical signs and symptoms. The clinical presentation of connective tissue

disease in childhood can range from an acute severe illness mimicking a serious infection, to an insidious onset of disease that may only lead to recognition many months after the onset of symptoms.²

Collagen Vascular Disease or Connective Tissue Disease

Diseases in which inflammation or weakness of collagen tends to occur are referred to as collagen diseases. Collagen vascular disease is an umbrella term that covers a range of connective tissue disease. Collagen vascular disease is in fact a misnomer as this disease also affects vascular structures and molecules other than collagen. Collagen vascular disease in broad term can be divided primarily into two groups namely:

- *Heritable collagen vascular disorders:* Marfan syndrome, Ehlers-Danlos syndrome, osteogenesis imperfecta, Stickler syndrome
- *Acquired autoimmune collagen vascular disorders:* SLE, JDM, scleroderma, Sjögren syndrome and MCTD.

This chapter deals with an approach to a child with a connective tissue disease and will look at salient features of the common CTDs in children and outline the clinical and diagnostic approach for these patients.

SYSTEMIC LUPUS ERYTHEMATOSUS

Epidemiology

Pediatric SLE (pSLE) is a prototypic autoimmune disease with a diverse array of clinical manifestations. Approximately 15 to 20 percent of SLE cases begin before age 19. The mean age at pSLE diagnosis is approximately 12 to 13 years. Data suggest an incidence of 6 to 18 cases/100000 white females, with higher rates among Blacks and Puerto Ricans.³⁻⁶

Clinical Features

The classic presentation of SLE is an adolescent female presenting with fever, arthralgia or arthritis who may have an erythematous butterfly rash extending over the cheeks and bridge of the nose. Mucocutaneous, musculoskeletal and kidney disease are the most common manifestations of pSLE.

Classification Criteria

The 1997 revised American College of Rheumatology (ACR) classification criteria are used by rheumatologists to classify SLE. The ACR system requires 4 of the 11 criteria to be present either at one time or over a period of observation to classify a patient to have SLE. The ACR criteria appear to be very useful in pediatric SLE as well, but of note are criteria for epidemiological purposes and not for diagnosis in the clinic (Table 1).⁷

Systems Involvement

SLE can involve many different systems in the body with their individual varied presentations:

- Hematological: Autoimmune haemolytic anemia, isolated thrombocytopenia, leucopenia, stroke in the young as a part of anti-phospholipid syndrome.
- Renal: Nephrotic syndrome, Acute nephritic syndrome and hypertension.
- Musculoskeletal: Arthralgia, Arthritis, myalgia, myositis, pain amplification syndrome.
- Central nervous system: Headaches, seizures, stroke, psychosis, chorea.
- Cardiovascular system: Pericarditis, Libmann Sacks endocarditis, myocarditis
- Mucocutaneous involvement: Photosensitivity, malar rash, “discoid-shaped, oral hard palatal ulcers,

alopecia, Raynaud phenomenon, panniculitis, livedo reticularis and vasculitic lesions.

- Gastro-intestinal involvement: Bowel vasculitis, lupus peritonitis, protein-losing enteropathy, celiac disease,⁹ Pancreatitis,¹⁰ splenomegaly, functional asplenia, hepatomegaly.
- Lung disease: Pleuritis, lupus pneumonitis, interstitial lung disease,¹¹ pulmonary hemorrhage, shrinking lung syndrome,¹² pulmonary vascular disease leading to pulmonary hypertension¹³
- Endocrine involvement: Hypothyroidism, corticosteroid induced diabetes mellitus, growth failure, ovarian failure and delayed puberty.
- Ocular disease: Retinal vasculitis manifestation by cotton wool exudates, central retinal vein occlusion, scleritis and episcleritis.¹⁴

Pediatricians should consider the diagnosis of pSLE in the following categories of patients:

- Prolonged marked constitutional symptoms without a diagnosis. The three common features that are present in most SLE patients and not covered in the SLE ACR criteria are fever, fatigue and weight loss. These are non-specific complaints and in India the child is often misdiagnosed to have tuberculosis
- Disease that involves more than a single organ system such as a photosensitive rash and arthritis; nephritis and pleuritis; haemolytic fever, photosensitive rash and weight loss
- Polyarthritis in an adolescent, especially a female,
- unusual presenting features (such as a myocardial infarction in a teenager), and
- Vasculitic rashes with constitutional features where the differential diagnosis would be a primary systemic vasculitis.

A thorough history and physical examination, a high index of suspicion and appropriate screening laboratory tests will allow the practitioner to make an early diagnosis.

The common differential diagnosis includes infections, malignancy, vasculitis and auto-inflammatory syndromes.

Laboratory Evaluation of pSLE

Screening

Is by the ANA (Anti-nuclear antibody) test. This is positive in over 95 percent of pSLE patients such that a negative ANA is usually a pointer *against* the diagnosis of SLE. These are specific antibodies produced against nuclear antigens. They can be detected by ELISA and Indirect immunofluorescence. The “gold standard” to measure ANA is by using Hep-2 cell line of human laryngeal epithelial carcinoma for indirect immunofluorescence. Both the titre and pattern of the nuclear antigen is studied.

Table 1: ACR criteria for classification of systemic lupus erythematosus⁸

- Malar rash
- Discoid rash
- Photosensitivity
- Mouth ulcers
- Arthritis
- Serositis (pleuritis or pericarditis)
- Renal disorder (proteinuria or urine sediment abnormalities)
- Neurological disorder (seizures or psychosis)
- Hematologic disorder (anemia, leukopenia or lymphopenia on two or more occasions, thrombocytopenia)
- Abnormal ANA titer
- Immunologic disorder (Positive finding of antiphospholipid based on: IgG or IgM anticardiolipin antibodies or Lupus anti-coagulant, abnormal anti-dsDNA or anti-Sm values)

ANA is positive in a low titre of 1:20 in many normal individuals. Malleson et al reported that 41 percent of ANA tests performed at British Columbia Children's Hospital in children without rheumatologic diseases were positive at titres of 1:20 or greater.¹⁵ A positive ANA in a dilution of 1:160 or more is suggestive of SLE or Mixed connective tissue disorder and the usefulness of the test is increased by reduction of false positive results.¹⁶

Further laboratory testing is guided by the following aims, which are true for evaluation of all CTDS where specific tests are carried out as per the diagnosis. For SLE patients:

- To study the extent of disease by doing the blood counts, LFTs, renal profile and urine analysis to look for an active sediment/ degree of proteinuria
- To study the severity of disease by looking at the C3/ C4/ DsDNA titres
- To exclude disease related mimics and exclude infections, e.g. with an X-ray Chest and Mantoux test.
- To look for thrombotic risk factors such as anticardiolipin antibodies, and lupus anticoagulant.

Outcome and Prognosis

The prognosis of children and adolescents with SLE who receive appropriate care is generally very good. Early recognition and treatment with immunosuppressants is usually associated with a profound improvement in the quality of life. Majority of patients experience a chronic course with periods of flare. The primary causes of an unsatisfactory outcome are poor compliance secondary to poor patient and family education, neurologic complications, intercurrent infections, renal disease, especially diffuse proliferative glomerulonephritis.¹⁷ Children with SLE are at increased risk for early atherosclerosis and coronary artery disease.¹⁸

JUVENILE DERMATOMYOSITIS

Epidemiology

Juvenile dermatomyositis (JDM) is the most common chronic idiopathic inflammatory myopathy of childhood. These children usually suffer from the characteristic skin and muscle abnormalities. The incidence of JDM is usually 0.19 cases per 100,000 per year for children younger than 16 years¹⁹ and average annual incidence rate is 3.2 cases per 1 million children.²⁰ It has a bimodal age distribution with one peak in the 5- to 14-year-old range, and a second peak in the 45- to 64-year-old range.²¹ The female-to-male ratio is 1.7:1 and the average age at onset is 7 years.²²

Clinical Features

JDM usually presents in four clinical phases:²³

- Prodromal period with nonspecific symptoms (weeks to months)

- Progressive muscle weakness and rash (days to weeks)
- Persistent weakness, rash, and active myositis (up to 2 years or longer)
- Recovery with or without residual muscle atrophy, contractures, and calcinosis.

Classic JDM manifests with an insidious progression of malaise, easy fatigue, muscle weakness, fever and a rash that may predate diagnosis by 3 to 6 months. The classical features of JDM presentation are with a heliotrope rash on the eyelids, proximal muscle weakness and Gottron's papules on the knuckles.

The muscle weakness in JDM is usually proximal with predominant involvement of the shoulder and the pelvic girdle muscles. Patients usually have difficulty in holding the head in the upright position or maintaining a sitting posture due to weakness of the anterior neck flexors. The skin overlying the involved muscle can become edematous and tender. Muscle examination usually reveals a marked proximal myopathy with positive Gower's sign and a Trendelenburg sign indicating the weakness of the hip abductors. Pharyngeal, hypopharyngeal, and palatal muscles are frequently affected increasing the threat of aspiration. Other less common musculoskeletal features include transient synovitis, arthralgia or arthritis.

Dermatomyositis sine myositis or amyopathic dermatomyositis is usually characterized by classic rash of JDM in the absence of clinical muscle involvement.

The specific mucocutaneous features of this disease are pathognomic of JDM. The three most typical cutaneous manifestations are heliotrope discoloration of the upper eyelids, Gottron papules, and periungual erythema and capillary loop abnormalities.²⁴ The heliotrope rash usually involves the upper eyelids and malar area with an indistinct margin. Gottron papules are the shiny, erythematous, scaly plaque like lesions seen on the extensor surface of the proximal interphalangeal joints of the hands predominantly. Photosensitivity occurs in up to 50 percent of patients.²⁵ With severe disease children with JDM can have vasculitic ulcers on extensor surfaces and gastrointestinal vasculitis as well.

Visceral vasculopathy occurs in a minority of children. Cardiopulmonary involvement in the form of nonspecific sinus tachycardia, pericarditis, hypertension, respiratory muscle weakness have also been reported.

Dystrophic calcification occurs in 12 to 43 percent of children and may occur in long-standing disease as large tumorous deposits in muscle groups, in bridging joints, or as an extensive subcutaneous exoskeleton. Lipodystrophy is another complication noted with JDM which may be generalized, partial or focal.²⁶ It is characterized by a slow but progressive loss of subcutaneous and visceral fat accompanied by hypertriglyceridemia, as well as by insulin resistance, abnormal glucose tolerance, acanthosis nigricans, hypertension and nonalcoholic steatohepatitis.²⁷

Diagnostic Criteria

Clinical Suspicion (Table 2)

JDM should be suspected in any child presenting with typical heliotrope rash, Gottron's papules with a proximal muscle weakness.

Laboratory Findings

Muscle enzymes

JDM is usually characterised by the presence of elevated muscle enzymes in the blood namely CPK, LDH, AST, Aldolase and ALT. It is important to remember that either of the mentioned muscle enzymes may be elevated in JDM. The flares of the disease are usually predicted by a combination of AST and LDH.²⁹ However, isolated LDH could be a marker of an underlying malignancy.

Autoantibodies

Antinuclear antibodies (ANAs) have been reported in a variable frequency of 10 to 85 percent.³⁰ Myositis-specific autoantibodies (MSAs) like those directed to the aminoacyl transfer RNA (tRNA) synthetases, signal recognition particle (SRP), and Mi-2 are seen exclusively in myositis patients with immunoprecipitation methods.³¹ Newer antibodies now identified in JDM include anti-p155 and anti-MJ.

Table 2: Bohan and Peter criteria for the diagnosis of JDM²⁸

Criteria for a diagnosis of juvenile dermatomyositis

- Symmetrical weakness of the proximal musculature
- Heliotrope discoloration of the eyelids, which may be accompanied by periorbital edema and erythematous papules over the extensor surfaces of joints, including the dorsal aspects of the metacarpophalangeal and proximal interphalangeal joints, elbows, knees, or ankles (i.e. Gottron papules)
- Elevation of the serum level of one or more of the following skeletal muscle enzymes: creatine kinase, aspartate aminotransferase, lactate dehydrogenase, and aldolase
- Electromyographic demonstration of the characteristics of myopathy and denervation, including the triad of polyphasic, short, small motor-unit potentials; fibrillations, positive sharp waves, increased insertional irritability; and bizarre, high-frequency repetitive discharges
- Muscle biopsy documenting histological evidence of necrosis; fiber size variation, particularly perifascicular atrophy; degeneration and regeneration; and a mononuclear inflammatory infiltrate, most often in a perivascular distribution
 - *Probable JDM:* Two criteria plus the typical rash for Dermatomyositis
 - *Definite JDM:* At least three criteria plus the typical rash for dermatomyositis

Nail Fold capillaroscopy

Nail Fold capillaroscopy can help analyze microvascular abnormalities like architectural disorganization, giant capillaries, hemorrhages, loss of capillaries, angiogenesis and avascular areas in dermatomyositis. It can also be used to monitor the effectiveness of the therapy.

Electrophysiology studies

Electromyography occasionally is useful in confirming the diagnosis of JDM. The characteristic electromyographic changes seen are myopathic motor units, decreased amplitude, denervation potentials (positive sharp waves), spontaneous fibrillations and high-frequency repetitive discharges.

MRI

Fat suppressed MRI and STIR image sequences have been used to diagnose JDM paving away the need of muscle biopsy. It demonstrates muscle edema and inflammatory changes by a hyperintense signal.³² MRI may be helpful in selecting a site for muscle biopsy.³³

Muscle biopsy

As mentioned previously with the advent of MRI, muscle biopsy is rarely required for establishing the diagnosis. Muscle biopsy demonstrates areas of muscle degeneration and regeneration with characteristic perifascicular atrophy with mononuclear cell infiltration.

Outcome and Prognosis

The long-term outcome of JDM has become increasingly important as the survival rate has improved. In general, the course of JDM is variable:

- Monocyclic disease occurs in about one-third of patients with findings of rash and muscle weakness. These patients have a good response to standard therapy
- Chronic continuous or polycyclic disease occurs in the remaining two-thirds of patients and is predictive of a poorer outcome.³⁴ These patients are at increased risk for persistent pain, calcinosis, and disability.

Risk factors for a poor prognosis include unremitting severe disease activity, cutaneous ulcerations, extensive calcinosis, dysphagia or dysphonia, advanced nail fold capillary abnormalities, a high serum creatine kinase level, a noninflammatory vasculopathy on muscle biopsy, and the presence of certain MSAs (such as antisynthetase and antisignal recognition particle autoantibodies). Delays in treatment and inadequate treatment are also important risk factors.

SCLERODERMA

Juvenile scleroderma syndromes are multisystem autoimmune rheumatic diseases characterised by is the presence of hard skin due to increased collagen deposition with onset before 16 years of age.

Scleroderma can be separated into two main categories:

Localized scleroderma (morphea) in which there is skin sclerosis but no vascular or internal organ involvement

Systemic sclerosis in which there is diffuse skin sclerosis involving many sites of the body together with internal organ involvement. This is further subdivided into diffuse cutaneous systemic sclerosis (dSSc) and limited cutaneous systemic sclerosis (lSSc).

JUVENILE SYSTEMIC SCLEROSIS

It is defined as symmetrical fibrous thickening and hardening (sclerosis) of the skin often combined with fibrous and degenerative changes in synovium, digital arteries, and certain internal organs, most notably the esophagus, intestinal tract, heart, lungs, and kidneys.³⁵

Epidemiology

Juvenile systemic sclerosis is extremely rare in children. Children younger than 10 years account for less than 2 percent of all cases.^{36,37} It occurs with equal frequency in boys and girls younger than 8 years old.

Clinical Features

The onset is often characterized by the development of Raynaud's phenomenon which is seen in almost 90 percent of the children. Cutaneous changes begin with edema, followed by induration of the subcutaneous tissues of the digits, hands, arms, and face and later sclerosis. Initial thickening of the skin is followed by later atrophy and areas of hypopigmentation or hyperpigmentation.³⁸ Morning stiffness, arthralgia, myositis are few of the musculoskeletal complaints. Dysphagia with gastroesophageal reflux, heartburn with postural aggravation, nocturnal aspiration and malabsorptive diarrhoea are sometimes noted. Cardiopulmonary involvement usually occurs in the form of arrhythmias, impaired ventricular function, cardiomyopathy, interstitial pulmonary fibrosis and pulmonary hypertension. Renal involvement is rarely seen in children but the abrupt onset of accelerated hypertension with acute renal failure (scleroderma renal crisis) is the most feared complication. The disease is further subdivided into two categories:

- Diffuse systemic scleroderma with skin involvement proximal to the elbows, presence of the anti-topoisomerase antibody and early involvement of the internal organs.
- Limited scleroderma has on the other hand skin involvement distal to the elbows, absence of Scl -70 and late internal organ involvement.

Classification Criteria (Table 3)

Laboratory Examination

Anemia of chronic disease, leukocytosis and eosinophilia occurs in approximately 15 percent of patients.⁴⁰

Table 3: Preliminary classification criteria for juvenile systemic sclerosis³⁹

Major criterion

- Sclerosis/ induration of the skin proximal to the metacarpophalangeal or metatarsophalangeal joints

Minor criteria

Skin

- Sclerodactyly
- Vasculopathy
- Raynaud phenomenon
- Nailfold capillary abnormalities
- Digital tip ulcers

Gastrointestinal

- Dysphagia
- Gastroesophageal reflux

Renal

- Renal crisis
- New-onset arterial hypertension

Cardiac

- Arrhythmias
- Heart failure

Respiratory

- Pulmonary fibrosis (HRCT/X-ray)
- DLCO
- Pulmonary hypertension

Musculoskeletal

- Tendon friction rubs
- Arthritis
- Myositis

Neurological

- Neuropathy
- Carpal tunnel syndrome

Serology

- Antinuclear antibodies
- SSc selective autoantibodies (anticentromere, antitopoisomerase I, antifibrillarin, anti-PM-Scl, antifibrillin or anti-RNA polymerase I or III)

A patient, aged less than 16 years, shall be classified as having juvenile systemic sclerosis if 1 major and at least 2 of the 20 minor criteria are present

High-titers of ANAs are frequently identified. Anti-topoisomerase I (anti-Scl-70) autoantibodies occur in at least 40 percent of patients with dSSc. Presence of these antibodies is also an independent risk factor towards development of progressive interstitial fibrosis. 2D ECHO and ECG should be done for cardiac evaluation and for determining pulmonary hypertension. Pulmonary function testing usually demonstrates decrease in timed vital capacity and forced expiratory flow, an early decrease in diffusion, and an increase in functional residual volume.

X-ray of the hands demonstrates the presence of acroosteolysis (decrease in soft tissue and resorption of

the tufts of the distal phalanges) along with bony erosions of distal interphalangeal and proximal interphalangeal joints. X-ray chest findings correlate poorly with pulmonary function. HRCT helps in identifying ground-glass opacification, subpleural micronodules, linear opacities, and “honeycombing”.⁴¹

JUVENILE LOCALIZED SCLERODERMA

Epidemiology

Juvenile localized scleroderma mainly involves localised areas of skin with few autoantibodies. It is more common than systemic sclerosis in childhood, by a ratio of at least 10:1⁴² with female-to-male ratio of 2.4:1. The mean age at onset of LS in the pediatric population is approximately 7 years.

Clinical Features

The onset of LS is subtle. It usually manifests as an area of localised erythema with induration. A localized form described as ‘en coup de sabre’ is usually associated with progressive hemifacial atrophy, ipsilateral uveitis, and various dental abnormalities.

Extra-cutaneous findings are more frequent in patients with linear scleroderma and consist essentially of arthritis, neurological findings or other autoimmune conditions. Seizures, headaches, behavioral changes, gastroesophageal reflux, uveitis, episcleritis and keratitis are few of the other findings.^{43,44}

Classification (Table 4)

Laboratory Results

The diagnosis of localized scleroderma is established by the clinical picture. No laboratory abnormality is diagnostic. However raised ESR, eosinophilia and hypergammaglobulinemia are quite characteristic of this disorder.

Rheumatoid factor is present in 25 to 40 percent of patients with ANA positivity of approximately 50 percent.⁴⁶ Antihistone antibodies, anti-Scl70 antibodies and anticardiolipin antibodies are few of the other antibodies found in this disorder.

Imaging in the form of MRI is useful only when CNS or eye involvement is suspected.

Outcome and Prognosis

Systemic Scleroderma

The outcome is usually poor and depends upon the extent of visceral involvement in dSSc. The prognosis can usually be divided into two groups one having a rapid development of internal organ failure leading to severe disability and eventually to death and the other group with slow, insidious course of the disease with lower mortality. The commonest causes of death

Table 4: The Mayo clinic classification of localized scleroderma⁴⁵

Plaque morphea

- Morphea en plaque
- Guttate morphea
- Atrophoderma of Pasini and Perini
- Keloid morphea
- [Lichen sclerosus et atrophicus]

Generalized morphea

Bullous morphea

Linear scleroderma

- Linear morphea
- En coup de sabre scleroderma
- Progressive hemifacial atrophy

Deep morphea

- Subcutaneous morphea
- Eosinophilic fasciitis
- Morphea profunda
- Disabling pansclerotic morphea

in children are related to the involvement of cardiac, renal, and pulmonary systems. Cardiomyopathy is a leading cause of early death. Patients with limited disease have a better prognosis.

Localized Scleroderma

The prognosis for LS is usually benign. The disease usually has an early inflammatory phase progressing to the extension of the lesion and finally stabilization and softening of the involved skin with increased pigmentation.⁴⁷

SJÖGREN'S SYNDROME

Sjogren's syndrome is probably the rarest of the connective diseases in childhood. Sjogren syndrome (SS) is defined as a chronic autoimmune disease characterized by inflammation of the exocrine glands principally the salivary and the lacrimal glands. SS may occur in 2 forms: primary (pSS), when the clinical manifestations of the syndrome are seen alone, and secondary (SSS), when associated with another autoimmune disease.

Clinical Criteria (Table 5)

Clinical Features with System Involvement

- Oral mucosal involvement-Xerostomia, difficulty in swallowing dry food, a change in taste, halitosis, increase in dental caries and recurrent parotitis.
- Ocular involvement: Keratoconjunctivitis sicca (KCS) manifested as dry eyes with sandy feeling.

Table 5: Proposed criteria for juvenile primary Sjögren's syndrome⁴⁸*Clinical symptoms*

- Oral (dry mouth, recurrent parotitis, or enlargement of parotid glands)
- Ocular (recurrent conjunctivitis without obvious allergic or infectious etiology, keratoconjunctivitis sicca)
- Other mucosal (recurrent vaginitis)
- Systemic (fever of unknown origin, noninflammatory arthralgias, hypokalemic paralysis, abdominal pain)

Immunological abnormalities (presence of at least 1 of: anti-SSA, anti-SSB, high titer ANA, RF)

Other laboratory abnormalities or additional investigations

- Biochemical (elevated serum amylase)
- Hematological (leucopenia, high ESR)
- Immunological (polyclonal hyperimmunoglobulinemia)
- Nephrological (renal tubular acidosis)
- Histological proof of lymphocytic infiltration of salivary glands or other organs
- Objective documentation of ocular dryness (Bengal red staining, Schirmer test)
- Objective documentation of parotid gland involvement (sialography)

Exclusion of all other autoimmune diseases

- Presence of 4 or more criteria

- Serologic testing for antibodies to Ro/SSA and La/SSB—considered the “hallmark” feature of this disease. ANA and positive RF are found in 70 percent of patients.

Course and Prognosis

Many patients with pSS have a benign course. The risk for B cell lymphoma as compared to pSS is very low.

MIXED CONNECTIVE TISSUE DISEASE**Epidemiology**

Mixed connective tissue disease (MCTD) is a syndrome where clinical features of multiple CTDs are present. It is one of the rarest of the CTD. The syndrome includes clinical features of rheumatoid arthritis (RA), scleroderma, SLE, and dermatomyositis in conjunction with a high antibody titer to an extractable nuclear antigen. MCTD is much more common in women with the median age of onset being approximately 11 years.

Classification Criteria (Table 6)*Clinical Features*

The early clinical features of MCTD are nonspecific and may consist of general malaise, arthralgias, myalgias, and low-grade fever. Almost any organ system can be involved in MCTD however, four clinical features that suggest the presence of MCTD are:

- *Other glandular involvement:* Dryness of the upper respiratory tract and rarely failure of the exocrine pancreatic function.
- Extra-glandular manifestations
 - Skin-Raynaud's phenomenon
 - *Pulmonary involvement:* Small airway obstructive disease and airway hyperactivity, interstitial lung disease
 - Renal Involvement—proximal and distal RTA, glomerulonephritis and interstitial nephritis.
 - Neurological involvement—Meningitis, myelopathy, cranial neuropathy, sensorimotor polyneuropathy, and mononeuritis multiplex.⁴⁹

Laboratory Examination

The evaluation of SS may consist of the following types of tests:

- Tests to confirm KCS—by a positive Schirmer test of wetting <5 mm in 5 min.
- Tests to quantify xerostomia: Salivary gland scintigraphy, parotid gland sialography or whole sialometry are frequently used.
- Salivary gland biopsy: Biopsy of the minor salivary glands of the lower lip demonstrating focal sialadenitis.

Table 6: Kasukawa criteria for mixed connective tissue disease⁵⁰*Common symptoms*

- Raynaud phenomenon
- Swollen fingers

*Anti-RNP Ab**Symptom**SLE*

- Polyarthritits
- Adenopathies
- Malar rash
- Pericarditis or pleuritis
- Leukopenia or thrombocytopenia

SSc

- Sclerodactyly
- Pulmonary fibrosis or restrictive changes in lung function or reduced DLCO
- Hypomotility or esophageal dilation

PM

- Muscle weakness
- Elevated muscle enzymes
- Myogenic signs on EMG

MCTD

If presence of at least 1 of the 2 common symptoms, anti-RNP antibodies, and the presence of at least 1 sign of at least 2 of the following connective tissue diseases: SLE, SSc, and PM.

- Raynaud phenomenon and swollen hands or puffy fingers.
- The absence of severe renal and central nervous system (CNS) disease
- More severe arthritis and the insidious onset of pulmonary hypertension
- Autoantibodies whose fine specificity is anti-U1 RNP, especially antibodies to the 68 Kd protein.

System Involvement

- Skin: Raynauds phenomenon, swollen digits, discoid plaques, malar rash, orogenital and buccal ulcerations, sicca complex
- Arthritis: Commonly seen, painful but predominantly non-erosive with RF positivity.
- Myositis: Rare but can present as low grade, insidious, and persistent inflammatory myopathy.
- Cardiac disease: Pancarditis of which pericarditis is commonest. Other abnormalities seen are right ventricular hypertrophy, right atrial enlargement, and inter-ventricular conduction defects
- Pulmonary involvement: Pulmonary hypertension, interstitial lung disease
- Renal disease: Usually absent
- Gastrointestinal disease: Disordered motility, duodenal bleeding, megacolon, pancreatitis, ascites, and protein losing enteropathy, primary biliary cirrhosis, portal hypertension and autoimmune hepatitis
- Central nervous system disease: Trigeminal (fifth cranial) nerve neuropathy, headaches and sensorineural hearing loss
- Hematologic: Low-grade anemia, hypergammaglobulinemia, leukopenia, thrombocytopenia, thrombotic thrombocytopenic purpura, Coombs positive hemolytic anemia, red cell aplasia

Laboratory Examination

Very high titers of ANAs are usually present. Anti-RNP antibodies in high titers have been the serological hallmark of MCTD. Antiphospholipid antibodies (including anticardiolipin antibodies and lupus anticoagulant) may be associated with pulmonary hypertension.⁵¹ Scleroderma-specific antibodies, including anticentromere, anti-Scl-70 (topoisomerase), and anti-PM-1 (Pm-Scl), are absent.

Other Investigations

- Chest X-ray: To assess for infiltrates, effusion, or cardiomegaly
- Echocardiography: For evaluation of pulmonary hypertension.
- Ultrasonography/CT scanning: Used to evaluate abdominal pain (indicated for evidence of serositis, pancreatitis, or visceral perforation related to vasculitis)
- MRI: Used to assess neuropsychiatric signs or symptoms
- Pulmonary function testing: To screen for declining diffusing capacity of lung for carbon monoxide
- ECG: To assess for myocardial ischemia and myocarditis.

Course of the Disease and Prognosis

Most patients with MCTD have a favorable outcome. Pulmonary hypertension is the most common disease-associated cause of death. Patients with severe Raynaud phenomena can develop ischemic ulcers and even outright gangrene of the fingers. MCTD tends to develop the widespread pain syndrome of fibromyalgia.

CONCLUSION

Though connective tissue diseases are not commonly seen by the general paediatrician they are important to diagnose early so that the child can be given the best possible outcome. The diseases have a protean manifestation and can present in several ways such that it is important to recognize a “disease pattern” and screen the patient appropriately with specific directed laboratory tests rather than “Panels” that serve to confuse more and helpless.

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Urticaria

Amit Luthra

INTRODUCTION

Urticaria [or hives or nettle rash, according to the German term ‘Nesselsucht’, which focuses on the typical reactions following skin contact with the stinging nettle (*Urtica dioica*)] is a common problem, developing in 10 percent or more of individuals by adolescence and in 15 to 20 percent of individuals during a lifetime. Urticaria consists of the sudden onset of circumscribed, erythematous, edematous papules or plaques, often showing central clearing. Lesions vary from a few millimeters to centimeters in diameter, and they generally are annular or circular but can assume bizarre, irregular shapes.

Angioedema or Quincke’s edema or Giant Urticaria is a circumscribed, nodular swelling of deep cutaneous and subcutaneous or submucosal tissues, most commonly on the face, genitals, and mucous membranes.

In children, urticaria without angioedema is more frequent and occurs in 80 percent of those affected, both urticaria and angioedema occur in 15 percent, and angioedema alone occurs in 5 percent. About 50 percent of children experience urticaria for more than 1 year, with a mean duration of 16 months. Females predominate in acute and chronic forms of the disease.

Nearly all cases of urticaria in infants and most cases in children are acute (by definition restricted to an occurrence of no longer than 6 weeks). Chronic urticaria is present when lesions recur repeatedly over a period of more than 6 to 8 weeks.

Papular urticaria is a reaction to an arthropod bite, most commonly fleas, mites, bedbugs, gnats, mosquitoes, chiggers, or animal lice. The cutaneous reaction varies according to the extent of previous exposure to the same or related species of arthropod. After repeated bites, sensitivity develops, producing a pruritic papule within approximately 24 hours; this is the most common reaction seen in young children. With prolonged, repeated

exposure, a wheal develops within minutes after a bite, followed 24 hours later by papule formation; this combination of reactions is seen commonly in older children. By adolescence or adulthood, characteristically only a wheal forms, unaccompanied by the delayed papular reaction. Ultimately, as the individual becomes insensitive to the bites, there is no reaction.

ETIOLOGY

The cause of acute urticaria can be determined, on average, in approximately 50 to 75 percent of cases, whereas an identifiable cause can be determined in less than half of cases of chronic urticaria. Although causes of urticaria are similar for children and adults, age—dependent differences in etiology exist. In infants younger than 6 months, urticaria is due largely to cow’s milk allergy. Between age 6 months and 14 years, up to half of all cases of urticaria, particularly acute urticaria, are associated with infections. *Streptococcus pyogenes* is the most commonly associated infectious agent and has been associated with angioedema as well. Chronic urticaria is most often triggered by physical factors, but up to 45 percent of cases of chronic urticaria are also associated with infections.

Viral upper respiratory tract and gastrointestinal tract infections are the primary infectious triggers of acute urticaria in children.

Urticaria also can occur in association with infection with mycoplasmal, treponemal, rickettsial, fungal, or parasitic organisms, in Kawasaki disease, or in association with the infestation or bites of arthropods. The presence of parasitic infection is particularly likely in individuals with peripheral eosinophilia and elevated serum immunoglobulin (IgE) values.

Treatment of associated infections results in an improvement in urticaria in only a minority of patients. Furthermore, it is commonly unclear whether the

infectious agent, the therapeutic drug, or the combination was responsible for triggering the episode of urticaria. Aspirin, in particular, is known to exacerbate urticaria due to a variety of other causes, including infections. The medication that most commonly causes urticaria is penicillin and its derivatives; up to 25 percent of patients with chronic urticaria have antibodies to penicillin (Table 1).

PATHOGENESIS

Urticaria is due to an immediate hypersensitivity response, causing release of mediators from cutaneous mast cells and basophils as well as transudation of fluid from cutaneous blood vessels. Histamine is a primary mediator of urticaria and acts via both H₁ and H₂ receptors to produce vasodilation and altered vascular permeability.

Physical agents or drugs can produce urticaria by non-immunologic means. The most common immunologic mechanism for release of mediators is interaction of an

allergenic antigen (e.g. food or drug) with IgE bound to a basophil or mast cell, producing a type I hypersensitivity response. IgG autoantibodies can be responsible for urticaria in some patients by interacting with and causing cross linkage of adjacent IgE bound to a basophil or mast cell, producing a type I hypersensitivity response, suggesting that urticaria may be a manifestation of autoimmune mast cell disease. Complement activation with formation of the anaphylatoxins C3a, C4a, and C5a is an alternative immunologic mechanism for generation of urticaria.

Immune complex reactions can stimulate mediator release via the complement system. This process is particularly important in urticaria associated with hereditary angioedema, serum sickness, blood transfusion reactions, cryoglobulinemia, collagen vascular disease, urticarial vasculitis, and the urticaria like lesions of Henoch-Schönlein purpura. The mechanism of urticaria due to infectious agents is postulated to involve (1) the formation of immune complexes with activation of complement and

Table 1: Major infectious and noninfectious causes of urticaria in infants and children

<i>Infectious</i>	<i>Complement Activation</i>
<i>Bacteria</i>	Blood transfusion reactions, cryofibrinogenemia, cryoglobulinemia hereditary angioedema, hypocomplementemia, serum sickness, urticarial vasculitis.
<i>Borrelia burgdorferi, Escherichia coli, Neisseria gonorrhoeae, Neisseria meningitides, Pseudomonas aeruginosa, Shigella sonnei, Streptococcus pyogenes, Yersinia enterocolitica.</i>	<i>Contactants</i>
<i>Fungi</i>	Animal danders, caterpillars, chemicals, cosmetics, epoxy resins, fish, foods, medications, moths, nickel, parabens, saliva, water (i.e. aquagenic), wood dust.
<i>Candida albicans, Cladosporium spp, Coccidioides immitis, Histoplasma capsulatum, Candida glabrata, Trichophyton spp.</i>	<i>Drugs</i>
<i>Helminthes</i>	Acetylsalicylic acid, allopurinol, amoxicillin, barbiturates, cephalosporin antibiotics, tetracycline, codeine, curare, meperidine, morphine, nonsteroidal anti-inflammatory agents (e.g. indomethacin), penicillin, phenytoin, polymyxin B, procainamide, quinidine, radiocontrast materials, sulfa-derived antibiotics, sulfonylureas, thiamine, thiazides, zidovudine.
<i>Ancylostoma duodenale, Ascaris lumbricoides, Echinococcus spp, Enterobius vermicularis, Fasciola hepatica, Necator americanus, Onchocerca volvulus, Schistosoma spp, Strongyloides stercoralis, Toxocara canis, Trichinella spiralis, Trichobilharzia spp, (avian blood flukes), Wuchereria bancrofti</i>	<i>Food additives, preservatives and dyes</i>
<i>Mycoplasma</i>	Azo dyes (e.g. sunset yellow, tartrazine) butylhydroxyanisole butylhydroxytoluene, 4-hydroxybenzoic acid, sodium benzoate, sodium metabisulfite.
<i>Mycoplasma pneumoniae</i>	<i>Foods</i>
<i>Protozoa</i>	Chocolate, egg, fish, fresh berries, milk, nuts, peanuts, shellfish, tomatoes.
<i>Entamoeba histolytica, Giardia lamblia, Plasmodium spp., Trichomonas vaginalis.</i>	<i>Genetic conditions</i>
<i>Rickettsia</i>	C3b inactivator deficiency, erythropoietic protoporphyria, hereditary angioedema (CI esterase inhibitor deficiency).
<i>Coxiella burnetii.</i>	<i>Inhalant allergens</i>
<i>Treponeme</i>	Animal danders, mold spores, pollens
<i>Treponema pallidum</i>	<i>Physical factors</i>
<i>Viruses</i>	Aquagenic, cholinergic stimuli, including emotional stress (psychogenic) exercise, heat, cold, dermatographism, pressure, sunlight, sweating; vibration
Adenovirus, coxsackievirus A9, A16, B4, B5, Echovirus 11, Epstein-Barr virus, Hepatitis viruses A, B, C, Influenza B virus, Human immunodeficiency virus; Measles virus attenuated, Mumps virus, Respiratory syncytial virus.	<i>Systemic disease</i>
NONINFECTIOUS	Autoimmune thyroid disease, bullous pemphigoid, carcinomas, dermatomyositis, inflammatory bowel disease, juvenile rheumatoid arthritis, Kawasaki disease, leukemia, lupus erythematosus, lymphoma, polymyositis, rheumatic fever, Sjögren's disease.
<i>Arthropod bites</i>	
Ants, bedbugs, bees, body lice, caterpillars, fleas, chiggers), mosquitoes, scabies mites, scorpions, spiders, wasps.	

release of anaphylatoxins or (2) the development of IgE antibodies to microbial antigens.

Clinical Manifestations

Circumscribed, raised erythematous, usually pruritic, evanescent areas of edema that involve the superficial portion of the dermis are known as urticaria; when the edematous process extends into the deep dermis and/or subcutaneous and submucosal layers, it is known as angioedema. The individual lesions of urticaria arise suddenly, rarely persist longer than 24 to 48 hours, and may continue to recur for indefinite periods.

Episodes of lesions of less than 6 to 8 weeks duration are considered acute, whereas those persisting longer are termed chronic. Headache, dizziness, the sensation of a lump in the throat, hoarseness, wheezing, shortness of breath, nausea, vomiting, abdominal pain, diarrhea, and arthralgias may occur as concomitant systemic manifestations of urticaria and angioedema.

Immunological IgE and IgE Receptor—Dependent Urticaria/Angioedema

Episodes of acute urticaria/angioedema occurring in individuals with a personal or family history of asthma, rhinitis, or eczema are presumed to be IgE dependent. In clinical practice, however, urticaria/angioedema infrequently accompanies an exacerbation of asthma, rhinitis, or eczema. The prevalence of chronic urticaria/angioedema is not increased in atopic individuals.

Specific Antigen Sensitivity

Common examples of specific antigens provoking urticaria/angioedema include foods, such as shellfish, nuts and chocolate; drugs and therapeutic agents, notably penicillin; aeroallergens; and Hymenoptera venom. Urticaria in patients with helminthic infestations has also been attributed to IgE-dependent process; however, proof of this relationship is often lacking.

Physical Urticaria/Angioedema

Dermographism is the most common form of physical urticaria. It appears as a linear wheal with a flare at a site in which the skin was briskly stroked with a firm object. A transient wheal appears rapidly and usually fades within 30 minutes. The clinically normal skin may be pruritic. Dermographism associated with substantial degrees of pruritus has been referred to as symptomatic dermographism. The peak prevalence occurs in the second and third decades.

Delayed dermographism develops 3 to 6 hours after stimulation, either with or without an immediate reaction, and lasts 24 to 48 hours. The clinical eruption is composed of linear red nodules. It may be associated with delayed

pressure urticaria. Cold dependent dermographism may occur only after cold exposure. A rare form that develops as punctuate wheals is known as cholinergic dermographism.

Pressure Urticaria

Pressure urticaria appears as erythematous, deep local swellings, often painful that arise from 0.5 to 6 hours after constant pressure has been applied to the skin. The peak prevalence occurs in the third decade. Pressure urticaria may be associated with fever, chills, and arthralgias as well as with an elevated erythrocyte sedimentation rate and leukocytosis. Spontaneous episodes are elicited under shoulder straps after manual labor.

Immediate pressure urticaria is a rare idiopathic disorder. It has also been described in patients with the hypereosinophilic syndrome.

Vibratory Angioedema

Vibratory angioedema may occur as an acquired idiopathic disorder, in association with cholinergic urticaria, or after several years of occupational exposure to vibration.

Cold Induced Urticaria

There are both acquired and inherited forms of cold induced urticaria/angioedema. The acquired forms are more common. Idiopathic, or primary, acquired cold induced urticaria may be associated with headache, wheezing, shortness of breath, hypotension, and syncope. Attacks occur within minutes after the appropriate exposures that include cold foods or liquids, the appearance of a wheal after the application of ice has been called a diagnostic cold contact test. If the entire body is cooled, as in swimming, hypotension and syncope, which is a potentially lethal event, may occur.

Solar Urticaria

Pruritus, erythema, wheals, and occasionally angioedema with bronchospasm and syncope develop within minutes after exposure to the sun or artificial light sources. Although this disorder may be associated with systemic lupus erythematosus or erythropoietic protoporphyria, it is usually idiopathic.

Cholinergic Urticaria

Cholinergic urticaria, also known as generalized heat urticaria, develops after an increase in core body temperature, such as during a warm bath or shower, exercise, or episodes of pyrexia. The eruption appears as distinctive, pruritic, small, 1 to 2 mm wheals that are surrounded by large areas of erythema. Systemic features may include dizziness, headache, wheezing, shortness of breath, nausea, vomiting, and diarrhea.

Heat Urticaria

Local heat urticaria is a rare form of urticaria in which wheals develop within minutes after exposure to locally applied heat.

Exercise—Induced Anaphylaxis

Exercise—induced anaphylaxis is a clinical symptom complex consisting of pruritus, urticaria, angioedema (cutaneous, laryngeal and intestinal) and syncope that is distinct from cholinergic urticaria.

Adrenergic Urticaria

Adrenergic urticaria occurs as wheals surrounded by a white halo that develop during emotional stress. The lesions can be elicited by the intracutaneous injection of noradrenaline.

Aquagenic Urticaria and Aquagenic Pruritus

Contact of the skin with water of any temperature may result in pruritus alone or, more rarely, urticaria. The eruption consists of small wheals reminiscent of cholinergic urticaria.

Patients with aquagenic pruritus should be followed for the emergence of a hematologic disorder.

Contact Urticaria

Urticaria may occur after direct contact with a variety of substances. It may be immunologic (IgE mediated) or nonimmunologic. The transient eruption appears within minutes and, when IgE – mediated may be associated with systemic manifestations. Proteins from latex products are becoming a prominent cause of IgE mediated contact urticaria. The risk group is dominated by biomedical workers and individuals with frequent contact with latex, such as children with spina bifida.

Papular Urticaria

It occurs as episodic, symmetrically distributed, pruritic, urticarial papules that are episodic, symmetrically distributed, pruritic, urticarial papules that are caused by bites of insects such as mosquitoes, fleas, and bedbugs. This condition is mainly seen in childhood.

DIAGNOSIS

Diagnosis is established from the history and clinical characteristics. Non-urticarial conditions that can have an urticarial phase include erythema toxicum neonatorum, erythema multiforme, erythema nodosum, anaphylactoid purpura, Kawasaki disease, diffuse cutaneous mastocytosis, and bullous pemphigoid.

Biopsy can be helpful in equivocal cases or when urticarial vasculitis is suspected. Biopsy of an urticarial lesion

is expected to show dermal edema, dilation of blood and lymphatic vessels, and a sparse perivascular mononuclear infiltrate with variable numbers of eosinophils. Urticarial vasculitis is characterized by swelling of endothelial cells and fibrinoid necrosis of postcapillary venules, red blood cell extravasation, leukocytoclasia (i.e. fragmentation of neutrophil nuclei) and perivascular and vascular inflammation with neutrophils.

Diagnostic tests in a child with acute urticaria are performed when findings other than urticaria suggest a specific etiology (e.g. streptococcal pharyngitis, bacterial enteritis). In chronic urticaria, laboratory evaluation, even if it is thorough, is unrevealing unless a specific allergen (food, drug, contactant, inhalant), infection, infestation, or underlying systemic disease is suspected. If a physical cause for urticaria is identified, additional testing is unnecessary. If angioedema is a prominent, consistent feature, the patient should be tested for hereditary deficiency of C1 esterase inhibitor by measuring plasma C4 complement concentration. Useful tests for identifying a cause of urticaria are:

- A complete count,
- Throat swab collection for *S. pyogenes* culture or anti-streptolysin O titer,
- Epstein-Barr virus serologic test,
- Serum hepatic enzyme measurements,
- Serologic tests for hepatitis viruses,
- Urinalysis and urine culture,
- Vaginal smear for *Candida* and *Trichomonas*,
- Stool examination for ova and parasites, and
- Radiographs of the sinuses and teeth.

MANAGEMENT

Infectious agents of acute and chronic urticaria should be identified and treated, when possible, and stimuli of physical urticaria, such as heat, cold, exercise, and emotional stress, should be minimized.

The most successful symptomatic approach to treatment of urticaria with medication is blockage of the effect of histamine at its receptor on cutaneous blood vessels. Regimens include therapies with H₁ antihistamines, combination H₁ and H₂ receptor blockers, and tricyclic antidepressants. Antihistamines that block H₂ receptors are the mainstay of treatment for urticaria. Hydroxyzine hydrochloride is the most effective of the classic H₁ antihistamines for suppression of the wheal and flare response, pruritus, dermatographism, and cholinergic urticaria. Whereas cyproheptadine is the drug of choice for cold induced urticaria. For patients who experience excessive sedation or mucosal dryness, the newer, nonsedating H₁ antihistamines, such as fexofenadine, loratadine, astemizole, and cetirizine, are effective alternatives. These agents have been shown to be comparable in efficacy with hydroxyzine and one another for treatment of urticaria.

The therapeutic response to the H₁ antihistamines can be improved with the addition of an H₂ receptor-blocking agent, such as cimetidine or ranitidine.

The dosage of antihistamines is often more important than the particular agent. Antihistamine therapy should be initiated at the upper end of the recommended dosage range and then gradually increased as needed until symptoms are relieved or side effects, particularly sedation, become prohibitive. In general, the dosage should not exceed approximately twice that recommended by the manufacturer. The current European Academy of Allergology and Clinical Immunology/Global Allergy and Asthma European Network/European Dermatology Forum (EAACI/GA LEN/EDF) guidelines call for up dosing of nonsedating antihistamines (up to four times the standard dose) in urticaria patients who do not respond satisfactorily to the standard doses. The effectiveness of antihistamines in children, particularly those with dermatographism, appears to be produced, at least in part, by their sedative action. Bothersome drowsiness can be minimized by administering most of the daily dose just before bedtime. Once urticaria has been adequately controlled, the dose of antihistamine should be tapered gradually, rather than stopped abruptly, to minimize the likelihood of a recurrence.

Topical corticosteroid agents are ineffective in urticaria, and systemic corticosteroids are rarely indicated in children, except in severe unremitting cases, especially those associated with asthma, laryngeal edema, or circulatory instability or when angioedema is particularly severe on the face.

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Pediatric Dentistry: An Update

Arindam Dutta

INTRODUCTION

The science and art of the dental management of the child patient is an entire discipline in itself and encompasses not only the treatment of dental disease but also places an equal emphasis on preventive aspects, monitoring the developing dentition and to inculcate a positive attitude toward dentistry. According to American Academy of Pediatric Dentistry (AAPD), *pediatric dentistry* is an age-defined specialty that provides both primary and comprehensive preventive and therapeutic oral health care for infants and children through adolescence, including those with special health care needs.¹ Boucher's Clinical Dental Terminology explains *Pedodontics* as a branch of dentistry; it includes training the child to accept dentistry; the prevention, detection, restoration and maintenance of the deciduous and permanent dentition; applying preventive measures for periodontal therapy and dental caries; prevention, interception and correction of various errors of occlusion.² As a specialty, *Pedodontics* was born in 1923 when 14 Detroit dentists led by Dr Walter McBride formed the Paediatric Study Club. This was followed by the formation of the American Society for Promotion of Children's Dentistry in 1927 and the publication of the *Journal of Dentistry for Children* in 1928. In India, the Indian Society for Paedodontics and Preventive Dentistry was established in 1928 and Dr Vacher is considered to be the Father of *Pedodontics* in our country.

This chapter discusses some of the most pertinent aspects of pediatric dentistry of relevance to the pediatrician. These have been included under the headings of the First Dental Visit, Dental Caries, Dental Trauma with special emphasis on Tooth Avulsion, Orthodontic Treatment, Strategies to Manage the Anxious Child, Extractions, and Oral Habits.

FIRST DENTAL VISIT

There seems to be a lot of confusion amongst parents, pediatricians, and dentists about the correct timing for the first dental visit. Many dentists may tell parents not to bring children to their practice before they have all their primary teeth (age two or three), sometimes even recommending to wait until age 6. Under unfavorable circumstances, delay of dental care can lead to catastrophic disease progression that is not in the best interest of the child. The AAPD recommends an initial postnatal oral evaluation within six months of the eruption of the first primary tooth and no later than 12 months of age.³ At this examination visit the dentist should record a thorough medical and dental history. Parents should be prepared to review the prenatal, perinatal, and postnatal period of their child's development. The oral examination at this early age is usually accomplished with the parent present in the office. It is most often only a visual examination. The child patient may be sitting in the parent's lap with the head in the dentist's lap (knee-to-knee position). One important aspect of this visit is to discuss the child's risk of developing oral and dental disease. Based on this assessment, the dentist will determine the appropriate recall interval for the next dental visit. This will not be more than 12 months for all individuals under 18 years of age.⁴ In high-risk cases, this may be as early as three months as dental decay in children can progress very rapidly. The dentist will also evaluate the child's oral and dental development, need for fluoride supplementation and discuss non-nutritive habits (finger sucking, pacifier), injury prevention, oral hygiene (including toothbrushing), and effects of diet on the dentition. At this visit, the parents should also be informed of the tentative eruption schedule of the child's primary dentition. Table 1 lists the chronology of human dentition.⁵

Table 1: Chronology of the human dentition⁵

<i>Teeth</i>	<i>Formation of enamel matrix & dentine begins</i>	<i>Amount of enamel matrix formed at birth</i>	<i>Enamel completed</i>	<i>Emergence into oral cavity</i>	<i>Root completed</i>
<i>Primary dentition</i>					
<i>Maxillary</i>					
Central incisor	14 wk <i>in utero</i>		1.5 mon	7.5 mon	1.5 yr
Lateral incisor	16 wk <i>in utero</i>		2.5 mon	9 mon	2 yr
Canine	17 wk <i>in utero</i>		9 mon	18 mon	3.25 yr
First molar	12-15 wk <i>in utero</i>		6 mon	14 mon	2.5 yr
Second molar	12-19 wk <i>in utero</i>		11 mon	24 mon	3 yr
<i>Mandibular</i>					
Central incisor	18 wk <i>in utero</i>		2.5 mon	6 mon	1.5 yr
Lateral incisor	18 wk <i>in utero</i>		3 mon	7 mon	1.5 yr
Canine	20 wk <i>in utero</i>		9 mon	16 mon	3.25 yr
First molar	12-15 wk <i>in utero</i>		5.5 mon	12 mon	2.25 yr
Second molar	12-18 wk <i>in utero</i>		10 mon	20 mon	3 yr
<i>Permanent dentition</i>					
<i>Maxillary</i>					
Central incisor	3-4 mon		4-5 yr	7-8 yr	10 yr
Lateral incisor	10-12 mon		4-5 yr	8-9 yr	11 yr
Canine	4-5 mon		6-7 yr	11-12 yr	13-15 yr
First premolar	1.5-1.75 yr		5-6 yr	10-12 yr	12-13 yr
Second premolar	2-2.25 yr		6-7 yr	10-12 yr	12-14 yr
First molar	At birth	Sometimes a trace	3-4 yr	6-7 yr	9-10 yr
Second molar	2.5-3 yr		7-8 yr	12-13 yr	14-16 yr
Third molar	7-9 yr		12-16 yr	17-12yr	18-25 yr
<i>Mandibular</i>					
Central incisor	3-4 mon		4-5 yr	6-7 yr	9 yr
Lateral incisor	3-4 mon		4-5 yr	7-8 yr	10 yr
Canine	4-5 mon		6-7 yr	9-10 yr	12-14 yr
First premolar	1.75-2 yr		5-6 yr	10-12 yr	12-13 yr
Second premolar	2.25-2.5 yr		6-7 yr	11-12 yr	13-14 yr
First molar	At birth	Sometimes a trace	2.5-3 yr	6-7 yr	9-10 yr
Second molar	2.5- 3 yr		7-8 yr	11-13 yr	14-15 yr
Third molar	8-10 yr		12-16 yr	17-21 yr	18-25 yr

Premature tooth exfoliation has been reported to be associated with some systemic diseases, such as hypophosphatasia, Papillon Le Fevere syndrome, cyclic neutropenia, Chediak Higashi syndrome, histiocytosis X and prepubertal periodontitis.⁶

TEETHING

Teething in the infant has been traditionally associated with several local and systemic disturbances. The

information pertaining to teething is very often based on parental observations. It is also difficult to separate the signs and symptoms of teething from the normal psychological and physiological changes, such as drooling and wakefulness. Teething is considered uncomfortable for the child, and signs and symptoms include swollen gums that are tender to palpation, drooling, chewing fingers and other inanimate objects, irritability, restlessness and night crying. Other signs commonly attributed to teething, such as diarrhea, cough, ear rubbing, rashes, fever

and convulsions, have not been found to have any relationship to teething. 224 normal children were studied for the association of 18 disturbances with the eruption of the deciduous teeth.⁷ Irritability, night crying, drooling, poor appetite, circumoral rash and inflammation of the gums were common findings. Tasanen studied teething infants in North Finland and showed that tooth eruption bore no relation to infection, diarrhea, fever, rash, convulsions, sleep disturbance, cough or ear rubbing.⁸ Teething was associated with daytime restlessness, loss of appetite, hand sucking, drooling and some appetite loss. In a 1975 study of perceptions of primary care pediatricians in Philadelphia, only five believed that teething was not responsible for symptoms such as irritability, eating problems, wakefulness and rashes.⁹ Eighteen felt that teething could be responsible for temperatures up to 39.4°C. Illingworth suggested that in 6 to 12-month-old infants, much of the evening and night-time crying that is attributed to teething may be due to bad habit formation: infants of this age have discovered that if they cry at night, they will be picked up, played with and given a thoroughly enjoyable time.¹⁰ Teething complaints are confined almost exclusively to the eruption of the deciduous dentition. In 1990, Wray suggested that the current understanding was that teething coincides with the stage of development when active immunity is struggling to take over from the waning passive immunity of the mother. This often results in ENT or gastrointestinal infection in a child with an obvious oral fixation who will naturally suck or chew their fingers.¹¹ More recently, a viral infection (herpes simplex virus) etiology has been proposed and investigated.¹²

Various treatments are now advocated for the relief of the discomfort or pain associated with teething. Rubbing substances into the gums and chewing on hard objects are still extremely common. Gum lancing is now relegated to history, although surgical removal of eruption cysts overlying a deciduous tooth may still be carried out when indicated. Chewing on clean, hard, cool objects will give relief from soreness and items, such as chilled teething rings and rattles, cold wet flannels, chilled hard vegetables, such as carrots and cucumber and an ice cube tied in a cloth have been tried. Teething biscuits and rusks are not suitable as they can promote tooth decay. In 1998, Government Safety Regulators in the United States asked manufacturers to stop using a softening chemical (disononyl phthalate) known to be a carcinogen in baby rattles and teething toys as it tends to leach out from the product. There have been no reported cases of phthalate related cancer in infants using teething products. The use of chilled topical preparations in gel form remains popular. Lignocaine-containing products have been shown to be more effective than similar, control preparations without lignocaine. However, many authorities advise that these gels are largely insufficient to treat the condition when used alone, due to the rapid washing away from the site

of discomfort. A sugar-free paracetamol suspension may be used for supplementation and is useful for its analgesic and antipyretic effects.

DENTAL CARIES

Dental caries is perhaps one of the most prevalent diseases affecting the human race. There are practically no geographic regions in the world that do not exhibit some evidence of dental caries. It affects persons of both sexes, in all races, socioeconomic strata and every age group.

Dental caries has been defined as an infectious, microbial multifactorial disease of the hard tissues of the teeth resulting in demineralization of the inorganic components and dissolution of the organic components.

Ostrom (1980) has defined caries as a process of enamel or dentin dissolution that is caused by microbial action at the tooth surface and is mediated by physiochemical flow of water dissolved ions.¹³ Hume (1993) states that caries is essentially a progressive loss of acid dissolution of the apatite component of the enamel, dentin and cementum of the tooth.

Site

Caries affects the occlusal surfaces of posterior teeth (pits and fissures of molars and premolars), the proximal and cervical areas as well as the roots of all teeth. It may also be found on the lingual and palatal surfaces of the anterior teeth as well as the maxillary posterior dentition. In its most initial form, it presents as a white spot lesion in enamel. This can be seen as a chalky opaque surface when a tooth has been dried out and is indicative of an initial mineral loss. In its most severe form, caries can affect all surfaces of the tooth. Figure 1 shows dental decay in the upper incisors and Figure 2 shows dental caries in the lower posterior dentition of a child. Figure 3 is a figurative representation of dental caries on a model posterior tooth (sagittal section) at different locations on the tooth and at varying depths in enamel and dentine.



Fig. 1: Dental caries in the maxillary anterior dentition
(For color version see plate 18)

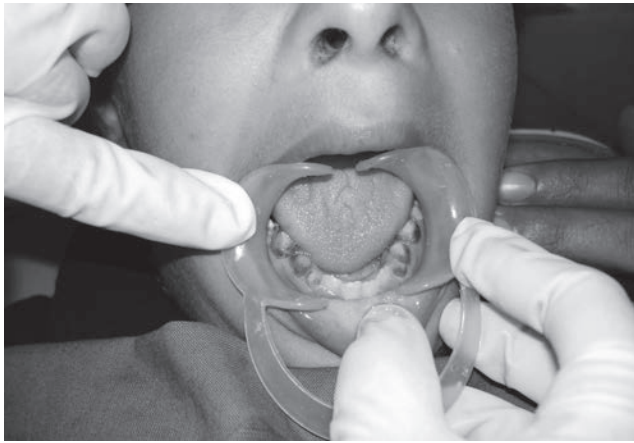


Fig. 2: Dental caries in the lower posterior dentition
(For color version see plate 18)

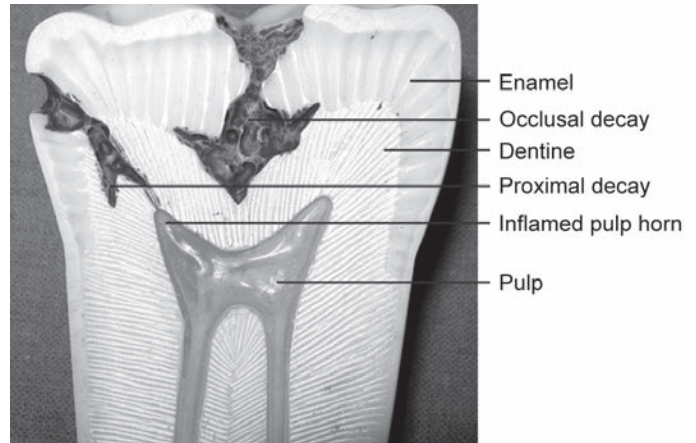


Fig. 3: Sagittal section of a tooth model showing decayed area occlusally and proximally (For color version see plate 18)

Symptoms

Chronic caries can often be asymptomatic. As a slowly progressing lesion, it may produce tooth destruction over a period of time without causing any overt discomfort for the child. However, caries would usually be associated with some form of sensitivity to hot and cold foods and beverages when it extends into dentine. If the pulp of the tooth also becomes involved, it would be likely for the child to suffer from variable amounts of pain—it could be an ache that is brought on when the child eats or drinks to an ache that is constant, throbbing, and unbearable in nature.

Prevalence of Caries

Dental caries is not a recent disease entity. Its existence has been demonstrated from the times of the prehistoric man, such as the Pithecanthropus or the Java Man. The current global epidemiology of caries shows a wide difference between the developed and the third world countries, primarily due to the lack of infrastructural support. Thus sub Saharan Africa, some regions of South America and underdeveloped Asia present with high caries experience as dental care facilities are almost non-existent whereas the developing world presents a slightly better condition. There is an increase in the amount of refined carbohydrate consumption in the developing nations but dental services are only concentrated around urban centers. The interplay of these two factors has resulted in an increased caries incidence in countries, such as India, Chile, Uganda and Thailand. The developed world has an abundance of preventive, interceptive as well as curative options, which has led to a steady decline in caries indices such as the Decayed Missing Filled Tooth index (DMFT) over a period of time.

Dental Caries in India is consistently increasing in prevalence and severity especially in children, with almost 70 to 80 percent suffering from this disease. The First

National Oral Health Survey was planned in 1984 by the Indian Dental Association found regional differences with an increase in caries incidence being noted in all the northern states barring Punjab in the age group of 5 to 6 years. However in the age group of 15 years, caries was shown to have declined. The eastern part of the country showed an increase in caries in both the deciduous as well as permanent dentitions, as did the southern states (except a few pocket areas, such as the Dakshin Kannada district). The western region, Bombay showed a slight decrease, but this too was well above the WHO goals.¹⁴ In the United Kingdom, the National Children's Dental Health Survey in 2003 revealed that the DMFT at age 12 (the key age at which children are internationally compared) was 0.7 in England, which is the lowest since records were first established. In the same survey, it was also found that 57 percent of 5 year olds, 62 percent of 12 year olds and 50 percent of 15 year olds in the UK had never experienced dental decay or required dental restorations.¹⁵ In the United States, National Health and Nutrition Examination surveys (NHANES) and National Institute of Dental Research Surveys has shown that caries prevalence in the permanent dentition of children between ages 5 and 17 years, at least half the children were free from decay; in the 1970s only a quarter were free from decay. However, unlike the dramatic decrease in prevalence for the permanent dentition, the primary dentition caries rates have remained unchanged among children from low income families. NHANES III measured caries in primary incisors of 1 year old children and found 2 percent incisors with an abnormal appearance suggestive of decay using the 'lift the lip' technique.¹⁶

Mechanism of Caries Formation

Cariogenic Bacteria + Suitable local substrate = Organic acids

Organic Acids in Plaque + Tooth mineral = Loss of enamel

Demineralized Tooth (Dentin) + Bacterial Proteolytic Enzymes = Cavitation¹⁷

Caries is a multifactorial disease, which requires an interaction between a susceptible host, i.e. the tooth, a microflora with cariogenic potential and a suitable local substrate to meet the requirements of the pathogenic flora. Newbrun added a dimension of time factor to the above three factors and termed it the caries tetralogy.^{18,19} This is diagrammatically represented in Figure 4.

The pathogenic flora includes *Streptococcus mutans*, which is perhaps the most important pathogen in the initiation of caries.²⁰⁻²⁴ Other microorganisms like *Lactobacillus acidophilus*, *Lactobacillus casei*, *Actinomyces viscosus*, *Prevotella*, *Selenomonas*, *Dialister*, *Fusobacterium nucleatum*, *Eubacterium*, *Lachnospiraceae*, *Olsenella*, *Bifidobacterium*, *Propionibacterium*, *Pseudoramibacteria lactolyticus* and other species of *Streptococcus* such as *S. mitis*, *S. mitior*, *S. salivarius* also play a role in the progression of caries.^{17,25} The microorganisms produce extracellular polysaccharide from either glucose or sucrose using an enzyme glucosyl transferase. In the process, organic acids are generated as by-products of the reaction. These are localized on to the tooth structure and held within plaque. The acid then produces an ionic imbalance between the tooth surface and its immediate environment. The constant homeostasis of Re- and demineralization is, therefore, disturbed and weighs in favor of the latter. This initiates the caries process.²⁶

Nursing Caries and Rampant Caries

Winter (1966) has described it as a lesion of acute onset involving many or all of the erupted teeth, rapidly destroying coronal tissue, often on surfaces normally immune to decay, and leading to early involvement of the dental pulp.²⁷

Numerous reports by pediatricians and pedodontists describe a rapidly progressing type of dental caries

that affects the primary teeth of children, usually during the first two years of life and as early as the first year.¹⁹ A unique caries pattern can be identified with the four maxillary incisors being affected first because of their position in the mouth as to be most frequently bathed by a feeding formula. Because of this appearance, it has also been termed labial caries.²⁸ If unchecked, the decay may extend to the maxillary and mandibular molars. Initially, the lower anterior teeth may not be involved because of the protective environment of the mandibular salivary secretions and the cleansing action of the tongue muscles.^{17,29} Should the lesions arrest, they pigment to a black or dark brown color and this has been termed melanodontic infantile.³⁰

Over the past few decades this clinical entity has been variously termed as rampant caries,²⁷ nursing bottle caries, nursing bottle mouth,³¹ bottle-mouth caries,³² nursing bottle caries,³³ baby bottle caries,³⁴ nursing bottle syndrome,³⁵ baby bottle tooth decay and nursing caries.¹⁹ However, of late, and by international consensus, all such clinical entities have been listed as "early childhood caries", a term that represents a complex disease involving maxillary primary incisors within a month after eruption and that spreads rapidly to involve other primary teeth.^{36,37} The classification for early childhood caries (ECC) is presented in Table 2.³⁷ The role of parental/ caregiver stress has also been evaluated in children with ECC.³⁸

Infancy caries is most often seen in children with an unusual dietary history such as the addition of syrup, honey or sucrose to the formula or the use of pacifier

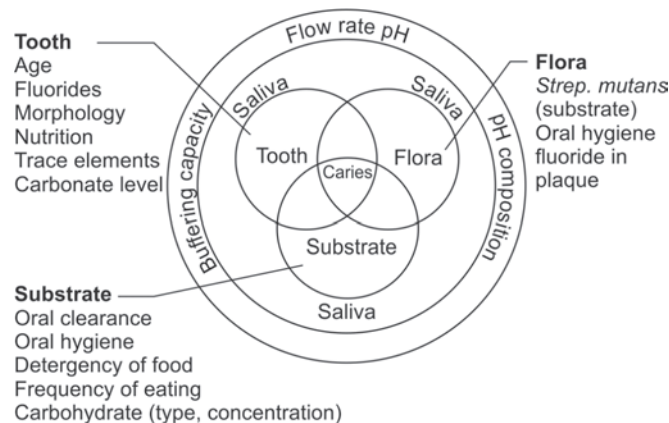


Fig. 4: Factors in caries development

Table 2: Classification of early childhood caries

Type I ECC (Mild to moderate)	<p>Cariou lesions involving the molars and incisors.</p> <p>Seen in 2 to 5 years.</p> <p>Cause is usually a combination of cariogenic semisolid or solid food and lack of oral hygiene</p> <p>Number of affected teeth usually increases as the cariogenic challenge persists.</p>
Type II ECC (Moderate to severe)	<p>Labiolingual carious lesion affecting the maxillary incisors with or without molar caries, depending on age.</p> <p>Seen soon after the first tooth erupts.</p> <p>Unaffected mandibular incisors.</p> <p>Cause is usually inappropriate use of feeding bottle or at will-breastfeeding or combination of both, poor oral hygiene</p>
Type III ECC (Severe)	<p>Cariou lesions involve almost all the teeth, including mandibular incisors.</p> <p>Usually seen in 3 to 5 years of age.</p> <p>Cause is a combination of factors and a poor oral hygiene.</p> <p>Rampant in nature and involves immune tooth surfaces.</p>

dipped in honey or other sweeteners.^{19,27,35} Initial etiological agents were thought to be the sucking of the comforter or the pacifier which was coated with a sweetening agent, namely sweetened malt, honey, sugar, jam or aniseed syrup. Rampant caries in young children was very common after the introduction of syrups in the United Kingdom. Prolonged use of the comforter feeding bottles containing milk and sugar, fruit juice and sugar, fruit syrup or sugared water increased the viscosity of the fluid and the time required to draw the formula through the nipple.²⁷ The hollow 'feeder' has also been implicated. This has a reservoir behind the teat that can hold 10 ml of fluid. Manufacturer's encourage parents to place honey, sugar, syrup into this area.

In addition to an increase in caries rates due to the use of improper formula in bottle-feeding, it has also been reported that prolonged and unrestricted night time breast feeding can result in increased caries rate (Preston et al 1977). The stagnation of the milk about the neck of anterior teeth and the fermentation of the disaccharide lactose, found in milk, contribute to the carious process. Under usual feeding regimens neither bottle nor breast milk predispose to caries. Only a prolonged and unrestricted bottle or breast milk-feeding regimen may play a role in caries production. Of more significance is the addition of caloric sweeteners to formulas.

Management involves parental counseling regarding the dietary habits of the infant and toddler, arrest and control of carious process, institution of preventive practices followed by restoration and rehabilitation of the dentition.

ODONTOGENIC INFECTIONS AND CARIES

The progression of caries is from the enamel of the crown of the tooth through to dentin and then to the pulp space of the tooth. Once the microbes from the carious lesion have invaded the pulp of the tooth, they or their toxins progress through the root of the tooth and the apical foramen (at the tip of the root) into the surrounding periodontal ligament and thence into the alveolus. In a chronic case, they may produce localized changes in bone that may result in the formation of a periapical granuloma or a periapical cyst. Sometimes, it can lead to the development of an abscess as well. If chronic, it usually drains through a sinus tract in to the mouth along the attached gingiva. At other times, it may lead to the formation of an acute abscess with concomitant intraoral swelling. A rapid spread of toxins through the facial spaces may lead to the development of cellulitis with a grossly enlarged and swollen face or neck, depending on location of the tooth. Institution of antibiotic therapy may be warranted in such instances with subsequent treatment involving drainage through the root canal of the tooth or an extraction of the offending tooth. Sometimes, as a swelling localizes,

intraoral drainage may be established with relevant incision and drainage methods.

Caries Risk Assessment

It is important to risk assess the patient in order to accurately quantitate a person's disease susceptibility and allow for preventive measures. Even though caries-risk data in dentistry are not sufficient to quantitate the models, the process of determining risk should be a component in the clinical decision making process. According to the American Academy of Paediatric Dentistry, Risk assessment:

- Fosters the treatment of the disease process instead of treating the outcome of the disease
- Gives an understanding of the disease factors for a specific patient and aids in individualizing preventive discussions
- Individualizes, selects, and determines frequency of preventive and restorative treatment for a patient
- Anticipates caries progression or stabilization.³⁹

Caries-risk assessment models currently involve a combination of factors including diet, fluoride exposure, a susceptible host, and microflora that interplay with a variety of social, cultural, and behavioral factors. Caries risk assessment is the determination of the likelihood of the incidence of caries (i.e. the number of new cavitated or incipient lesions) during a certain time period or the likelihood that there will be a change in the size or activity of lesions already present. With the ability to detect caries in its earliest stages (i.e. white spot lesions), health care providers can help prevent cavitation.

Risk assessment tools can aid in the identification of reliable predictors and allow dental practitioners, physicians, and other nondental health care providers to become more actively involved in identifying and referring high-risk children. Table 3 incorporates available evidence into practical tools to assist physicians, and other nondental health care providers in assessing levels of risk for caries development in infants and young children. As new evidence emerges, such tools can be refined to provide greater predictability of caries in children prior to disease initiation. Furthermore, the evolution of caries-risk assessment tools and protocols can assist in providing evidence for and justifying periodicity of services.

Detection of Dental Caries

Some of the traditional methods of caries detection have included a visual and tactile examination of the dentition.⁴⁰ Carious areas appear brownish-black in chronic caries to yellowish white in more acute and rapidly progressing lesions. Invariably, these would either be leathery or soft in consistency. Depending on the site of decay, it could also appear as a greyish hue just below the intact surface of enamel, the carious process itself having progressed in to dentine through a small pit on the occlusal surface of

Table 3: Caries-risk assessment form for 0-3-year-olds
(For physicians and other non-dental health care providers)
(From the American Academy of Paediatric Dentistry)

<i>Factors</i>	<i>High-risk</i>	<i>Moderate risk</i>	<i>Protective</i>
<i>Biological</i>			
Mother/primary caregiver has active cavities	Yes		
Parent/caregiver has low socioeconomic status	Yes		
Child has >3 between meal sugar-containing snacks or beverages per day	Yes		
Child is put to bed with a bottle containing natural or added sugar	Yes		
Child has special healthcare needs		Yes	
Child is a recent immigrant		Yes	
<i>Protective</i>			
Child receives optimally-fluoridated drinking water or fluoride supplements			Yes
Child has teeth brushed daily with fluoridated toothpaste			Yes
Child receives topical fluoride from health professional			Yes
Child has dental home/regular dental care			Yes
<i>Clinical findings</i>			
Child has white spot lesions or enamel defects	Yes		
Child has visible cavities or fillings	Yes		
Child has plaque on teeth		Yes	

Circling those conditions that apply to a specific patient helps the healthcare worker and parent understand the factors that contribute to or protect from caries. Risk assessment categorization of low, moderate, or high is based on preponderance of factors for the individual. However, clinical judgment may justify the use of one factor (e.g. frequent exposure to sugar containing snacks or beverages, visible cavities) in determining overall risk.

Overall assessment of the child's dental caries risk: High ☐ Moderate ☐ Low ☐

enamel. A variant of the tactile method uses dental floss in between teeth. The shredding of floss upon withdrawal is indicative of a possible area of proximal decay. Further diagnostic methods include radiographic examination.⁴¹ A variety of radiographs may be utilized, though the horizontal bitewing intraoral views are the most reliable. These are especially useful for the detection of proximal decay at sites that are not clinically visible. Other radiographs such as the long cone periapical intraoral view are beneficial for the assessment of the crown and root structures of the tooth, including the area of bone in the vicinity of the root tip. This radiograph will also provide information regarding any changes in the bony architecture at the periapex of the tooth. A dental panoramic tomogram provides a more generalized view of the dentition and perioral tissues. Gross carious lesions can be appreciated but detail of carious radiolucencies cannot be appreciated in the anterior teeth, especially the mandibular anteriors, due to their overlap with the cervical spine area. Modern techniques of caries detection have also been investigated and introduced to the market, such as quantitative

light induced fluorescence,⁴² laser fluorescence (available as Diagnodent, KaVo, Biberach, Germany. Use is shown in Figure 5)⁴³ and electrical conductance and resistance measurements.⁴⁴ Some experimental techniques of caries detection have been reported, such as multiphoton imaging, infrared thermography, infrared fluorescence, and optical coherence tomography.⁴⁵

Preventive Approach for Dental Caries

One of the simplest ways of preventing the development of dental decay is the institution of good oral hygiene measures from birth itself. Before the eruption of teeth, oral hygiene can be maintained by cleaning the gum pads with a moist cotton gauze after feeding. The mainstay of oral hygiene measures for children is toothbrushing once the first tooth erupts. The recommended frequency for brushing is twice a day, for at least two minutes at each brushing exposure. A smear of tooth paste may be applied to the brush for very young children below the age of 2 years and a pea sized tooth paste amount used for children over this age.⁴⁶ The Fones technique of tooth brushing



Fig. 5: Diagnodent uses laser fluorescence for caries detection

has been recommended and involves circular motions of brush movement on teeth. In areas that do not receive fluoridated water, the child may be encouraged to spit out the toothpaste at the end of brushing without rinsing the mouth to help retain fluoride around teeth and thus prolong its period of contact with dental hard tissues. Special kids' toothpastes are available that have the appropriate fluoride levels of around 500 ppm.

Fluoride's role in decreasing the prevalence of caries has been well accepted for many years. However, the beliefs about fluoride have changed. It is now established that the presence of fluoride in and on enamel surface is the key to the effectiveness of fluoride.⁴⁷ Fluoride is incorporated throughout the tooth crown formation during development of the tooth. In the pre-eruptive phase, fluorides have also shown to make the pits and fissures on the occlusal surfaces of molars and premolars shallower, thereby making them more amenable to oral hygiene procedures.^{48,49} In the post-eruptive phase also, fluoride continues to enter the enamel surface causing crystals

to change from predominantly carbonate apatite and hydroxyapatite to fluorapatite and fluor-hydroxyapatite crystals. These fluoride rich crystals are less acid soluble than the original enamel apatite.⁵⁰ Fluorides also possess the capacity to aid in the remineralization of incipient demineralization of tooth structure where cavitation has not taken place yet.⁵¹ The re-growth by fluoride incorporation chemically forms new crystals that are larger and more acid resistant and contain a higher concentration of fluoride.⁵² Fluorides can be administered through systemic as well as topical application.^{53,54} The various routes of administration are demonstrated in Figure 6.^{53,55} The topical route is considered more efficacious.^{54,56}

The anatomy of the posterior dentition is complex. The occlusal (biting) surface of the molars features many pits and fissures in enamel that are potential traps for plaque and microorganisms that could lead to the development of decay. The recognition of such susceptible areas of the surface of teeth during a regular dental examination is important. As a preventive measure, such areas could be preventatively sealed off using a flowable, often light cured material known as pit and fissure sealant. In the most conservative form of treatment using pit and fissure sealants, the tooth is not prepared with the drill at all and the pit and fissure sealant is retained onto the tooth using adhesive technology. The rationale behind its use is to help eliminate a potential area where plaque may accumulate in spite of good oral hygiene measures. Pit and fissure sealants can be recommended both for molars as well as premolars, the latter in the permanent dentition only. They have been found to be very effective in preventing decay.⁵⁷

The relation between diet and dental caries has also been established. The relation between carbohydrates and dental caries is well known. Several monosaccharides, disaccharides and polysaccharides have cariogenic potential. The factors that affect caries initiation and

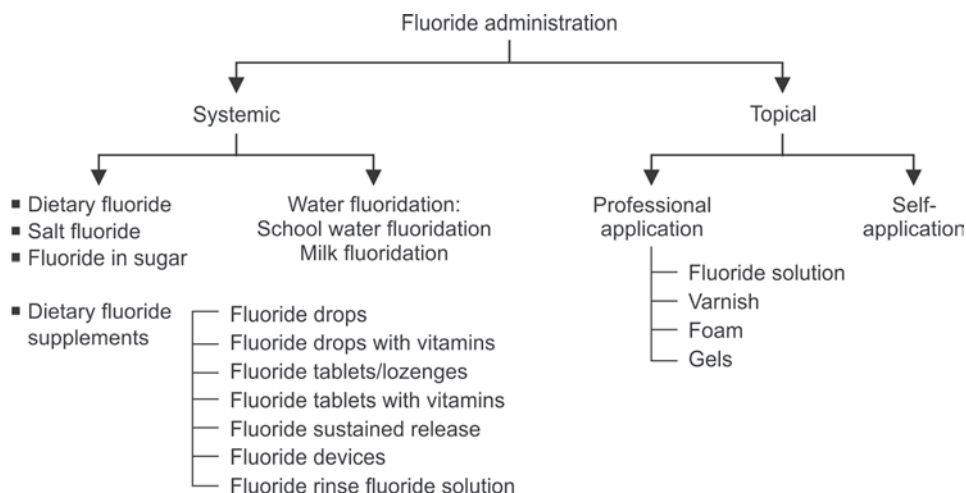


Fig. 6: Routes of fluoride administration

progression are, in some measure, related to the chemical form of the carbohydrate. For example, simpler carbohydrates, such as sucrose and lactose will have a higher cariogenic potential than a complex polysaccharide, such as cellulose which has no cariogenic potential. Further, the clearance rate of the carbohydrate from the mouth plays a very significant role. Sticky foods will have remain in the oral cavity for longer periods of time and thus have more cariogenicity. This is related to reduction in the pH of the mouth and plaque biofilm that promotes the growth and activity of acidogenic and aciduric microorganisms, which have the ability to metabolise these carbohydrates through extracellular enzymes.¹⁷ With sticky foods possessing cariogenic potential, the return of pH to normal following a sugar exposure is very slow. The frequency of the consumption of carbohydrate is also important. Thus strategies for dietary modification form an integral part in caries prevention and management. Oral hygiene measures would play an important role after a meal to aid in clearing away sugar from around the teeth thus restoring the pH in the mouth and reducing an acidic environment. Other potential measures could include changing the chemical nature of carbohydrate to make it less available for bacterial breakdown, such as the replacement of glucose (an aldose hexose) with sorbitol or xylitol. The provision of a terminal alcohol group instead of an aldehyde group helps resist acid formation by altering biochemical pathways and thus reducing dental caries. In another method, the addition of substances to a carbohydrate diet has been attempted to counteract products of bacterial metabolism. An example is the addition of phosphate groups to a carbohydrate containing diet which helps alter relative solubility of enamel and thus alters the caries rate.

Restorative Approach to Caries Management

Initial areas of demineralization can be managed through a minimally invasive approach that involves addressing dietary factors, improving oral hygiene measures, use of high fluoride content toothpastes (containing 2800 ppm or 5100 ppm fluoride), daily fluoride mouth rinses (0.05 percent sodium fluoride) and attempting re-mineralization using amorphous calcium phosphate-casein pyrophosphate combination (available as GC Tooth Mousse). However, if a definitive cavitation in tooth structure exists, then the line of management is the excavation of the decayed tooth structure and restoration of the remaining tooth with a suitable restorative material. This would help restore the tooth structure back to its original form, function and esthetic self. Several direct restorative materials are useful for this purpose and include glass ionomer cements and its variants, composite resins, amalgam, compomers, giomers and ormocers. An indirect restorative technique for the management of decay, known as the Hall technique for stainless steel preformed crowns has also been recommended with good success rate.

Pediatric Endodontics

If the carious process extends to involve the pulp of the tooth, then this is a definite indication for endodontic intervention, especially if the tooth is to be retained for a sufficiently long period in the mouth prior to its exfoliation and subsequent succession with a permanent tooth. Endodontics involves extirpation of the irreversibly inflamed or necrotic pulp, shaping and cleaning of the root canal system and then obturation of the same with a suitable filling material that is amenable to resorption (to facilitate exfoliation of the tooth). A more conservative procedure in endodontics would be a pulpotomy, wherein the pulp would be removed from the pulp chamber and amputated at the root canal orifices. This procedure would be undertaken only when it is reasonably certain that pulp within the root canals is not inflamed. Following the endodontic procedure, the badly broken down tooth could be protected with the help of a stainless steel crown in the case of molars and an adequate restoration of coronal tooth structure for the anterior teeth.

DENTAL TRAUMA

Dental trauma often results in a scenario that involves both general dentists and many dental specialists. Ideal treatment relies upon the expertise of a broad spectrum of dental specialists, such as oral surgeons, pediatric dentists, endodontists, orthodontists, prosthodontists and periodontists. Urgent care is frequently provided by the oral and maxillofacial surgeon or the pediatric dentist in a hospital accident and emergency department setting. Subsequently the patient may be referred to a general dentist or an endodontist for secondary level care, such as endodontic and restorative management. Later the orthodontist and prosthodontists and periodontist may become involved with additional treatment.

Incidence and Prevalence

Toddlers in the age group of 1.5 to 2.5 years are very susceptible to dental traumatic injuries. Maximum incidence of trauma is at the age of 4 years in the primary dentition and between 8 and 11 years for children in the permanent dentition. A sex distribution of boys to girls has been found to be in the ratio of 1:2.⁵⁸

Prevalence

Kessler has examined over 40,000 children over a period of 15 years and found the prevalence of anterior tooth trauma to be 4.6 percent. Andreasen in 1972 found a prevalence rate of 30 percent whereas Garcia Godoy (1990) reported very high figures of 72 percent. The prevalence of dental trauma in high school children ranged between 6 percent in an Australian study by Burton et al⁶¹ and 34 percent in an English study by Hamilton et al.⁶⁰ (Table 4). In the UK, a prevalence of 6 percent has been reported for

Table 4: Incidence of trauma in the anterior dentition

Country	Author	Incidence	Age group	Social group predominantly affected
Australia	Stockwell ⁵⁹	1.7 patients/100 children/year	6-12 years	Lower socioeconomic group
England	Hamilton et al ⁶⁰	4 patients/100 children/15 months	–	Higher socioeconomic group

8-year-old children and 17 percent for 12-year-old children in 1993.⁶² A study in Sweden observed a relatively high prevalence of traumatized teeth in children aged 7 to 15 years (30 percent) but this study also included traumatized primary teeth.⁶³ Gupta et al. examined 2100 school children between the age group of 8 and 14 years in a South Indian district and found prevalence rate of 13.8 percent.⁶⁴ A New Zealand study by Dearing observed a prevalence of traumatized incisors of 19 percent,⁶⁵ while a Swiss study revealed a prevalence of trauma to permanent teeth in children aged 6 to 18 years of 11 percent.⁶⁶ In South Africa, an overall trauma prevalence of 16 percent in primary school children was found.⁶⁷ The black population had a dental trauma prevalence of 13 percent and the white population a prevalence of 21 percent. An American study found prevalence of traumatized incisor teeth to be significantly higher among non-Caucasians compared with Caucasians, 17.5 percent and 21.7 percent respectively.⁶⁸

Etiology of Dental Traumatic Injuries in Children

Fall injuries seem to be a common cause of dental trauma. In the preschool age, these may be attributed to activities associated with learning to walk and stand. School age children suffer dental trauma often because of sports injuries, more so during their teens when they engage in contact sports. Children with malocclusions, especially proclined teeth are at an increased risk for injuring their maxillary anterior dentition. The late teens may be associated with automobile accidents. Another important cause of dental trauma is the battered child syndrome. It is extremely important for the attending clinician to be able to discern and recognize such an injury. Fights and physical violence, foreign bodies hitting the face and medical problems (like convulsive fits) are also likely causes for a traumatized dentition. The extent of injury itself may be determined by several factors, such as the energy of impact, resiliency and shape of the impacting object, direction of the impacting force and cushioning barriers that intervene between the impacting object and the teeth (such as the lip).

Classification of Dental Traumatic Injuries

Table 5 presents the classification of dental traumatic injuries from different authors. Figures 7 to 10 are some examples of dental traumatic injuries. Dental injuries can be quite disturbing for the child and the parent and usually need immediate attention from the dentist or other health care personnel available. Of all the different types

of injuries, an avulsion injury is one of the most dramatic and a cause for considerable distress. This injury is discussed in greater detail here as awareness regarding the appropriate on site management strategy and telephonic advice to the parent by the dentist/doctor is critical in determining the outcome and prognosis for the tooth that has been avulsed.

AVULSION

The term avulsion is implied for teeth which are completely displaced out of its socket (alveolus). It is alternatively referred to as *exarticulation*.

Cause

Any impact trauma can lead to avulsion. The main etiologic factors in the permanent dentition appear to be sports injury, automobile accidents and fights whereas in the primary dentition, falls against hard objects are a frequent cause.

Incidence

Reported incidence of tooth avulsion ranges from 1 to 16 percent of all traumatic injuries in the permanent dentition and from 7 to 13 percent of injuries to the primary dentition. The maxillary central incisors are the most frequently avulsed teeth in both deciduous and permanent dentitions. The most frequently involved age group is 7 to 11 years, with boys experiencing avulsion three times as often as girls. Single tooth avulsions are very common, but multiple avulsions are also occasionally encountered.

Examination

Thoroughly examine the patient irrespective of the fact of whether or not the tooth has been returned to the socket before coming to the dental office. Radiographs and clinical examination should be first directed at detecting possible alveolar fractures. If such fractures exist, prognosis is significantly reduced. The avulsed tooth itself should be examined for debris and contamination. One of the most important aspects is to learn the length of time of avulsion since the extra-alveolar time determines, to a large extent, the treatment modality undertaken as well as prognosis.

Biologic Considerations

When a tooth is avulsed, the attachment apparatus of the root, namely the periodontal ligament and cemental layer, are damaged. Concomitantly, the blood vessels at the apex

Table 5: Classification of dental traumatic injuries

Andreasen ⁶⁹	WHO Classification ⁷⁰	Garcia-Godoy ⁷¹	Ellis ⁷²
Crown infraction. Incomplete fracture of the enamel	Fracture of enamel of tooth	Enamel crack	Simple fracture of the crown, involving little or no dentine
Uncomplicated crown fracture. A fracture confined to the enamel or dentine but not exposing the pulp	Fracture of crown without pulpal involvement	Enamel fracture	Extensive fracture of the crown, involving considerable dentine, but not the dental pulp
Complicated crown fracture. A fracture involving enamel and dentine, and exposing the pulp.	Fracture of crown with pulpal involvement	Enamel-dentine fracture without pulp exposure	Extensive fracture of the crown, involving considerable dentine and exposing dental pulp
Uncomplicated crown-root fracture. A fracture involving enamel, dentine, cementum, not exposing the pulp	Fracture of root of tooth	Enamel-dentine fracture with pulp exposure	The traumatized tooth that becomes non-vital, with or without loss of crown structure
Complicated crown-root fracture. A fracture involving enamel, dentine and cementum, and exposing the pulp	Fracture of crown and root of tooth	Enamel-dentine-cementum fracture without pulp exposure	Total tooth loss
Root fracture. A fracture involving dentine, cementum, and the pulp	Fracture of tooth, unspecified	Enamel-dentine-cementum fracture with pulp exposure	Fracture of the root, with or without loss of crown structure
Concussion. Injury without abnormal loosening or displacement but with marked reaction to percussion	Luxation of tooth	Root fracture	Displacement of tooth, without fracture of crown or root
Subluxation (loosening). Injury with abnormal loosening but without displacement of the tooth	Intrusion or extrusion of tooth	Concussion	Fracture of the crown en masse and its replacement
Intrusive luxation (central dislocation)	Avulsion of tooth	Luxation	
Extrusive luxation (peripheral dislocation, partial avulsion)	Other injuries including laceration of oral soft tissues	Lateral displacement	
Lateral luxation		Intrusion	
Exarticulation (complete luxation)		Extrusion	
Comminution of alveolar socket		Avulsion	
Fractures of facial or lingual alveolar socket wall			
Fractures of alveolar process with and without involvement of the socket			
Fractures of the mandible or maxilla with and without involvement of the tooth socket			
Laceration of gingiva or oral mucosa			
Contusion of gingiva or oral mucosa			
Abrasion of gingiva or oral mucosa			

of the tooth are severed, thus rendering the pulp necrotic (Figure 11).

Treatment Objectives

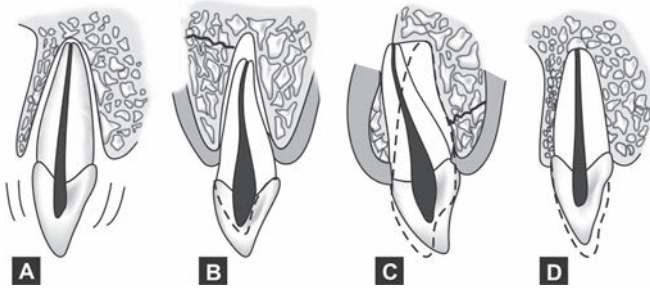
Treatment is directed at avoiding or minimizing the damage to the attachment apparatus and combating pulpal necrosis. If the tooth has an open apex, then revitalization should be promoted whereas in the case of a closed apex,

potential toxins from the root canal should be eliminated by endodontic therapy.^{73,74}

Clinical Management

Management outside the dental office

The single most important factor in the success of management is the speed with which the tooth is replanted



Figs 7A to D: Luxation injuries. (A) Subluxation; (B) Extrusive luxation; (C) Lateral luxation; (D) Intrusive luxation



Fig. 10: Upper right central incisor with enamel and dentine crown fracture and extrusive luxation. The Upper left central incisor with lateral luxation (For color version see plate 19)

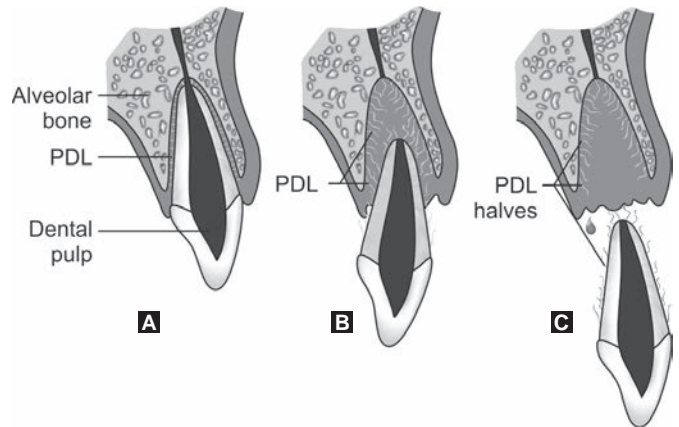


Fig. 8: Lip injury and crown fracture for the upper left central incisor exposing the pulp and with lateral luxation (For color version see plate 18)



Fig. 9: Same patient as in Figure 8 with a closer view (For color version see plate 18)

back in its socket. The prime focus in the immediate post-traumatic phase is prevention of drying of the tooth. Every effort should be made to replant the tooth within the first 15 to 20 minutes after exarticulation. If the dentist is notified by phone of a tooth avulsion, the following instructions must be relayed by the dentist/attending physician to the emergency room attendant, parent or any responsible adult who may be able to carry out the steps.⁷⁵



Figs 11A to C: An avulsed tooth: (A) Normal tooth; (B) PDL fibers stretch; (C) PDL fibers broken (PDL: Periodontal ligament)

- Hold the tooth by the crown (not by the root) and rinse gently (but not excessively) in running tap water (not icy) or saline.
- Do not scrub the tooth
- Gently replace the tooth in its socket, as close as possible to the original position as possible. Ask the patient to bite gently on a piece of cloth, gauze or handkerchief.
- Rush the patient to the dental office.

If doubt exists on the ability to replace the tooth in the socket adequately, the tooth should be stored quickly in an appropriate medium until the patient can get to the dental office for replantation.⁷⁶ Several options are available and are listed in order of preference as under:

- *Avulsed-tooth preserving system (Save-a-Tooth, Biologic Rescue Products, Conshohocken, PA):* This contains Hanks

Balanced Salt Solution (HBSS) and is a pH-preserving fluid and trauma reducing suspension apparatus with several advantages. It is composed of glucose, sodium chloride, potassium chloride, calcium chloride, magnesium chloride, sodium bicarbonate, sodium phosphate, magnesium sulfate. It possesses a pH of 7 and osmolarity ranging from 270 to 290 osm/liter. This system could be made available at schools, contact sport events in hospitals and emergency rooms. However, its high cost and non-availability in different parts of the world precludes its use.⁷⁷

- *Viaspan (Dupont Pharmaceuticals, Wilmington, USA):* This is a cold storage medium for organ transplantation possessing a pH of 7.4 and osmolarity of 320 osm/liter. This has proven to be a superior long-term storage medium preserving 76.7 percent vitality of periodontal ligament cells after 24 hours and 37.6 percent after 168 hours. It has also shown to reduce the incidence of root resorption. However, its high cost (\$300/liter) and short shelf life deter its widespread use.⁷⁷
- *Contact lens solution:* This solution is commonly available at many homes or easily purchased from a drug store. It does not preserve vitality as well as the previous two solutions, but is still extremely effective over short time durations. It consists of sodium chloride, a copolymer of polyoxyethylene and polyoxypropylene, sodium phosphate and preserved with polyhexamidine.⁷⁸
- *Milk:* This is considered the best storage medium for uncomplicated avulsion because it is usually readily available at or near an accident site, has a pH and osmolarity compatible to vital cells and is relatively free of bacteria. Milk effectively maintains the vitality of periodontal ligament cells for 3 hours, which usually allows adequate time for the patient to reach the dentist for replantation.^{74,77,78}
- *Keep tooth in mouth:* Placing the tooth in the buccal vestibule or under the tongue helps keeping it bathed in the saliva. The tooth is kept moist and at body temperature. But it is not an ideal method because of incompatibility of pH, osmolarity and the microbial loading in the oral cavity. Further, in the case of a young patient, or where the patient has lost consciousness, risk of accidental ingestion or aspiration is always high.^{14,74}
- *Keep tooth in physiologic saline solution*
- *Water*

Management in Dental Office

Emergency Visit

Recognizing that the dental injury might be secondary to a more serious injury is essential and, if need be, referral to an appropriate expert is recommended. The focus of the emergency visit is the attachment apparatus. The

aim is to replant the tooth with maximal number of viable periodontal cells on root surface that have the potential to regenerate and repair. Endodontics, on the other hand, is not initiated at the emergency visit and not extraorally, if any hope exists of vital periodontal fibers on the root surface.

A full history must be taken and encompass reconstructing the accident, site of injury, time of injury, dry time for tooth, storage medium for tooth and any other injuries sustained by the patient.

Local anesthesia is generally administered for conducting a thorough clinical examination. If the tooth is in situ and acceptably replanted at the site of avulsion, then determine whether it is in proper position and alignment with the adjacent teeth. The tooth should not be traumatized by occlusion. The mobility of the tooth should be noted and a radiograph taken. The vitality of the pulp must be assessed. If the replantation done at the accident site is unacceptable, then the tooth is gently removed and replanted after obstruction to correct placement is removed.

If the tooth was not replanted at all, then the replantation procedure is governed by the time since avulsion and the status of the root apex of the tooth (open or closed). Flow charts 1A and B represent the management protocol suggested by the American Academy of Paediatric Dentistry for the management of an avulsed tooth with an open or a closed apex.⁷⁹ In these cases, the socket should be left as unaltered as possible. Gentle irrigation to remove debris and light aspiration of blood clot is permissible. However, curetting the socket is definitely contraindicated.

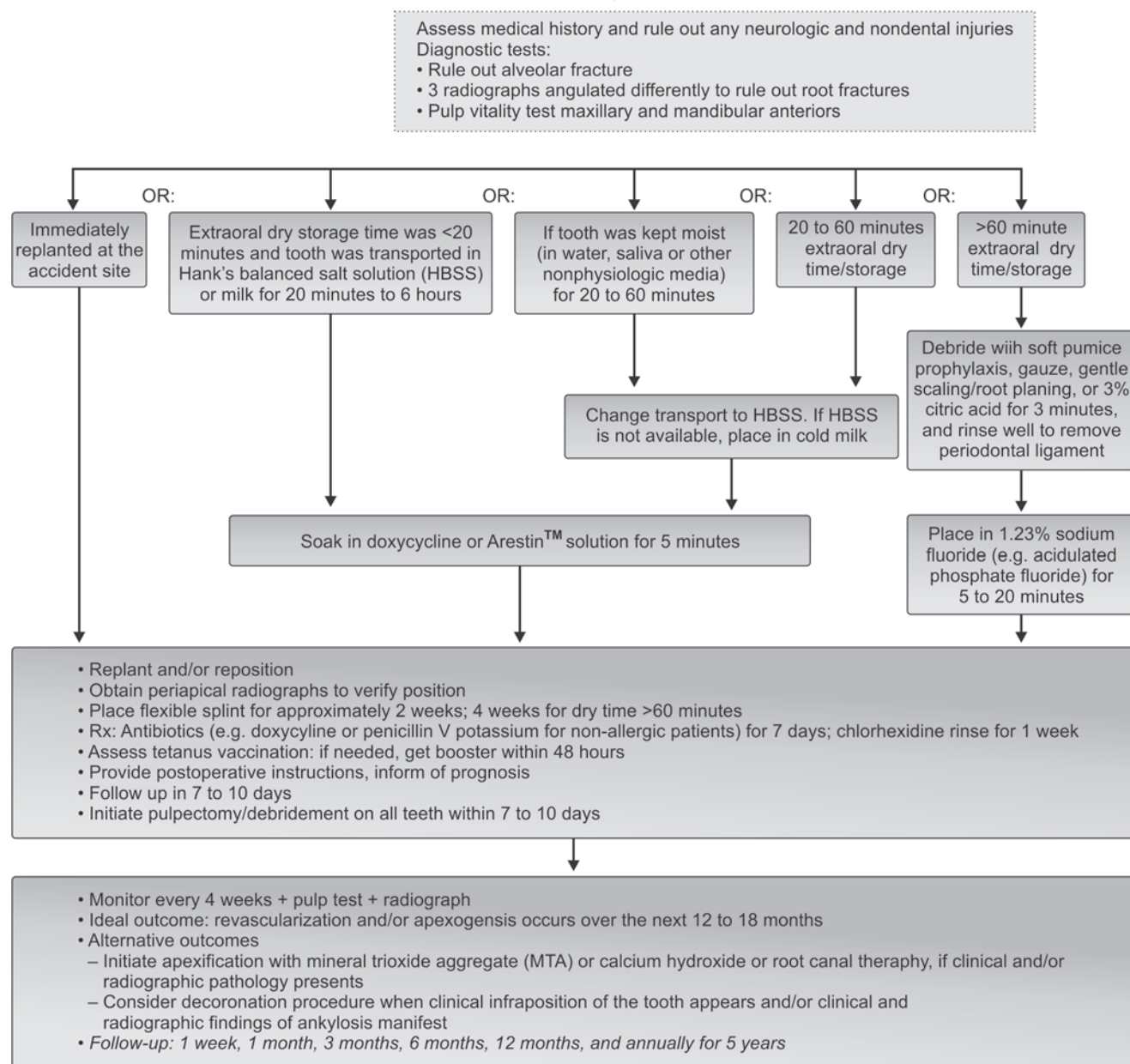
A semirigid physiologic splint should be placed for a period of 7 to 10 days.⁸⁰ Splinting affords stability to the tooth and allows physiologic movement of the tooth minimally during healing. It must also permit adequate maintenance of oral hygiene. The most commonly used splints are the acid-etch resin splint and the arch wire splint. When the splint is in place, the patient is asked to bite gently in a bite block (usually fabricated of softened wax) which forces the avulsed tooth as far into the socket as possible. If an alveolar fracture also exists, then the splint must remain in position for 4 to 8 weeks.

- Soft tissue management includes clearing the area of all dirt and debris and suturing all lacerations.
- Adjunctive therapy in the form of antibiotics and analgesics is recommended. Additionally, an antimicrobial mouthwash such as chlorhexidine gluconate is to be prescribed for a period of 7 to 10 days. The need for tetanus protection should also be evaluated.

Second Visit

This visit would include assessing the vitality of the tooth, removing the splint and deciding upon future options of whether to perform a root canal treatment. Subsequent

Flow chart 1A: Management an avulsed permanent incisor with an closed apex (Apex <1 mm)
(From American Academy of Paediatrics)



follow-up visits are mandated to monitor the status of the tooth.

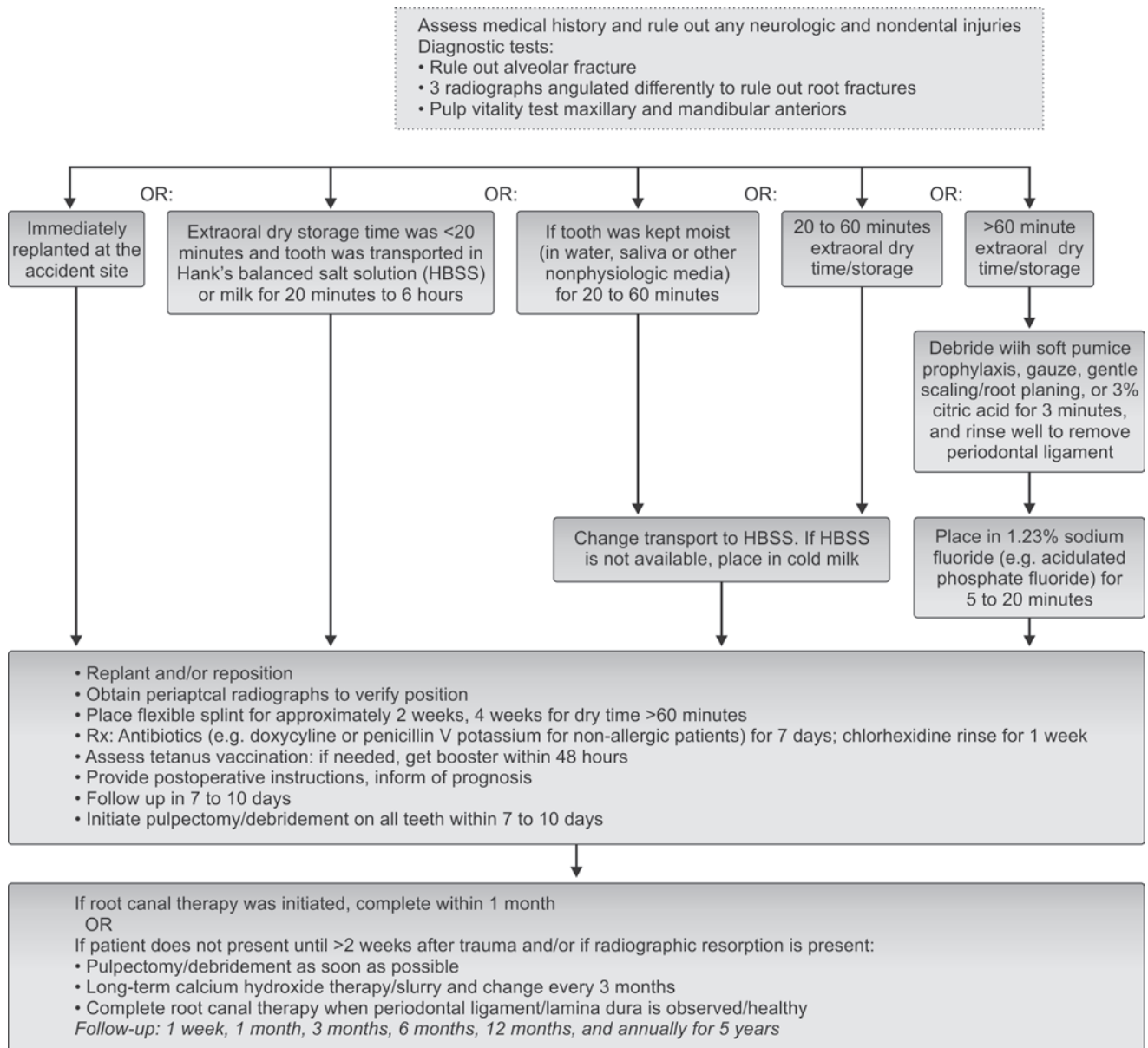
Prevention of Trauma in Children Engaging in Sports Activities

For children who participate in contact sporting activities, such as boxing, football and the like, it is always safer for the child to wear a protective mouth guard. The mouth guard serves to protect the teeth from impact trauma and distributes the force uniformly across the bony buttresses of the maxillofacial region rather than transmitting them on to the teeth. Mouth protectors are very useful in children predisposed to trauma, such as those with proclined

incisors and incompetent lips. The mouth guards could be either of the preformed or the custom made variety and can be worn by the child during the course of the activity only. Three different types of mouth protectors have been described:⁸¹

- *Stock protector:* These are made of latex rubber and are often used by boxers. They are not recommended for use by children as they are often poorly retained with the help of the opposing teeth. They also carry the risk of airway obstruction
- *Protector made in mouth:* These are again of two types:
 - A firm outer shell shaped as a dental arch which is filled with resin and placed in to the mouth. The

Flow chart 1B: Management an avulsed permanent incisor with an closed apex (Apex <1 mm)
(From American Academy of Paediatric Dentistry)



resin sets in the mouth but remains resilient at mouth temperature (Coe Dental Guard)

- A blank of polyvinyl acetate-polyethylene or polyvinyl chloride material which softens in water at about 75°C. Once softened, it is placed in the mouth and moulded with the tongue and fingers (Coe Redigaurd).

Both these variants can be accurately fitted in the mouth under the professional supervision of the dentist.

- *Professionally made protector:* These are the recommended mouth protectors because they are made on

an accurate model of the maxillary dentition. They are usually 3 to 6 mm thick. During heavy exercise, if the patient breaths through the mouth, the mouth will open while the mouth guard is still in place. However, there will be a gap between the guard and the lower dentition. Should there be a traumatic impact, the mandible will swing close and there is a risk for a base of the skull injury. Therefore, the mouth protector should be constructed so as to open the bite to a 'position of heavy breathing' to avoid this unfavourable consequence.

ORTHODONTIC TREATMENT

Orthodontics is that branch of dentistry concerned with prevention, interception and correction of malocclusion and other abnormalities of the dentofacial region. The word orthodontics is derived from the Greek words *orthos* meaning correct and *odontos* meaning teeth. The term “orthodontics” was first coined by le Felon.

In 1922, the British Society for the Study of Orthodontics defined the specialty as one that includes the study of the growth and development of the jaws and face particularly, and the body generally as influencing the position of the teeth; the study of action and reaction of internal and external influences on the development and the prevention and correction of arrested and perverted development.⁸²

Man has recognized the presence of dentofacial deformities and the need for its treatment centuries back. Crude appliances that were seemingly designed to regulate the teeth have been excavated by archeologists from around the world including Egypt, Greece, and Mexico.

Normal alignment of teeth not only contributes to the oral health but also goes a long way in the overall well-being and personality of an individual. Correct tooth position is an important factor for aesthetics, function and for overall preservation or restoration of dental health. The prevalence of malocclusion in the United States is estimated to be 35 to 95 percent of the population. Moderate to severe treatment need has been estimated to be at 30 to 40 percent of the population (NHANES III data).⁸³ While most malocclusions may not adversely affect the health of an individual, they nevertheless are capable of producing undesirable functional and esthetic imbalances. The following are some of the unfavorable sequel of malocclusion^{82,83} (Figs 12 and 13).

Poor Facial Appearance

Malocclusion is capable of adversely affecting the facial appearance of an individual.

Risk of Caries

Malalignment of teeth makes oral hygiene maintenance a difficult task, thereby increasing the risk of caries.

Predisposition to Periodontal Diseases

Malocclusion associated with poor oral hygiene is a frequent cause of periodontal diseases. In addition, teeth that are placed in abnormal positions can be a cause for traumatic occlusion with resultant periodontal tissue damage.

Psychological Disturbances

Malocclusion that adversely affects the appearance of person leads to psychological disturbances. Unsightly appearance of teeth makes a person highly self-conscious and turns him into an introvert. Thus treatment of malocclusion in such patients helps in improving the mental wellbeing and confidence.

Risk of Trauma

Teeth that are severely proclined are at a high risk of injury especially during play or by an accidental fall.

Abnormalities of Function

Many malocclusions cause abnormality in the functioning of the stomatognathic system, such as improper chewing, deglutition, defects in speech, improper respiration and so on.



Fig. 12: Radiographic examination prior to orthodontic treatment



Fig. 13: Patient undergoing orthodontic treatment with a fixed appliance (For color version see plate 19)

Temporomandibular Joint Problems

Malocclusion associated with occlusal prematurities and deep bite are believed to be a cause of TMJ problems such as pain and dysfunction.

Aims and Objectives of Orthodontic Treatment

The aims and objectives of orthodontic treatment have been summarized by Jackson as the Jackson's triad. The three main objectives of orthodontic treatment are:³¹

- Functional efficiency
- Structural balance
- Aesthetic harmony.

Functional Efficiency

Many malocclusions affect normal functioning of the stomatognathic system. The orthodontic treatment should thus aim at improving the functioning of the orofacial apparatus.

Structural Balance

The orofacial region consists of the dentoalveolar system, the skeletal tissue and the soft tissue including musculature. Stable orthodontic treatment is best achieved by maintaining a balance between these three tissue systems.

Esthetic Harmony

By far the most common reason for seeking orthodontic care is to improve the appearance of the teeth and face. Many malocclusions are associated with unsightly appearance of teeth and can thus affect the individual's self-image, wellbeing and success in society. Thus the orthodontic treatment should aim at improving the aesthetics of the individual.

Scope of Orthodontic Treatment

Orthodontic treatment involves the three main tissue systems concerned in dentofacial development, namely the dentition, the skeleton and the facial and jaw musculature. Orthodontic treatment can bring about changes in the dentition, the skeletal system and the enveloping soft tissue.

Alteration in Tooth Position

Orthodontic treatment is made possible by the fact that teeth can be moved through the bone to ideal locations by applying appropriate force on them. Most malocclusions involving the dental system can be effectively treated by moving teeth so as to normalize the occlusion.

Alteration in Skeletal Pattern

Malocclusion may be associated with skeletal disharmony involving the jaw bones (i.e. maxilla and mandible).

Deviations from the normal can arise in size, position and relationship between these skeletal components. It is within the scope of an orthodontist to apply appropriate orthopedic forces that are capable of restraining, promoting or redirecting skeletal growth as to normalize the skeletal system. The orthodontist can bring about changes in all the three planes of space, i.e. sagittal, transverse and vertical.

Alteration in Soft Tissue Pattern

The soft tissues that envelop the dentition are greatly influenced by the placement of the dentition. It is possible to bring about favorable changes in the soft tissue pattern by orthodontic treatment.

Services Offered by an Orthodontist

As most children are often seen by a paediatrician first, the early recognition of a malocclusion can fall into their purview.⁸³ Appropriate referral to a general dental practitioner or an orthodontist can then be made. The services offered by an orthodontist can be broadly classified as:

- Preventive orthodontics
- Interceptive orthodontics
- Corrective orthodontics
- Surgical orthodontics.

Preventive Orthodontics

Preventive orthodontics is that part of orthodontic practice which is concerned with the patient's and parents' education, supervision of the growth and development of the dentition and the craniofacial structures, the diagnostic procedures undertaken to predict the appearance of malocclusion and the treatment procedures instituted to prevent the onset of malocclusion.

Preventive orthodontics is a long range approach and it is largely a responsibility of the general dentist. Many of the procedures are common in preventive and interceptive orthodontics but the timings are different. Preventive procedures are undertaken in anticipation of development of a problem. Interceptive procedures are undertaken when the problem has already manifested, e.g. extraction of supernumerary teeth before they cause displacement of other teeth is a preventive procedure, while their extraction after the signs of malocclusion have appeared is an interceptive procedure.

The following are some of the procedures undertaken in preventive orthodontics:^{82,84}

- Parent education
- Caries control
- Care of deciduous dentition
- Management of ankylosed tooth
- Maintenance of quadrant wise tooth shedding timetable
- Check-up for oral habits and habit breaking appliance if necessary

- Occlusal equilibration, if there are any occlusal prematurities
- Prevention of damage to occlusion, e.g. from Milwaukee braces
- Extraction of supernumerary teeth
- Space maintenance for permanent dentition after the extraction/premature exfoliation of the deciduous dentition
- Management of deeply locked first permanent molar
- Management of abnormal frenal attachments.

Interceptive Orthodontics

Interceptive orthodontics includes procedures that are undertaken at an early stage of a malocclusion to eliminate or reduce the severity of the same. By undertaking appropriate interceptive procedures, it is possible to prevent establishment of a full-fledged malocclusion that may require long-term orthodontic treatment at a later age.

The procedure undertaken in interceptive orthodontics include:^{82,85,86}

- Serial extraction of the primary teeth in a planned, predetermined sequence at an appropriate age so as to guide the permanent teeth into correct positions
- Correction of developing crossbite
- Control of abnormal habits
- Space regaining
- Muscle exercises
- Interception of skeletal malrelation by the use of headgears and myofunctional appliances
- Removal of soft tissue or bony barrier to enable eruption of teeth.

Corrective Orthodontics

Orthodontic procedures undertaken to correct a fully established malocclusion. This entails therapy with fixed appliances, which may extend over a period of two to three years.

Surgical Orthodontics

They are surgical procedures that are undertaken in conjunction with or as an adjunct to orthodontic treatment. The surgical orthodontic procedures are usually carried out to remove an etiologic factor or to treat very severe dentofacial skeletal deformities that cannot be treated by orthodontic therapy alone.

MANAGEMENT OF THE ANXIOUS CHILD PATIENT

Dental anxiety is a common problem all over the world, and it not only prevents many patients from seeking care but it also causes stress to the dentists undertaking dental treatment. Dental anxiety should be seen as a multifactorial problem, and must also be seen as a continuum with

fear it is almost impossible to separate the two in much of the research undertaken in the field of dentistry, where the two words have often been used interchangeably. Fear is an unpleasant feeling that arises as a normal response to realistic danger. Anxiety is an emotion similar to fear, but arising without any objective source of danger. Phobia is a fear of a situation that is out of proportion to its danger, can neither be explained nor reasoned out and is largely beyond voluntary control and leads to the avoidance of the feared situation. The identification of these conditions will lead to the appropriate management for the child.

Fear is one of the primary emotions acquired soon after birth. Infant may be unaware of the stimulus causing fear, but as the child grows up, he is able to rationalize each stimulus and identify the ones which produce fear. Fear in children is generally classified as being either objective or subjective. Objective fears are those which are produced by direct physical stimulation of the sensor organs and are generally not of parental origin. These fears are felt, seen, heard, smelt or tasted. A child who has had an unpleasant experience at the dental office tends to acquire objective fears and thus not come back on their own volition. Subjective fears, on the other hand, are based on feelings and attitudes that have been suggested to the child by others without the child having had the experience personally. Such fears may be acquired from parents, friends, books, television and the like. For example, a mother's fear before a dental appointment may get transmitted to the child. These fears are more intense and disproportionate as compared with objective fears. Research in this area suggests that the extent of anxiety a person experiences does not relate directly to dental knowledge, but is an amalgamation of personal experiences, family concerns, disease levels, and general personality traits. Such a complex situation means that it is no easy task to measure dental anxiety and pinpoint etiological agents.

Measures to Overcome Fear

- Educating parents is extremely important prior to the dental visit so that they can prepare the child for dental treatment
- Fears should be given proper direction and control by parents. The child needs to be channeled to believe that there is no danger in dental treatment and that this is not a threat or a punishment
- The dentist needs to allow the child to develop a sense of attachment to him. This helps develop an environment of trust
- Parents should inform the child of what to expect in the dental office. Negative aspects and experiences should not be related to the child
- Parents need to be informed of the possibility of parental anxiety being transmitted to the child either directly or indirectly

- Parents need to be made aware of the modification of fear response in a child with age
- Children may develop a positive attitude by seeing pictures or videos of a dentist treating a smiling or a laughing child
- The waiting room should be decorated with posters, children's books, cartoons and videos playing children's entertainment programs
- For a preschool child, the mother should accompany the child to the surgery, not project her feelings on to the child and be encouraging and smiling
- Between ages 4 and 6 years, a child may begin to fantasize. This can be used to help overcome a fearful situation. For example, a playful situation could be conjured at home where the child simulates visiting the dentist, imagines himself sitting on a dental chair and have his teeth examined
- At school age, child begins to learn to manage fears by suggestion and imagination
- Around 7 years of age, the child is open to reasoning and explanation of treatment by the dentist
- At around 8 to 14 years of age, the child develops considerable emotional control and should not be bullied or laughed at
- In their teeth, children can be made to comply with dental treatment by informing them that the treatment would make them look better and smarter.
- d. Timid behavior/shy: usually due to overprotective parents. Due to anxiety, may prevent the child from listening attentively to the dentist.
- e. Whining type: A complaining type of behavior and the child complains of pain even for a painless procedure. He may allow treatment but may be crying through the procedure.
- e. Stoic behavior: Generally cooperative, sits, quietly, passively and accepts all dental treatment. This behavior may be seen in physically abused children.
- Lampshire (1970)
 - Cooperative: Physically and emotionally relaxed and cooperative through the procedure
 - Tense cooperative: Child is tense and cooperative at the same time
 - Outwardly apprehensive: Avoids treatment, usually child hides behind mother, avoids looking or talking to the dentist.
 - Fearful: Requires considerable support to help overcome the fears of dental treatment.
 - Stubborn/defiant: Passively resist treatment by using techniques to avoid accepting treatments that have been successful with them in the past.
 - Hypermotive: Children who are acutely agitated and resort to screaming, kicking and crying.
 - Handicapped: Children with special needs.
- Wilson's Classification (1933)
 - Normal or bold: Child is brave enough to face new situations, is cooperative and friendly with the dentist.
 - Tasteful or timid: Child is shy, but doesn't interfere with the dental procedures and is generally cooperative.
 - Hysterical or rebellious: Child is influenced by home environment, shows temper tantrums and is rebellious.
 - Nervous or fearful: Child is tense and anxious and fears dentistry.

Types of Behavior Encountered in Clinics

- Classification by Wright (1975)
 - Cooperative behavior: Relaxed and minimally apprehensive child
 - Can be treated with a straight forward behavior shaping approach
 - Lacking cooperative ability: very young child (0-3 years) or a child with special needs
 - Potentially cooperative: These children have the ability to cooperate but are unable to do so because of objective/subjective fears. Age varies from 3 to 13 years
 - Negative uncooperative:
 - a. Uncontrolled or Hysterical or Incurable: usually seen in preschool children (3-5 years). Temper tantrums characterized by pushing/ pulling legs and arms, crying and refusing to cooperate
 - b. Defiant behavior: seen in children of any age group. A stubborn child may throw temper tantrums. The children can be made to cooperate but firm guidelines need to be set.
 - c. Tense cooperative: Borderline behavior between positive and negative. The child is cooperative, does not resist treatment but is tense at mind. He may accept treatment but cry at an anxious moment.

Helping Anxious Patients to Copy with Dental Care

- Establish an effective preventive programme
- Establish good dentist-patient relationship
- Ensure treatment is pain-free
- Manage time effectively.

BEHAVIOR MANAGEMENT STRATEGIES

Nonpharmacologic Techniques

Communication

This is most important for the effective management of the child. A combination of both verbal and nonverbal communication techniques should be used. Verbal

communication is best for children over 3 years of age. The clinician's voice should be constant, gentle, express empathy and firmness at the same time. The content of the conversation should be such that the child feels that the dentist is his well-wisher. The child's name, age and general background should be known and the child should be addressed by his or her name and questions related to school, likes and dislikes can be asked to help make the child more comfortable in the operatory. Euphemisms can be used to explain dental terminology; the dental drill could be the whistling willy, the rubber dam a raincoat, dental caries could be addressed as the tooth bug, anaesthetic solution as the water to put teeth to sleep and a radiograph as a tooth picture. Non-verbal communication is via body language, smiling, eye contact, expression of feeling while speaking and showing concern.

Tell-show-do

The majority of young children have very little idea of what dental treatment involves and this will raise anxiety levels. Most children will cope if given friendly reassurance from the dentist, but some patients will need a more structured programme. One such structured method is the tell-show-do technique. As its name implies it centers on three phases:

- *Tell*: explanation of procedures at the right age/educational level
- *Show*: demonstrate the procedure and explain the purpose of each instrument to the child
- *Do*: follow on to undertake the task, praise being an essential part of the exercise.

This method is used in a graded fashion, starting from the least fear inducing object or procedure and moving on to more fearful objects. This method can be used in the first visit for the child (if old enough to comprehend, usually more than 3 years of age) and in subsequent visits when new procedures are being introduced.

Desensitization

The desensitization technique helps to alleviate fears and anxiety in children and is a method to reduce maladaptive behavior. The method has three different stages to its implementation. In the first stage, the child patient is taught how to learn to relax. In the second stage, different fear producing stimuli are identified starting from the least fear producing in an increasing grade to the most fear producing in relation to the child's principal fear and in the third phase these stimuli are introduced to the child in a similar fashion. The clinician must be cautious while introducing these stimuli; the child must first learn to relax before that fear stimulus is introduced. If the stimulus has been introduced before the child learns to relax, then the repeated introduction of the stimulus will further heighten the child's fear. At each stage and stimulus, the

tell-show-do technique must also be applied. It is important to first identify the principal fear producing stimulus such as the drill, the needle and the like. Then a hierarchy of stimuli related to this principal fear can be constructed. To illustrate an example for desensitization: if a child is fearful of the dental clinical environment, then the graded stimuli may be bringing the child to the reception room of the dental office which would have been decorated in a child friendly manner (Fig. 14), in the next phase, meeting the dentist and the dental nurse, then being taken across to the dental surgery, being made to sit in the dental chair and finally having a dental examination. If the child is fearful of a procedure, such as a filling involving the drill, then in a graded fashion, the child may be first exposed to a prophylaxis cup being moved over the child's teeth with the hand, then polishing teeth with the prophylaxis cup, introducing a fine diamond in a slow speed hand piece in to the mouth but not touching the teeth, the same procedure in the next stage but this time touching the tooth and in the final phase attempting caries excavation with a hand piece. The procedure is more difficult with needle desensitization.

Positive Reinforcement

Reinforcement has been defined as the strengthening of a pattern of behavior, which increases the probability of that behavior being displayed in the future. Approval from the dental team for good behavior will seem to reinforce the pattern of behavior and such behavior will then become the norm for the child in that particular situation. Usually good behavior will carry rewards that will help reinforce that behavior pattern. Such rewards can be by using appreciating keywords such as 'well done, terrific', 'very good' and the like. It is important to use these frequently and supplement them with encouraging body



Fig. 14: Oral hygiene instruction for a group of children in a child friendly non-threatening environment as a method of desensitization (*For color version see plate 19*)

language and a smile. At the end of the treatment session, good behavior should be commended again. Some form of reward, such as a cartoon sticker will also tend to help reinforce the cooperation in subsequent visits. It is important to avoid any reinforcement of poor behavior. If a child is uncooperative and treatment cannot be completed, and the child is allowed to return to the parent, a negative behavior pattern has been established. In such circumstances, it is best to continue and do some small task such as the placement of a temporary filling and then inform the child that the treatment session has finished for that day. The dentist should not display any form of anger. Disapproval methods for negative behavior are limited and may include expressing disappointment or not giving the child the reward (and informing them that the reward is being withheld).

Modeling

This makes use of the fact that individuals learn much about their environment from observing the consequences of other people's behavior. The procedure involves allowing the child patient to observe one or more individuals (models) who demonstrate appropriate behavior in a particular situation (for example while receiving dental treatment). Live models can include the child's siblings, parents or other child patients (Fig. 15). Other methods of modeling include posters, filmed models and other audiovisual aids. Learning through modeling is only effective when the observer is in a state of arousal, meaning that they are attentive and capable of receiving the information. It also helps if the model has more status and prestige as compared to the child so that the child feels like imitating the models behavior. It also helps if the child is able to recognize the positive outcome achieved from the behavior of the model. This technique is especially useful for children who have not had any previous dental experience.

Distraction

This technique attempts to shift attention from the dental setting towards some other kind of situation. Distracters such as videotaped cartoons, stories and music have been used to help children cope with dental treatment.

Coping

This is a mechanism by which the child is able to accept dental treatment. It has been defined as the cognitive and behavioral efforts made by an individual to master, tolerate or reduce stressful situations. The child patient under stress may prefer to draw support, comfort and reassurance from an authority figure in the dental office, this may be a dentist or a nurse. Coping has been considered to be either behavioral or cognitive in nature. Behavioral coping are physical and verbal activities in which the child



Fig. 15: Modeling (For color version see plate 19)

would engage to overcome the stressful situation. In cognitive coping strategies, the child may remain silent but is mentally undergoing thought processes that he has been trained with to make him feel calmer.

Voice Control

This technique utilizes the modification of the intensity and pitch of one's own voice in an attempt to dominate the interaction between the dentist and the child. Sometimes, this has been used alone and in other instances in combination with methods such as the Hand over mouth Exercise. Change in the tone of voice from gentle to firm is effective in gaining the child's attention and reminding him that the dentist is the authority figure and has to be obeyed.

Hypnosis

Hypnosis is an altered state of consciousness characterized by heightened susceptibility to produce desirable behavioral and physiologic changes. When used in dentistry, it has often been termed hypnodontia or psychosomatic suggestion therapy.

Aversive Conditioning

A child who displays a negative behavior and does not respond to moderate behavior modification techniques falls in to the category of Frankel's definitive negative behavior. Aversive conditioning can be a safe and effective method of managing extremely difficult behavioral problems. Under this category, the hand over mouth exercise (HOME) is one of the common techniques used. It was introduced by Dr Evangeline Jordan in 1920 with the purpose to gain the attention of the child so that communication can be achieved. Its use is indicated for a healthy child who can understand but exhibits defiance and hysterical behavior during treatment. It was recommended for use

for children aged between 3 and 6 years. It is important for the child to be able to understand simple verbal commands. It is not meant for use in children under 3 years of age, in handicapped and frightened children or children with special needs. Seeking consent before using this procedure is important. The technique involves placing the operator's hand over the child's mouth to completely stop the verbal outburst until the child shows willingness to cooperate. At this stage the hand is removed from the child's mouth and the child is complimented for good behavior. In this method, the child's airway is not restricted and the total duration of HOME is 20 to 30 seconds. Several variations of HOME have also been proposed such as hand over mouth and nose, airway restricted, towel over mouth, dry or wet towels over nose and mouth.

Physical restraints are a last resort for handling the uncooperative child in the nonpharmacologic techniques. Restraints may be required for children who are hypermotive, stubborn and defiant. The physical restraints have been classified as being either active or passive and are meant to restrict movement for the head, hands or feet and body of the child. The active restraints involve the child being actively held in the chair or parents lap to prevent any movement. A passive restraint is usually a commercially available product. For the body, restraints include the Pediwrap, Papoose board, sheets and bean bags with straps; for extremities, examples are Velcro straps and Posey straps. For the head, a head positioner or a forearm body support may be used. Mouth props are useful at the time of local anesthesia to prevent the child from closing his mouth. These have also been of help in young children who feel fatigued and the mouth prop helps keep the mouth open for a long appointment. Of late, many aversive techniques have fallen out of favor for use in the clinical environment and the use of pharmacologic techniques has been employed for the difficult child patient.

Pharmacologic Techniques

Sedation

Conscious sedation techniques have been employed for the management of the anxious child. Conscious sedation has been defined as a minimally depressed level of consciousness that retains the patient's ability to maintain a patent airway independently and continuously and to respond appropriately to physical stimulation and/or verbal command. The sedated child patient is therefore conscious throughout the procedure and in command of all normal protective reflexes. There are several routes for administering sedation to the patient and include the inhalation route, oral, intramuscular, intravenous and rectal routes. In the United Kingdom, inhalation route is a

common technique for sedating the child patient; others are rarely used. The inhalation sedation technique was pioneered, named relative analgesia. It is divided in to 2 stages: an initial stage of relative analgesia and then total analgesia. The drugs used in this technique are a mixture of oxygen and nitrous oxide as gases. Three planes of analgesia have been described depending upon the concentration of nitrous oxide used. Plane 1 produces moderate sedation and analgesia at levels of 5 to 25 percent nitrous oxide. At concentrations of 20 to 55 percent nitrous oxide, Plane 2 is achieved which includes dissociation sedation and analgesia. Plane 3 is acquired at 5 to 70 percent nitrous oxide which is known as total analgesia. Even though some analgesic effect is accrued from the procedure, the use of local anesthetic is still required, but the patient is more open to the suggestion of having this performed once he has been sedated. Specially designed continuous-flow machines are required for the methods and they have several safety features built in to them. Two commonly used machines in the UK are the Quantiflex RA and the MDM machines. In this procedure, a nasal mask is placed over the patient's nose and this is attached to tubing with oxygen and nitrous oxide inlets and outlets. At the start of treatment, a 100 percent oxygen concentration is maintained and the patient is allowed to breathe for at least 2 minutes. During this time, the operator checks for any leaks around the patient's nasal mask and ensures that the bag attached to the relative analgesia machine is moving. The flow rate of the gas can also be adjusted to an optimum at this stage. Following this, nitrous oxide is incrementally introduced and the dose titrated to a level that the patient is comfortable to accept. The maximum nitrous oxide concentration that is possible for delivery is 70 percent. The patient may have different sensations as nitrous oxide is increased ranging from tingling in the extremities, have a warm sensation in the body, sense of detachment, feeling drowsy to euphoria similar to alcoholic intoxication. These sensations are usually, but not always regarded as being pleasant. The main advantage of this technique is rapid recovery and the patient can be discharged within 5 minutes of from the end of the procedure. Usually, no special instructions are required preoperatively. However, children with upper respiratory infections, pulmonary disease and nasal obstructions are not candidates for relative analgesia.

General Anesthesia

This is the last resort for the management of the extremely anxious child patient. It is frequently used when multiple treatment are to be performed on the uncooperative child. Several teeth may be extracted and restored as well as preventive treatment also provided in the same general anesthesia session (Fig. 16).



Fig. 16: Treatment under general anesthesia
(For color version see plate 19)

EXTRACTION

An ideal extraction is the painless removal of the whole tooth or root or the remaining portion of the tooth with minimal trauma to the investing tissues so that the wound heals uneventfully and no future problems are created. For the young child who requires the removal of a primary tooth, the dentist should recognize the proper sequence of all the procedures. The dentist prepares the child by using a sensitive approach through his selection of words that indicate to the child the nature of the procedure. Figure 17 shows an extraction of a lower right molar tooth.

Indications^{14,87}

- Teeth which are hopelessly carious and not restorable.
- When there is extensive decay, which has resulted in death of the pulp and decay reaches to the furcation area of the roots
- When the primary teeth interfere with the normal eruption and alignment of their permanent successors:
 - Improper resorption of root causing deflection of erupting tooth found mainly in lower anteriors
 - Irregular resorption of the roots of molars, one root being resorbed more slowly than the others
 - Retained primary teeth when a permanent tooth is present and in normal position to erupt
- When there is a sinus opening through the mucoperiosteal membrane overlying the root
- When radiograph shows the evidence of periapical pathosis of poor prognosis
- When the root is fractures as a result of trauma and root canal therapy will not yield successful outcome
- When rudimentary supernumerary teeth or mesiodens are found in radiograph preventing the eruption of permanent teeth or causing any malalignment.

Contraindications

- Acute infections like stomatitis, Vincent's infection and herpetic stomatitis should be eliminated before an extraction is done because if virulence or the number of the organisms is high, it could result in bacteremia/viremia in the host. Exception to this condition is acute dentoalveolar abscess with cellulites, which requires immediate extraction of the primary tooth or an endodontic infection
- Malignancy contraindicates extraction as trauma enhances the speed of growth and spread of tumors. On the other hands, extractions are strongly indicated if the jaws and associated areas are to receive radiation therapy for the same malignancies
- Blood dyscrasias
- Diabetes mellitus

Many of these contraindications are relative in nature and extractions can be performed with adequate care, precautions and premedication. There are two absolute contraindications of extractions:

- Hemangioma
- Arteriovenous fistulas

In patients with hemophilia, rubber band extractions were previously used. A rubber band is placed around the tooth and results in the necrosis of the attachment apparatus with the tooth slowly extruding out of the socket. Today, appropriate cover with desmopressin, tranexamic acid mouthwashes and factor concentrates may be used, depending on severity of disease and nature of procedure.

Preoperative Preparation of the Parent and the Child

Preparing the Parent

- Dentist must have parental consent before the procedure
- When there is a doubt whether a carious primary tooth can be restored, the possibility of its being removed should be discussed with the parent before the treatment begins³⁸
- The parent may be concerned about excessive post-operative bleeding or pain. Reassure the parent that such pain usually does not occur when primary teeth are removed.
- Instruct the parent not to discuss with the child what the dentist will do. Rather, let the dentist do it. The parent's choice of words can be poor and they can unintentionally make the child fearful.

Preparing the Child¹⁴

- The 8 to 10 years olds who need teeth removed should have a working through period. This age group better adjusts to the removal of teeth when they are told four to seven days in advance of the procedure. However,

the younger children should be told on the day of the appointment about the procedure

- Tray containing the armamentarium for the removal of the teeth should be kept behind the dental chair
- Never hold the needle in front of the child
- Before giving local anesthesia, explain to the child that a sensation of pinching or an ant biting may be felt.
- It is extremely important that the child realizes the difference between pressure and pain
- Explain the sensation of numbness so that the child is prepared for it
- When checking for efficacy of the local anesthetic, note the eye reaction of the child as the verbal response may not be reliable

Precautions while Extracting

- While extracting the primary teeth, care must be exerted not to place the beaks of the forceps high up on the roots. There is a great possibility of damaging or inadvertently removing the partially formed permanent tooth with the primary tooth. In such an event, the permanent developing tooth must be replaced and the soft tissues sutured over the alveolus to hold the tooth in position (Fig. 17).
- Currettes should not be used for removing granulo-mas following primary tooth extraction because of danger of injury to the permanent tooth.

Control of Hemorrhage in Children Following Extraction

- Pressure packing with a moist gauze sponge held over the operative site for half an hour is the best method. The child should be asked to hold the gauze in between the teeth for this time duration
- For persistent bleeding, gel foam dipped in thrombin can be utilized. Surgicel may also be used for the purpose

Postextraction Instructions for the Child

- Child is to hold gauze in the mouth over the extraction socket for half an hour. Subsequently, the gauze pack is removed and immediately disposed out of the child's sight. After it has been ensured that a blood clot has been formed, the child should be dismissed from the dental clinic
- Child is not instructed to bite their lips as it may lead to ulceration. This is important since the effect of the anesthesia would last for about an hour and the child may constantly bite the lip in an attempt to feel the presence of the lip
- Clear instructions not to spit out the saliva but to swallow it. Spitting may dislodge the blood clot and lead to dry socket formation
- All liquid intake is to be from a glass. Straws are an absolute contraindication following extraction as the

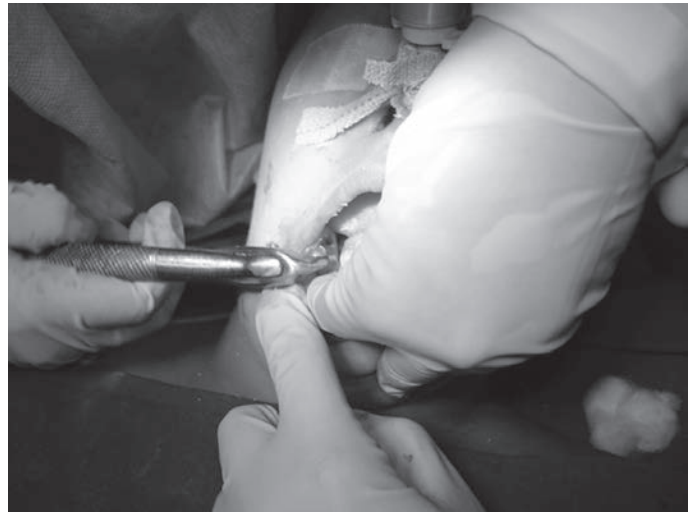


Fig. 17: Extraction in the lower right quadrant
(For color version see plate 19)

negative force generated during the process of sucking may again disturb the blood clot

- Vigorous mouth rinsing to be avoided

Postextraction Instructions for the Parent

- Reinforce all the instructions given to the child
- A light, soft diet is recommended comprising of cold food only. No hard food is to be given to the child during the first 24 hours after extraction. Icecream, porridge, juices and the like, which do not entail any chewing should be the foodstuffs of choice.
- Appropriate analgesics can be prescribed for a period of two days^{88,89}
- A bloody pillow may be seen on the next day. This is attributable to slight oozing of blood from the socket, which gets mixed with saliva. If this saliva finds its way on to the pillow, it gives the parent an impression that there has been tremendous bleeding from the socket overnight. Parent should be reassured that this is not a cause to worry and should thus be pre-warned of such an event
- Instructions to call the dental surgeon in case of any symptoms developing in the child.

Extraction of Natal and Neonatal Teeth

Teeth that appear in an infant right from birth have been termed natal teeth and those that appear within the first month of life are known as the neonatal teeth.^{90,91} The occurrence of natal and neonatal teeth is rare; the incidence varies from 1:1,000 to 1:30,000.^{90,91} The teeth most often affected are the mandibular primary incisors.⁹² The occurrence of such teeth has been especially associated with the Riga Fede syndrome, a condition caused by the natal or neonatal tooth rubbing the ventral surface of the tongue during feeding leading to ulceration.^{90,93,94} Natal

or neonatal molars have been identified in the posterior region and may be associated with systemic conditions or syndromes (e.g. Pfeiffer syndrome, histiocytosis X).^{2,95,96} Although many theories exist as to why the teeth erupt prematurely, currently no studies confirm a causal relationship with any of the proposed theories. The superficial position of the tooth germ associated with a hereditary factor seems to be the most accepted possibility.⁹¹ These teeth generally belong to the deciduous complement and are frequently found to be slightly mobile. If the tooth is not excessively mobile or causing feeding problems, it should be preserved and maintained in a healthy condition if at all possible. There are reports of breast feeding problem with such teeth.⁹⁷ Close monitoring is indicated to ensure that the tooth remains stable. If excessively mobile, it carries the risk of being aspirated by the child during feeding. Failure to diagnose and properly treat this can result in dehydration and inadequate nutrient intake for the infant.⁹³ Treatment should be conservative and focus on creating round, smooth incisal edges.⁹⁸ If conservative treatment does not correct the condition, extraction is the treatment of choice. An important consideration when deciding to extract a natal or neonatal tooth is the potential for hemorrhage. Extraction is contraindicated in newborns due to risk of hemorrhage. The lack of circulating thrombin in the initial period of life, it is imperative that an initial dose of vitamin K be administered to the child to promote the formation of clotting factors. Subsequently extraction of such teeth can be done.

ORAL HABITS

Oral habits may be part of normal development; a symptom with a deep rooted psychological basis or may be the result of abnormal facial growth. Some of these have also been linked with medical conditions or adverse outcomes, including associations between acute otitis media and early cessation of breast feeding.⁹⁹ Digit sucking, lip and nail biting, bruxism, mouth breathing, tongue thrusting, etc. may be considered as some of the common habits seen in children.¹⁴ These habits bring about harmful unbalanced pressures to bear upon the immature, highly malleable alveolar ridges, the potential changes in position of teeth, and occlusion, which may become decidedly abnormal, if these habits are continued for a long time. It is important for the paediatrician, general dentist and the paedodontist to institute an early program of interceptive orthodontics in order to achieve harmonious occlusion and esthetics.

Definitions

Dorland: Habit can be defined as a fixed or constant practice established by frequent repetition.

Buttersworth: Defined a habit as a frequent or constant practice or acquired tendency, which has been fixed by frequent repetition.

Mathewson: Oral habits are learned patterns of muscular contractions.

Classification

- Obsessive (Deep rooted)
 - Intentional
 - a. Digit sucking
 - b. Nail biting
 - c. Lip biting
 - Masochistic
 - a. Gingival stripping
- Non-obsessive (Easily learned and dropped)
 - Unintentional
 - a. Abnormal pillowing
 - b. Chin propping
 - Functional habits
 - a. Mouth breathing
 - b. Tongue thrusting
 - c. Bruxism.

Development of Habit

The newborn develops some instincts, which are composed of elementary reflexes. An instinct is one where the pattern and order are inherited, while in a habit the pattern and order are acquired, if constantly repeated during the lifetime of an individual. At the beginning the infant makes an effort by frequent learning and practice, later on the muscles start responding more readily.

Sucking Reflex

The process of sucking is a reflex occurring in the oral stage of development and is seen even at 29 weeks of intrauterine life and may disappear during normal growth between the ages of 1 and 3-1/2 years. It is the first coordinated muscular activity of the infant. It is important for meeting both psychological and nutritive needs during feeding and apart from seeking nutritional satisfaction they also experience pleasurable stimuli from lips, tongue and oral mucosa and learn to associate these with enjoyable sensations, such as closeness of a parent. Babies who are restricted from sucking due to a disease or other factors become restless and irritable. This deprivation may motivate the infant to suck the thumb or finger for additional gratification.

Sucking Habits/Thumb/Digit Sucking

It is thought that such sucking behavior arises from psychological needs, so that normally developed infants have an inherent biological drive for sucking. These habits are often without psychological abnormality, though thumb or pacifier sucking beyond preschool years may reflect some psychological disturbance.

Sucking habits have been classified as:

- Nutritive sucking habits, e.g. breast feeding, bottle feeding

- Non-nutritive sucking habits (NNS habits), e.g. thumb or finger sucking, pacifier sucking

Johnson: Classified NNS habits based on factors that influence the severity of the habit. (Table 6)

Thumb sucking is a habit of concern to specialists in various fields, such as psychiatrists, psychologists, pediatricians, pediatric dentists, orthodontists and speech therapists. Despite extensive research considerable controversy still exists regarding sucking habits.

Thumb sucking and finger sucking can more generally be termed as digit sucking.¹⁰⁰

Classification

- *Normal thumb sucking:* Considered normal during the first and second year of life and is usually seen to disappear as the child matures. It is not known to generate any malocclusion
- *Abnormal thumb sucking:* When thumb-sucking habit persists beyond the preschool period then it could be considered as an abnormal habit. If the habit is not controlled or treated during this stage, it may cause deleterious effects to the dentofacial structures.

This can again be divided into:

- *Psychological:* The habit may have a deep-rooted emotional factor
- *Habitual:* The habit does not have a psychological bearing however the child performs the act out of habit. The habit is a cause for concern due to its potential to cause malocclusion.

Table 6: Classification of NNS habits

Levels	Descriptions
Level I (+/-)	Boys or girls of any chronological age with a habit that occurs during sleep.
Level II (+/-)	Boys below age 8 with a habit that occurs at one setting during waking hours.
Level III (+/-)	Boys under age 8 years with a habit that occurs at multiple settings during waking hours.
Level IV (+/-)	Girls below age 8 or a boy over 8 years with a habit that occurs at one setting during waking hours.
Level V (+/-)	Girls under age 8 years or a boy over age 8 years with a habit that occurs across multiple settings during waking hours.
Level VI (+/-)	Girls over age 8 years with a habit during waking hours.

(+/-) designates willingness of the parents to participate in treatment.

Subtelny has graded thumb sucking into 4 types:

Type A: This type is seen in almost 50 percent of the children where a whole digit is placed inside the mouth with the pad of the thumb pressing over the palate while at the same time maxillary and mandibular anteriors contact is present.

Type B: This type is seen in almost 13 to 24 percent of the children wherein the thumb is placed into the oral cavity without touching the vault of the palate while at the same time maxillary and mandibular anteriors contact is maintained.

Type C: This type is seen in almost 18 percent of the children where the thumb is placed into the mouth just beyond the first joint and contacts the hard palate and only the maxillary incisors but there is no contact with the mandibular incisors

Type D: This type is seen in almost 6 percent of the children when very little portion of the thumb is placed into the mouth.

Theories

Various theories have been proposed by psychologists to explain non-nutritive digital sucking and include the classical Freudian theory, the learning theory, oral drive theory and theory proposed by Johnson and Larsen which is a combination of psychoanalytic and learning theories (Fig. 18).

Maintenance of the Habit

Most children would cease digit sucking early in their developmental process by the age of three to four years. But an acute increase in the child's level of stress or anxiety due to some underlying psychological or emotional disturbances can account for continuation of a digit sucking habit, with conversion of an empty habit into a meaningful stress reduction response.

Causative Factors¹⁴

Socioeconomic Status

Families with high socioeconomic status have ample sources for providing nutrition to the child and the mother can feed the baby frequently to satisfy the infant's hunger. However, mothers belonging to the low socioeconomic group are unable to provide the infant with sufficient breast milk and the infant thus suckles intensively for a long time to get the required nourishment thereby also exhausting the sucking urge. Thus children from higher socioeconomic families have been reported to have a higher incidence of thumb sucking.

Working Mother

The sucking habit is commonly observed to be present in children with working parents. Such children may be

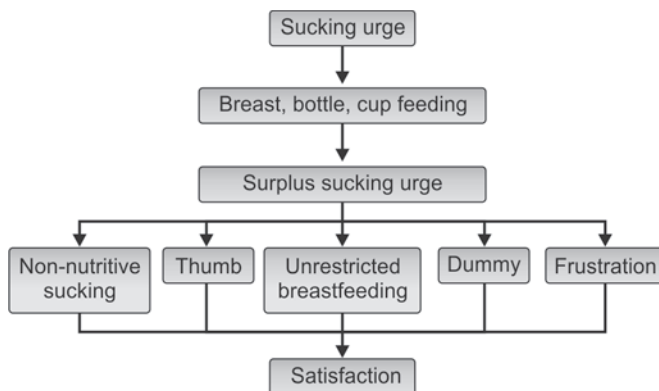


Fig. 18: Etiology of different sucking habits

taken care of by helpers/at nurseries and thus tend to develop some feeling of insecurity.

Number of Siblings

The development of the habit can be indirectly related to the number of siblings. As the number increases the attention meted out by the parents to the child gets divided. A neglected child may attempt to compensate his feelings of insecurity by the habit.

Order of Birth of the Child

It has been noticed that the later the siblings rank of a child, the greater the chance of having an oral habit.

Social Adjustment and Stress

Digit sucking has also been proposed as an emotion based behavior related to difficulty with social adjustment or with stress. The psychological effects may be compounded by the emotional impact of peer pressure and punitive and scolding parents.

Feeding Practices

Various controversies exist in this regard as to the influence of feeding modes to the development of the habit. Thumb sucking is seen to be more frequent among breast-fed children. Yet abrupt weaning from the bottle or breast has so been hypothesized to contribute to acquiring an oral habit.

Age of the child

The time of appearance of digit sucking habit has significance.

In the neonate: Insecurities are related to primitive demands as hunger.

During the first few weeks of life: Related to feeding problems.

During the eruption of the primary molar: It may be used as a teething device.

Still later: Children use the habit for the releases of emotional tensions with which they are unable to cope, taking refuge in regressing to an infantile behavior pattern.

In spite of contrasting views regarding the etiology there is some agreement that if the habit continues beyond the age of 6 to 7 months, it is difficult to break it until the child is 4 to 5 years. Thus it was suggested that the habit should be viewed by the clinician as a behavioral pattern of multivariate nature. Thumb sucking may begin for one reason and be sustained by other factors at different ages.

Diagnosis of Digital Habits

History

This should involve questions pertaining to feeding habits, parental care, work and occupation of mother, psychological evaluation and stress for the child, the nature of the habit, other habits concomitantly practiced by the child, the frequency, occurrence and duration of the habit.

Extraoral Examination

The digits

Digits that are involved in the habit will appear reddened, clean, chapped and with a short fingernail (a clean dish-pan thumb). Fibrous roughened callus may be present on the superior aspect of the finger and a deformation of the finger may be seen.

Lips

Upper lip may be short and hypotonic, passive or incompetent during swallowing and this leads to a further increase in the proclination of the upper anterior teeth.

Facial Appearance

A long narrow face with a narrow maxilla and a retruded mandible.⁹⁹

Other Features

Active thumb suckers also have a higher incidence of middle ear infections and frequently have enlarged tonsils accompanied by mouth breathing.⁹⁹

Intraoral Examination

Most studies have reported on the effects in the primary dentition and have used questionnaires to identify the habit type. Several dental anomalies that can be drawn from such studies include:

Maxillary anterior proclination and mandibular retroclination

Associations between dental arch abnormalities and digit sucking were reported as early as 1870s. When a child places a thumb between the teeth, it is usually placed at an angle so that it presses labially against the lower incisors and lingually against the upper incisors. This direct

pressure is responsible for the displacement of the incisors.^{101,102} This may lead to the development of a Class II Division I malocclusion.

Anterior open bite

This type of malocclusion arises due to a combination of factors:

- Interference with normal eruption of incisors due to an interposed thumb
- Excessive eruption of posterior teeth due to separation of the jaws, which alters the vertical equilibrium on the posterior teeth.⁹⁹

Constriction of maxillary arch

This may be because of the failure of the maxillary arch to develop in width due to an alteration in the balance between cheek and tongue pressures.⁹⁹

Posterior crossbite

It occurs as a consequence of constriction of the maxillary arch. The unbalanced muscle forces on the maxilla exerted by the cheek muscles are not met by the pressure from the lingual musculature, which is normally present.¹⁰³

Prevention

The etiology of thumb sucking focuses on a predominant psychological background. Its prevention should be directed toward the motive behind the habit. Parents when questioned may reveal that the child practices the habit when bored and left to himself, or it could be just before he goes to sleep. In such cases, the parents can be counseled on keeping the child engaged in various activities. When parents are at home, they should be advised to spend ample time with the child. At night, this can be reinforced by singing lullabies, playing soothing music or by narrating stories till the child sleeps. Care should be taken when feeding infants in that the duration of feeding should be adequate so as to enable the child to exhaust his sucking urge and feel completely satisfied.

Treatment Considerations

- *Psychological status of the child:* Diagnosis and management of any psychological problem should be planned before treatment of any potential or present dental problem.¹⁰⁴
- *Age factor:* If the child desists with the finger sucking habit within the first three years of life, the damage incurred, such as open bite, is temporary provided the child's occlusion is normal. No treatment is provided in this age group. If a malocclusion is caused by digit sucking and the habit is discontinued between the age of 4 and 5, self correction of the habit can be expected. When this continues after six years or into the mixed dentition phase, the malocclusion will not self-correct.

- *Motivation of the child to stop the habit:* This approach involves dealing directly with the child and explaining the problems associated with the habit. The first step, which would facilitate the treatment is to instill a desire in the child to stop.
- *Parental concern regarding the habit:* It is important that the child should not be embarrassed or criticized rather help should be offered to deal with this difficult habit. Negative reinforcements in the form of threats, nagging and ridicule would only entrench the habit.
- *Other factors:* Self-correction again depends on the severity of malocclusion, anatomic variation in the perioral soft tissue and the presence of other oral habits, such as tongue thrusting, mouth breathing and lip biting habits.

Treatment Plan

- Psychological therapy
- Reminder therapy
 - Extraoral approaches by employing hot tasting, bitter flavored preparations or distasteful agents applied to fingers or thumbs. For example, Cayenne pepper, quinine or asafetida. This is only effective if the habit is not firmly entrenched. A long sleeve gown has been also attempted which prevents the child putting the digit directly into the mouth and thus eliminating the pleasurable sensation from digit sucking.¹⁰⁵
 - Intraoral approaches include various orthodontic appliances employed to break or attenuate the habit. Removable appliances include palatal crib, rakes, palatal arch, lingual spurs and so on. Fixed appliances such as upper lingual tongue screens appear to be more effective in breaking these habits. If the child has made appreciable changes in his habit by 3 months, the appliances can be safely withdrawn.
- Mechanotherapy
 - Fixed intraoral antithumb sucking appliance
 - Blue grass appliance.¹⁰⁶

Haskell (1991) introduced this appliance, for children with a continued thumb sucking habit, which is affecting the mixed or permanent dentition. It consists of a modified six sided roller machined from Teflon to permit purchase of the tongue. This is slipped over a stainless steel wire soldered to molar orthodontic bands and placed intraorally for 3 to 6 months. Instructions are given to turn the roller instead of sucking the digit.

Mouth Breathing

This habit may develop due to nasal obstructions which may be transient, nasal congestion or sometimes during periods of exercise or activity. Some children are known

to be mouth breathers primarily because of chronic nasal congestion (asthma/allergy), enlarged adenoids or those with cleft deformities. The prevalence of this habit is hard to quantify. A study has reported it to be 40 percent for first-grade children when observed for 15 minutes.¹⁰⁷ Another study asked parents whether their children were regular mouth breathers and reported a prevalence of 9 percent at age 4 years. Mouth breathing can effect orofacial development as it affects the position of the tongue.⁹⁹ Mouth breathers also tend to have an open mouth posture. Because of these factors, the tongue is usually lower in the mouth rather than resting against the roof of the palate. Thus the maxillary arch is generally narrower in these children. The open-mouth posture for the mouth breathing children also leads to an over-eruption of the molars. This leads to a downward and posterior rotation of the mandible. This leads to an increase in face height and a retrusive mandible. It is desirable that an early correction of the respiratory problem be made so as to avoid the development of altered skeletal patterns of growth. Referral to an otolaryngologist should be undertaken to prevent complicated fixed orthodontic treatment at a later date.

Bruxism

Bruxism is the habitual grinding of teeth while the child is sleeping. Its incidence has been reported between 20 and 24 percent in children and it may be linked to stress and some parasomnias.^{108,109} Studies have suggested that this decreases with age, is largely self-limiting and rarely requires intervention.

CONCLUSION

The pediatrician is most often the first port of call for all parents whose child is unwell. This also includes dental problems. It is important for the physician to be able to recognize some of the maladies and make an appropriate onward referral to a dentist or dental specialist for required management. Advice in emergency situations to the parents may also be required and a closer understanding of dental disease and issues relating to dentistry will help improve health care provision for the child patient.

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Industrialization and Globalization: Negative Aspects

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Environmentalism is a universally accepted concept, however, its actual meaning and its relationship to health outcomes is not always clear. In 1984, 2,000 people died of a hazardous chemical release accident in Bhopal, India. On March 24, 1989, 11 million gallons of North Slope crude oil poured into the unsullied waters of Prince William Sound when the Exxon Valdez struck a reef. Contingency plans created for dealing with such a spill failed after 12 years of trouble-free operations. The Prince William Sound has become a laboratory for scientific research in oil pollution of a pristine environment.¹

The Persian Gulf War resulted in massive environmental pollution. Oily clouds from burning wells rose as high as 20,000 feet. From the blackened burning landscape to the fine mist of oil particles suspended in the air, the Gulf suffered an environmental insult the human health effects of which are yet to be determined. The US military now struggles to understand the cause of an illness termed the “Gulf War Syndrome”.

In 1992, at Rio de Janeiro, the earth summit developed a comprehensive document termed Agenda 21 for planning in areas affecting relationships between the environment and the economy.² Agenda 21’s proposal to adopt precautionary approaches in managing the life cycle of toxic chemicals to prevent and reduce risk to human health and the environment involved four programs:

- Promote the prevention and minimization of hazardous waste
- Promote and strengthen institutional capacities in hazardous-waste management
- Promote and strengthen international cooperation in the management of trans-boundary movements of hazardous waste
- Prevent illegal traffic in hazardous waste.

Emergence of new diseases and old diseases can be traced to factors of social disruption, war, human behavior, lack of public health infrastructure, and environmental disruption (Table 1).³

Table 1: Impact of environment

<i>Categories</i>	<i>Examples</i>
Human behavior	Sexual behavior; drug use; travel; diet; outdoor recreation; use of child-care facilities
Environmental changes	Deforestation and reforestation; changes in water ecosystems; flood and drought; famine, global warming
Public health insurance	Curtailment or reduction in prevention programs; inadequate communicable disease surveillance; lack of trained personnel (epidemiologists, laboratory scientists, vector and rodent control specialists)
Microbiological adaptation and change	Changes in virulence and toxin production; development of drug resistance; microbes as cofactors in chronic disease
Societal events	Economic impoverishment; war or civil conflict; population growth and migration; urban decay.
Health care	New medical devices; organ or tissue transplantation; drugs causing immunosuppression; widespread use of antibiotics
Food production	Globalization of food supplies; changes in processing and packaging

Climate change is another potential public health challenge that can result in disease emergence. The global temperature has increased between 0.3°C and 0.6°C during last century and has been strongest at night in the Northern Hemisphere. A CO₂, a major “greenhouse” gas, arises from natural sources as well as human-related fuel combustion. Computer modeling predicts that, should the atmospheric CO₂ double over next 100 years, the global temperature would increase 1.5°C to 4.5°C (3°F to 9°F). Such a temperature change would cause the seas to rise 15 to 90 cm and alter the ecological pattern of infectious diseases such as malaria, yellow fever, encephalitis, cholera, and dengue fever.⁴

Another effort was made a few years later when the world body met at Vancouver.

THE VANCOUVER STATEMENT ON THE GLOBALIZATION AND INDUSTRIALIZATION OF AGRICULTURE—JUNE 1998

Five decades of the so-called Green Revolution have not only led to the destruction and contamination of water, soil, biodiversity, and human communities, but exacerbated hunger worldwide. One of the most critical impacts of industrial agriculture is climate change, which will destroy the natural basis of agriculture itself. The patenting of life, corporate ownership and manipulation of our genetic heritage is one of the greatest threats ever imposed by industrial agriculture: the human right to feed, clothe and shelter ourselves and our families is at stake.

Institutions and treaties such as the World Trade Organization, the General Agreement on Tariffs and Trade, Codex Alimentarius, North American Free Trade Agreement, the Food and Agriculture Organization, and the European Union have accelerated the process of agricultural industrialization and globalization while promoting the rights of corporations over those of people.

- Farmers around the world are farming in ways that respect their unique ecological and cultural communities. Building on their wisdom, all farms of the twenty-first century can be ecologically regenerative, community sustaining, biologically and culturally diverse, as well as energy conserving. We must not only build upon the existing knowledge and vision of farmers, but we must expand partnerships and create coalitions that serve to re-empower them.
- In order to rescue our food system, we need more skilled farmers who have access to land, seed, and the knowledge of local biological systems.
- A healthy food system needs clean land, air, water and soil and the right to save seeds to ensure future harvests.
- Scientific organizations and transnational corporations that are experimenting with, and releasing poisons, synthetic compounds and genetically modified

organisms into the biosphere should be held fully accountable for the safety of their practices and products.

- Corporations, scientists and governments should honor the precautionary principle and take preventive action in the face of scientific uncertainty in order to avoid cultural and ecological harm.
- They concluded that the consumers have a right to know where their food comes from, what is in it, and how it was produced. Furthermore, farmers and consumers have a right to maintain local control over food production, distribution and consumption.
- Our bodies, our plants and animals, our air, water, land, and soil, are not commodities and are not patentable. When a food production system violates the rights of citizens and the natural order of the planet's ecosystems, it is essential that we the people make use of our inalienable freedom to correct those who abuse.

SEMICONDUCTOR MANUFACTURING HAZARDS

Electronics is projected to be the world's largest industry in terms of revenue. Semiconductor integrated circuits, known as chips, underpin the entire electronics industry. This completed chip poses many health problems. Three broad areas of concern are:

- The clean room environment
- The manufacturing process and tools
- Selected chemicals used.

CLEAN ROOM ENVIRONMENT

In clean room workstation, air is always being pushed out towards the worker's breathing zone. Though this ventilation technique protects the product under the hood from any particles in the room, but can expose the worker to vapors of other air contaminants being generated in the workstation. As the bulk of air entering the clean room is re-circulated from the core areas, workers can be exposed to any contaminants released in the core area. Among these contaminants are gas leaks from uncontrolled lines or cylinders, oil mists from pumps and tools, vapors from wet chemical spills, and air from work aisles that communicate with the same core. Exhaust ventilation is provided to remove contaminated air. It is necessary to provide a fine balance between the laminar airflow and exhaust to prevent the product from being contaminated, as well as to prevent emissions from escaping from the front of the wet station towards the worker.⁵

CLEAN ROOM HEALTH PROBLEMS

Semiconductor clean rooms are hot, dry, and windy. Humidity is maintained constant from 15 to 50 percent to protect wafers from condensation of water droplets. This warm, relatively dry air moves constantly at 80 to 100

linear feet per minute. These three conditions, especially the rapid air movement, dehydrate the stratum corneum of the skin and the mucous membranes. "Low humidity occupational dermatosis" can manifest as pruritus, urticaria or eczema.

Upper Respiratory Problems

Complaints of mucous membrane, dryness of eyes, nose and throat are relatively common. Recurrent epistaxis, sinusitis, and laryngitis may occur in a small percentage of workers.

Eye Problems

The semi-desert conditions of the semiconductor clean room can also contribute to eye problems. Some workers complain of constantly irritated eyes, but usually this can be ameliorated by the use of over-the-counter eye drops to moisturize the conjunctivae.⁵

Multiple Chemical Sensitivities

A proposed and controversial syndrome termed multiple chemical sensitivities refers to the occurrence of diverse symptoms involving multiple organ systems (e.g. CNS, GIT, skin, respiratory tract) occur when the individual is exposed at very low levels to multiple chemically unrelated compounds.⁶

Mass Psychogenic Illness

Chemical odors are common in clean room settings. The combination of these odors with monotonous work, and the tendency to be isolated from management, makes a natural setting for mass psychogenic illness. Mass psychogenic illness (MPI) is not a clinical diagnosis; it is a sociologic phenomenon describing the collective behavior of a group of people. The words psychogenic illness implies that psychopathology is present in the affected individuals. Quite the opposite, the response although not conscious, is a natural health coping reaction to a stressful work situation perceived to be unresolvable.⁷

PLASTIC MANUFACTURING

Articles made from plastics are found in appliances, automobiles, toys, home furnishings, clothing, insulation, food and beverage containers, and countless other applications.

Health Hazards

Most of the polymerization processes take place in closed systems, and health hazards of resin manufacturing are similar to those of the petrochemical industry.⁸⁻¹¹ Various procedures in plastic manufacturing which may cause hazards may be broadly categorized as follows:

- Workers may have exposure to dust and vapors containing chemical intermediates, polymers, and additives

during loading, mixing, palletizing, and maintenance operations.

- Plastic processing equipment operates using high temperatures and pressures and needs to be equipped with proper guards and safety rails to avoid serious burns, amputations, and crush injuries.
- Finishing operations may expose workers to a variety of other chemical compounds, such as solvents and adhesives.
- Cutting of plastics may result in repetitive motion injuries, such as tendonitis, sprains, and carpal tunnel syndrome.

Combustion Product Hazards

Overheating of plastics results in thermal decomposition, as well as release of oligomers, monomers, and other combustion products. Although combustion hazards are primarily respiratory irritants (hydrochloric acid, aldehydes), significant pulmonary injury from nitrogen oxides and phosgene, as well as systemic poisoning from CO and cyanides, may occur.

Plastics are produced by polymerization of ethylene and propylene. And both ethylene and propylene are asphyxiant gases. Several of the organometallic catalysts used are potent respiratory and skin irritants. Occupational asthma has also been reported due to both the agents.⁸

High-density polyethylene is used to form containers ranging from fuel tanks to milk bottles. Low-density polyethylene has higher clarity and is used for films, coatings, shrink-wrap, and food packaging. Polypropylene is used in containers, including medical syringes, as well as automotive components.

Polyvinyl Chloride

Polyvinyl chloride (PVC) is made through polymerization of vinyl chloride monomer (VCM), which is a known human carcinogen, and is associated with tumors of the brain, liver, and the lung. In India, VCM is imported in a compressed and liquefied form and is very dangerous to transport as any leaks can lead to explosions. A chemical called tetrahydrofuran is used as a solvent in the polymerization of PVC. It may be inhaled or ingested causing irritation of the eyes, nose and respiratory tract, headache, dizziness, and potential damage to the central nervous system, liver, and kidneys.¹⁰

The PVC is used in upholstery fabrics (as PVC rexine), shoe soles, teethingers for babies, flexible toys like dolls, pipes or tubing's, medical disposables like blood or plasma transfusion bags, and more recently as venetian blinds and shower curtains.

Of all the plastics used in India, PVC has the biggest market share at 28 percent. Polyvinyl chloride is now trying to enter areas such as stationary, apart from providing

cabling, such as for the telecom industry. The PVC is the world's most toxic plastic, spreading sickness in each stage of its life-cycle.

Plasticizers are additives, which reside between the PVC molecules and give the plastics their flexibility. As they are not chemically bound, they have the tendency to migrate into foods wrapped in PVC plastic, carrying other components of the plastic such as stabilizers.

The PVC can be colored by mechanically dispersing solid pigment particles so that each is covered with binder molecules, without trapping air between binder and pigment. Since colorants are not polymerized with pigment, they too can migrate. The additives used commonly include phthalates, colorants containing lead and calcium, and stabilizers containing barium.

As PVC contains chlorine, on burning it releases a toxic acidic gas, as well as dioxins and other organochlorines. The incineration of a kilogram of PVC produces up to 50 g of dioxin (TEQ), which is enough to initiate cancer in 50,000 laboratory animals. The smoke also contains hydrogen chloride (HCl) and this combines with moisture (for example, in the lungs) to form hydrochloric acid, which causes serious burns. It is for this reason that in Delhi, many firemen suffered from acute respiratory distress after several hours of fighting the great PVC fire in 1995.

Toys and Teethers

For children exposure to PVC outside the womb begins with toys. Many flexible, chewable plastic toys are made of PVC. When children bite or chew them, they also take in phthalates, as they are not bonded well with plastics and easily leach out. The most commonly used phthalate, DEHP, is a possible human carcinogen. It may cause renal failure, hepatic toxicity, reproductive abnormalities, including testicular atrophy, subtle affects on sperm production, and cell line transformation.

A study of PVC toys in India showed that Indian toys were most phthalate rich. These included teether's, in which DEHP was found.

Furthermore, PVC flooring releases high concentrations of plasticizers and contributes to 'sick building syndrome', a condition commonly reported in modern office blocks, when persons inside the buildings begin to feel tired and ill. A child is particularly very susceptible to PVC flooring as they spend a lot of time on the floor, and close to the floor.

The PVC is also widely used in the medical sector. It makes the patient more ill as phthalates leak out of the tubing's into their bodies. Phthalates like DEHP migrate into fluids and have been detected in the blood found in blood banks. Dialysis patients who receive long-term and regular blood transfusions, their blood comes in contact with the PVC tubing of a dialysis machine, hence, predisposing them to high levels of DEHP per treatment.

Medical Surveillance

Medical surveillance in terms of annual examination of workers working on vinyl chloride, including liver enzymes and assessment of lung functions is recommended.¹²

Elevations of serum bile acids and hyaluronic acid have also been reported in workers. An elevation of von Willebrand factor has also been reported in individuals diagnosed with angiosarcoma,¹³ and levels have been used to track disease progression. Vinyl chloride induced mutations in *p53* and *k-ras* genes have been identified through identification of altered serum proteins, and these show promise in identifying excessive exposure as well as disease risk.¹⁴

Polystyrene

Polystyrene packaging materials are used widely for food products such as egg cartons, plates, cups, and disposable food containers. There is potential exposure to unreacted styrene monomer during resin production, particularly during mixing, loading, and maintenance operations.

At high concentrations, styrene is a respiratory and mucous membrane irritant. Skin contact may result in the development of primary irritant dermatitis. The manifestations of overexposure to styrene include lightheadedness, dizziness, and in-coordination. Limited clinical investigations of workers with long-term exposure to styrene have suggested subtle central and peripheral nervous system injury as well as possible liver damage.¹⁵ Styrene is mutagenic and has been associated with the induction of chromosomal aberrations in humans, although human epidemiologic studies have shown a definitive cancer risk.¹⁶

Various other plastics may cause dermal, respiratory, mutagenic, and carcinogenic problems. They are given in Table 2.

HEALTH HAZARDS OF RUBBER AND TYRE INDUSTRY

The environmental impact associated with the disposal of tyres is quite substantial and frequently overlooked because of the obvious importance of worker exposure issues. The most important human health and environmental problem surrounding the treatment, storage, and disposal of tyres are associated with their large-scale combustion hazard.

- Tyre fires are commonly associated with arson, although lightning strikes are also a recognized ignition source, as are spontaneous outbreaks that are caused by a combination of heat and vibration. Once ignited, tyres produce approximately 18,000 BTUs per second of heat energy, compared with approximately 6,000 BTUs per second for a traditional class 'A' fuel fire.²²

Table 2: Plastic resins and their impact

<i>Name of the compound</i>	<i>Source of exposure</i>	<i>Clinical features</i>	<i>Preventive measures</i>
1. Acrylic	Used in coatings, lights, windows, and face shields	Methacrylates are upper respiratory and mucous membrane irritants ¹⁷	Limit skin contact Patch testing confirms the diagnosis
2. Fluoropolymers and chloropolymers	Used in nonstick cookware, in forming sheaths and coatings for wires and cables	During processing fluorinated and chlorinated hydrocarbons are employed. Overexposure may cause solvent narcosis ¹⁸ Polymer fume fever may occur due to thermal decomposition	Local exhaust ventilation to limit exposure to thermal decomposition products Prevent polymer fume fever by good housekeeping and restricting smoking
3. Phenolic resins	Used in production of building materials, such as plywood and adhesives. Resoles are used in electrical components and in laminating. Phenolic resins are used to coat fabrics imparting crease resistance	Contact dermatitis may result from the handling of raw materials. Dust produced may cause pulmonary impairment and X-ray changes consistent with pneumoconiosis	Avoid skin contact Proper respiratory protection should be worn while handling resin powders
4. Polyurethanes and urethanes	They are widely used in furnishings and construction in the form of flexible and rigid foams. The polyol compound reacts with diisocyanate to form a prepolymer	Diisocyanate workers polyurethane manufacturing workers, upholstery workers, spray painters, coating workers ¹⁹ show altered pulmonary functions and asthma along with contact dermatitis	Careful material handling and process ventilation during manufacturing Proper eye, skin and respiratory protection
5. Amino resins	These are thermoset materials used in adhesives, coatings, and insulation materials. They are formed by a chemical reaction of formaldehyde with an amino group	Exposure to formaldehyde causes respiratory and mucous membrane irritation. Release of formaldehyde from finished products may cause air quality problems	Proper ventilation Avoid skin contact
6. Epoxy resins	Used as protective coatings and laminates for metals, woods, and other plastics. Also used as glues, floor coverings, and paints and coatings	Allergic dermatitis and respiratory sensitization is the main health hazard ²⁰	
7. Epichlorohydrin	Used in manufacturing of epoxy resins, glycol, plasticizers, dye-stuffs, lubricants, adhesives, and pharmaceutical products	Epichlorohydrin reacts with nucleic acids and may cause chromosomal aberrations in lymphocytes of exposed workers Dermal contact may cause vesiculated burns Pulmonary exposure may cause pneumonitis ²¹	Minimize the exposure

The tyres produce tremendous quantity of oil, which also contribute to the persistence of fire's persistence. Toxicologically, tyre fires produce tremendous quantities of:

- Particulates
- Heavy metals particularly zinc and lead
- Emission of organics including benzene, toluene, and styrene
- Volatile products of incomplete combustion (PIC)
- Polycyclic aromatic hydrocarbons (PAHs)
- Dioxins and furans. Levels of benzene > 1 ppm in air have been measured within 300 miles of tyre fires.

- Tyre piles are well-known sources of rodent infestations and are common mosquito breeding grounds
- A number of accelerators and other compounds used in the rubber industry– including thiurams; amines; guanidines; disulfides; and certain thiazoles are skin sensitizers causing contact and allergic contact dermatitis in rubber workers²³
- Mucus hypersecretion and mild airway obstruction have been reported in workers exposed to carbon black, additives, talc, and curing fumes. Chronic lung diseases, such as pneumoconiosis, pulmonary fibrosis, bronchitis, and emphysema can occur in workers

exposed chemically to carbon black as well as to dust and particulates.

Medical Surveillance and Prevention

Reduction in the release of air contaminants into the work environment through the use of proper ventilation and substitution of less toxic materials presents a continuing challenge for the rubber industry. As smoking potentiates the effects of some of the chemicals, workplace smoking restrictions policies and smoking cessation programs may be extremely beneficial for rubber workers.

Carcinogenic and Mutagenic Properties of Chemicals

Various chemicals with carcinogenic properties have been identified. Some are carcinogenic to humans, other probable carcinogens, and yet another category comprises of animal carcinogens.

Commonly used accelerators and curing agents (thiuram compounds including tetramethylthiuram disulfide, and tetramethylthiuram monosulfide) have been demonstrated to be carcinogenic.²⁴

Talc, widely used as an anti-tacking agent, is mainly associated with respiratory disease. However, some talcs may contain asbestos fibers and fibrous tremolite.

Carbon blacks contain variable amounts of compounds, some of which have not been identified. The most probable carcinogenic hazard of carbon black is associated with benzene extractable chemicals, consisting mainly of aromatic hydrocarbons and sulfur compounds.

Cancer of the bladder has long been recognized as a problem within the rubber industry and has been associated with specific aromatic hydrocarbons. The cause was probably an organic antioxidant added to the rubber mixture-3-naphthylamine. However, other compounds such as *a*-naphthylamine, benzidine, and 4-aminobiphenyl (xenylamine).

Phthalate Esters

Phthalate esters are plasticizers used in numerous plastic products, including rubber tyres. They contaminate soil and water and are considered weak animal carcinogens.

Curing Fumes and Other Curing Emissions

During vulcanization process, fumes and vapors are emitted into the air because of volatilization of rubber ingredients. Many airborne nitrosamines are formed during rubber processing and are found in the work atmosphere.²⁴

Polycyclic Aromatic Hydrocarbons

Polycyclic aromatic hydrocarbons (PAHs) are fused benzene ring compounds present in crude oil and generated by burning organic materials. The PAHs are found

in aromatic oils, which are extensively used in the rubber industry as plasticizers and softeners. A tyre may contain as much as 20 percent aromatic and paraffin oils.²⁴

The PAHs are potent skin carcinogens in animal models. Normally, in the rubber industry, humans do not frequently come in contact with these aromatic oils. However, uncured rubber, with which workers have much contact, contain large amounts of these oils.

Mineral oils such as coal tar oils, petroleum and other tar products, are widely used in the rubber industry as extenders. The use of mineral oil has also increased over the years because they are cheap and impart desirable properties to the finished rubber. They may induce carcinogenic effects in mammals, including humans. This carcinogenic effect may be due to the presence of the PAHs.²⁵

Nitroso Compounds and Nitrosamines

During vulcanization, air is excluded, and the mold contains a reducing atmosphere. Products that can be formed during vulcanization and released from the surface of the rubber include amines and organic sulfides derived from the accelerators. These compounds demonstrated to be carcinogenic in a number of animal models, have been identified in the extrusion, milling, calendaring, curing, and cooling (post curing) areas of tyre factories.²⁶

Nitroso compounds are divided into nitrosamines and nitro amides. Most of these have been demonstrated to be potent carcinogens. The antidegradent process and curing process and curing process involve amines, nitrosamines, and quinolines, which are suspected carcinogens.

Rubber Industry and Cancer

Various malignancies have been associated with certain jobs in the rubber industry.²⁷

- Malignancies of the lung have been associated with curing jobs
- Malignancies of the lymphatic and hematopoietic system – particularly lymphatic leukemia
- Stomach cancers have been associated with jobs in the production line, including compounding and mixing, milling, and extrusion
- Bladder cancer was one of the first identified cancers in the rubber industry. This is due to B-naphthylamine, which is an accelerator.

The rubber industry employs hundreds of chemicals in a variety of processes, and reactions leading to potentially hazardous exposures can occur in multiple environments. Decomposition products from chemical reactions may account for many unknown exposures to potential carcinogens at various sites with excess lung cancer, leukemia, and lymphomas having been described in certain occupational groups. As a result, control of exposures is an important preventive health issue.

AUTOMOBILE AIRBAG HAZARDS

The deployment of air bag requires a controlled rapid generation of gas within centimeters of the driver's face. In newer vehicles, the same scenario is true for the passengers. This results in the release of products of combustion and creates a unique and potentially hazardous situation within the confines of the passenger compartment. Previously, automotive reactions of this nature were isolated to the engine compartment and, in the case of internal combustion engine, shielded by massive metal blocks. The airbag, however, aims a high-speed chemical reaction of similar intensity directly at the automobile occupant. Instead of massive steel shielding, the airbag offers only the protection of a cloth bag, fiber screens, and a thin metal inflator body. The engineering required to protect humans from this protective device is substantial and impressive.

Most airbags contain sodium azide (N_3Na) salt. This is the major functional component and the one with greatest potential for toxicity. Sodium azide is the primary constituent that reacts to produce the nitrogen gas.

Boron and potassium nitrate are primarily used as the primary ignition material. Nitrocellulose and other materials may be used as enhancers or as autoignition material. Together they ignite the propellant, initiating the chemical reaction that ultimately leads to inflation and off gassing of combustion products.

Source of Exposure

Though there is little or no potential for toxic exposure to sodium azide in automobiles, but toxicity may occur in laboratories and manufacturing plants. Exposure may be through inhalation of azide gas, through hydrolysis in aqueous solutions of the azide salt or from ingestion of the sodium azide salt.

Clinical Features

It may cause respiratory toxicity and pulmonary edema. Methemoglobinemia can occur as a result of oxidation of hemoglobin similar to nitrites.

Signs and symptoms are dose dependant.

- Ingestion of ≤ 40 mg produces headache
- 40 to 60 mg results in syncope and hypotension
- 80 to 150 mg may cause angina, dyspnea, tachycardia, nausea, vomiting, diarrhea, and headache²⁸
- Doses of 1 to 2 g may be fatal.²⁹

In the industrial setting, the two most common routes of exposure are inhalation and skin absorption. Dermal absorption may occur in workers who may tamper with or come in contact with the salt.

However, from a practical perspective, the components of airbag module offer little potential for toxicity. The public is at little risk from any of the chemicals, because the chemicals are sealed in metal and not easily accessible

for tampering. The public's principal risk of exposure is when an airbag is deployed; however, the thermal degradation destroys the modules chemical components and yields principally nitrogen gas with traces of other gases and particulates.

Postdeployment Vehicle Occupant Injury and Toxicity

Orthopedic, ocular, and cardiothoracic injuries and deaths have been associated with airbag deployment. These have even occurred at speeds as low as 15 miles per hour. Such injuries occur because of the physical force of the inflating air bag, which at its maximum speed travels between 50 to 200 mph.³⁰

The most common groups of physical injuries are those that damage the eyes, orbits, and facial structure of the vehicle occupant. Various chemical hazards to automobile occupants can be encountered after activation or deflation of an airbag.

- The airbag is inflated with nitrogen, which is produced when approximately 80 g total of sodium azide is detonated. Powdered residue can produce ocular and nasal irritation. The nitrogen gas is warmed by the explosion, sometimes to temperatures high enough to physically burn the occupant's extremities or face³¹
- Alkaline powder present around the driver's compartment may produce chemical keratitis and other eye burns
- The asthmatics are prone to the aggravation of their pre-existing disease.

Medical Monitoring

Not all workers in the manufacture of airbags need to be medically monitored. Only those employees whose jobs require the use of respirators, that is, those directly involved in the manufacture, grinding, pressing, and to a lesser extent packaging of the explosive components-require monitoring. The physician must perform a medical evaluation, stressing cardiac, pulmonary, auditory, and psychological factors. The employee must be examined for facial deformities, adequate hearing, tympanic membrane rupture, adequate respiratory and cardiovascular function, endocrine disorders, neurologic disorders, and psychological conditions.

HAZARDS OF BIOTECHNOLOGY

Biotechnology is defined as the application of biological systems to technical and industrial processes. This implies the integration of a variety of biological sciences with chemical and process engineering in a way that optimizes the biological system.³²

Applied Microbiology Overview

Applied microbiology has been defined as the use of microorganisms to produce useful products for the benefit

of the mankind. For centuries, yeasts, molds, and bacteria were used to produce meats, fruits, and vegetables and to enhance the quality of life with products including beverages, cheese, bread, foods, and vinegar. Microorganisms are used not only to produce antibiotics, but are also used as tools in basic research and are one of the fields of molecular genetics and molecular biology. A number of industries have been created out of the use of microorganisms as natural factories. The emergence of genetic engineering techniques has allowed us to produce an ever-increasing number and variety of gene products in bacterial and cell cultures.

Biotechnology is the application of biological systems to basic and applied technical and industrial processes. They are all based on the use of microorganisms or cell to serve as a catalyst in the conversion of substrate to product. A concern that is common to all applications is the need to maintain aseptic conditions. This is because all products are made by a pure culture (a population of cells derived from a single strain or clone). To avoid contamination, all phases of the process must be carefully evaluated and monitored.

Biotechnology activity involves the following:

- Isolation and preservation of the organism or cell that is to serve as the biocatalyst or the source of biocatalyst of interest
- Preparation of the biocatalyst
- Process scale up for the biocatalyst or large-scale growth of the microorganism
- Separation of the desired product
- Purification of the product.

Biohazards of the Biotechnology Process

The biotechnology processes may include the isolation of growth medium components, viable and nonviable organisms, and suspended solids. Most reported health problems are associated with downstream processes.³³ Various problems at various levels include:

- Cell separation and disruption processes have the potential to generate substantial aerosols³⁴
- The extraction of intracellular enzymes involves handling large quantities of cell debris and places the greatest demands on biosafety³⁵
- Centrifuges and rotary vacuum filters are also capable of creating contaminated aerosols
- Disruption processes such as ultrafiltration, chromatography, and dialysis are less likely to generate aerosols. However, aerosol generation may occur in the event of failures in seals or piping
- Exposure may also occur during activities such as filling bags, vials, or other containers³³
- With many biological products, the risk of allergic reaction is greatest after the product is more concentrated during purification and packaging³⁵

- The degree of risk may be influenced by the product formulation— whether solid, powder, or liquid form. Effluent from the process may be an additional source of exposure for workers and may have a significant influence on the environment at the point of discharge.³⁴

People at greatest risk are biotechnologists from various disciplines. These disciplines include biochemistry, biology, chemistry, computer science, and medicine.

Types of Hazards

There are three main groups of hazards associated with biotechnology: biological, chemical, and physical hazards.

Biological Hazards

Biological hazards are associated with three properties of microorganisms:

- Potential for a few species to cause illness or disease
- Potential for undetected genotypic or phenotypic changes to alter a tested and approved process
- Ubiquity of the organisms that can contaminate the system.

Aerosols

The health risks associated with biological aerosols depend on the nature of the hazard, the concentration, and on the size and related distribution of the aerosol particles in the lung.

- The size, shape, and density of the particle determine the site of deposition in the body. Bioaerosols from biotechnological process are likely to range in size from individual cells of process organisms to clumps of cells adhered together in a matrix of cultured broth
 - In allergic responses, such as allergy to pollens and molds, larger size and greater concentration of aerosol particles are of significance
 - In airborne infections small particles are significant because of their greater number and the greater probability of being inhaled.³⁶ Single cells and small clumps of cells with an aerodynamic diameter of $< 4 \mu\text{m}$ are capable of penetrating deep into the lung.³⁷
- Stirring or bubbling may lead to formation of thread of film of liquid that can breakdown into small droplets and evaporate into aerosols
- Mixing of culture with pipette, Vortex mirror, and mixer overflow may lead to formation of particles
- Lyophilized cultures if not opened carefully, or dropped or broken may contaminate the environment.

Ubiquity of Organisms

If a contaminant entered that was able to maintain itself, it would disrupt the system in several ways.

- By direct interference or inhibition of the biocatalyst (enzyme, cell, or microorganism)

- It could destroy the catalyst or the product by using it as an energy source
- The contaminant could induce substances that are difficult to separate from the product, thereby rendering the product unusable.

Various local barriers in biotechnology laboratories and included in Table 3:³⁸

Chemical Exposure to the Biotechnology Industry (Table 4)

Common operations of biotechnology include gel electrophoresis, high-performance liquid chromatography (HPLC), and protein and nucleic acid engineering. Some of the commonly used chemicals with toxic properties are enlisted below:

- *Acetonitrile*: It is a common solvent and extractant used by biotechnologists for HPLC. It is toxic by any route of exposure, and massive exposures have been reported to cause death by cyanide asphyxiation after inhalation in workplaces. Survivors of acute exposure suffer from a variety of reversible symptoms and findings affecting the central nervous system, blood, and possibly kidneys.³⁹ Exposure to small quantities may cause malaise, nausea, and headache.
- *Methylene chloride*: It is a multipurpose solvent, used to remove paint or grease. It is a recognized animal and possibly human carcinogen.⁴⁰ It is particularly toxic for paint strippers as they are exposed to higher doses of the chemical.
- *Tetramethylenediamine*: This chemical is used in gel electrophoresis to examine DNA fragments. It is an eye irritant as well as potential sensitizer. It is known to be mutagenic.
- *Acrylamide*: It is a white crystalline powder used to make polyacrylamide gel. Researchers have made up their own gels from acrylamide powder, with potential for dust exposure during weighing, transferring, and mixing operations. Acrylamide is the second most common potential source of toxic exposure for biotechnology researchers, including skin contact with powder and with gel preparations. Dermal absorption at high doses may cause neurotoxicity in the form of symmetric progressive distal neuropathy. Contact dermatitis of the palms may precede the neurological syndrome. Acrylamide also causes

direct testicular degeneration in exposed rodents⁴¹ and is recognized as a genotoxin with primary mechanisms of heritable translocations and spermatocytosomal clastogenesis.

Given the toxicity of acrylamide, it is essential to formulate certain policies to reduce acrylamide exposure. They include:

- Source reduction: purchase in smallest container in amount required. This would not only reduce the waste disposal, but also the preparation may be mixed without weighing
- Weigh out in tarred closable containers in fume hood. This reduces the exposure during weighing
- Purchases in solution reduce the skin exposure
- By using ventilated groove box or hood with a dedicated balance, bottle is opened only under local exhaust
- Use gloves to prevent skin exposure.
- Chilled water is used to meet the precise temperature and humidity conditions required for cell line production. Chemical hazards of chilled water maintenance unit include exposure to a variety of corrosive or sensitizing elements, including strong alkaline and acid chemicals, amines, and hepatotoxic chemicals, such as dimethylformide. Recirculating chilled-water units also pose a potential nuisance odor hazard. Such units often contain antifreeze additives such as ethylene glycol. Foul-smelling bacteria, such as *Clostridium glycoliticum*, may metabolize antifreeze within standing chilled-water during intervals between the operations. Any break in chilled water pipes releases the odorous metabolites. Recirculating chilled water is also a source of *Legionella pneumophila*, responsible for Legionnaire's disease.⁴² Prevention of this work-related illness requires frequent biocidal treatments and routine microbiological sampling of treated water.

Physical Hazards

Biotechnology is a dynamic industry. Various physical hazards of production activities are given in Table 5.

Medical Surveillance

Medical surveillance of workers involves the collection and use of medical information, biological monitoring, medical screening, or other health data for developing strategies for the prevention of disease. Biological monitoring is the use of tests of body fluids or skin to indicate exposure, and medical screening is the early detection of a health effect to prevent overt disease or to increase chances of recovery.

The purpose of periodic monitoring of biotechnology work include detecting evidence of exposure to biological or chemical hazards, detecting early clinical signs or symptoms of disease, assessing control measures,

Table 3: Local barriers in biotechnology laboratories

Biological safety cabinets (Classes I, II, and III)
Chemical fume hoods
Glove bags
Enclosed centrifuges
Enclosures for sonicators
Safety blenders
Enclosed fermentation equipment

Table 4: Impact of metals and other chemicals

<i>Metals</i>				
<i>Metal</i>	<i>Use</i>	<i>Acute exposure</i>	<i>Chronic exposure</i>	<i>Preventive measures</i>
Beryllium	Exposure occurs during melting, grinding, buffing, and general lathing operations of beryllium containing alloys	High concentrations may cause irritation of the eyes, and respiratory tract	Delayed-onset pulmonary granulomatosis and damage to liver, kidney, and circulatory system, dermatitis, and skin ulcers	<ol style="list-style-type: none"> 1. Proper protective gloves, eye protection, and masks should be worn during casting, polishing, or grinding 2. Use power suction methods for cleaning 3. Dispose of wastes and contaminated clothing properly
Mercury	Exposure occurs through the contact or handling of mercury and its compounds, inhalation of vapors or respirable dusts. Accidental spillage may occur	High mercury accumulation, evidenced by X-ray fluorescence of the head and wrist (>40 µg/g), led to neurological and neuropsychological as well as visual problems	Chronic mercurism may cause loss of appetite, nausea, diarrhea, speech disorders, mucosal ulcers, gingivitis, CNS disturbances, nephritis, thrombocytopenia, and aplastic anemias	<ol style="list-style-type: none"> 1. Adequate ventilation 2. Office monitoring of mercury vapor 3. Personal monitoring 4. Biological evaluation of dental personnel 5. Use water spray and suction while grinding amalgam 6. Use sealed amalgam capsules 7. Proper mercury storage 8. Clean spills immediately 9. Avoid skin exposure
Nickel	Used in production of prosthetic devices. Exposure occurs by inhalation or ingestion of dust produced during grinding	Irritation to the eyes, mucous membranes, and respiratory tract	It is a potential carcinogen causing lung and nasal cancer	<ol style="list-style-type: none"> 1. Use protective gloves eyewear, and masks when fabricating or grinding nickel-containing alloys 2. Use high-velocity evacuation systems⁴⁵
<i>Other Chemicals</i>				
<i>Name</i>	<i>Source of exposure</i>	<i>Health effects</i>	<i>Preventive measures</i>	
Acetic acid	Photographic solutions	Eye, nose, throat, and skin irritation; bronchitis; skin and eye burns	<ol style="list-style-type: none"> 1. Use protective gloves and eyewear. Wash skin or eye contact immediately with running water 2. Adequate ventilation 3. If spill occurs use soda lime or commercial acid spill 4. Use forceps to handle any object in acid, avoid splashing 	
Chlorine	Disinfectant	Eye, nose, throat, mucous membrane, and skin irritation; bronchitis; dermatitis; and dental erosion	Wear proper protective eyewear and gloves	
Ethylene oxide	Sterilizing agents	Skin, respiratory and eye irritation; skin sensitization; peritoneal cancer; leukemia; adverse reproductive effects	<ol style="list-style-type: none"> 1. Direct exhaust from sterilizers to an outdoor location 2. Ensure use of interlocks to prevent opening of sterilizers while they are being operated 3. Use protective gloves and forceps to remove things from sterilizers 4. Strictly control the source of ignition 	
Glutaraldehyde	Sterilizing agents	Eye, nose, and throat irritation; dermatitis; contact with eye may cause severe burns	Wear protective gloves	

Contd...

Hydroquinone	Methacrylate and denture base resins; photographic solutions	Eye and skin irritation, conjunctivitis and keratitis	Wear protective eyewear and gloves
Methyl methacrylate	Denture base resins	Eye, mucous membrane, respiratory, and skin irritation; dermatitis	Wear proper protective eyewear and gloves
Phenol	Disinfectant	Mouth, nose, throat, and skin irritation; liver and kidney damage; severe skin burns from contact	Wear proper protective gloves. If potential for high exposures is present, wear NIOSH approved mask
Latex	Used in gloves	Hypersensitivity to latex may cause skin problems	Use vinyl, neoprene, or other latex substitute gloves
Soaps and detergents	On average dental personnel wash their hands 15 times a day	Contact dermatitis due to destruction of protective layer of epidermis	Use hand cleaners, which do not contain abrasives, defat the skin, cause allergic sensitization, and breakdown with storage
Ionizing radiation	Radiological exposure	Radiation exposure may rarely cause leukemia and shortened life span	Judicious use of X-rays and more sensitive fast-speed films, and better techniques

Table 5: Physical hazards of production activities

Type	Source
Burn	Pressurized steam, liquid nitrogen/acetone/dry ice
Hypothermia	Cold room (up to 12 hours continuously)
Electrical	Heavy equipment, electrophoresis units
Cuts	Glass bottles, glass bioreactors
Anoxic	CO ₂ and N ₂ lines
Ergonomic	Drums, large bottles, media preparation, and other scaled-up equipment
Repetitive trauma	Computer modeling
Shift work	24-hour microbial support (monitoring) of large-scale production; product isolation and purification

detecting changes in employee health status, and identifying patterns of disease indicating a workplace exposure. The periodic evaluations should focus on changes from the baseline exam as a result of potential exposures, such as the development of allergy or signs or symptoms of adverse effects of infectious agents or biologically active agents.

Primary Prevention

In the biotechnology industry, primary prevention is by hazard control, safe work practices, and immunizations. When working with biological agents, two key components of a medical surveillance program are determining the immune status of the employee and eliciting the employee's vaccination history. Because many of the biological agents are opportunistic pathogens, an individual

whose immune status is compromised should be advised to refrain from working with them. Employees should be offered vaccinations if available for the agents in use. All employees exposed to blood, body fluids, or tissue cultures should be offered hepatitis B vaccination.⁴³ Various underlying disease conditions that require screening include:

- Conditions that could interfere with the immune system including, steroid treatment for various medical conditions, or immunosuppressive therapy for cancer or connective tissue diseases, acute viral infections, poorly controlled diabetes, severe alcoholism and pregnancy.
- Workers with chronic dermatitis, eczema, or psoriasis have an increased susceptibility to infection because of altered cutaneous defenses and therefore must wear gloves or avoid exposure to potentially infectious agents.⁴⁴

Product Hazards

Biotechnology workers in fermentation or cell culture production areas with purification processes encounter risks of adrenocortical suppression,⁴⁴ gynecomastia in male workers and menstrual bleeding in female workers.

Control Measures

Containment represents the integration of personnel procedures and practices with laboratory design and engineering features to minimize the exposure of workers to hazardous or potentially hazardous agents or substances.

Personnel Practices

- When entry restrictions are necessary, a hazard warning sign incorporating the universal biohazard symbol should be posted on all access doors to restricted area

- Supervisions should prohibit smoking, eating, and drinking as inadvertent ingestion is a potential route of exposure to microorganisms
- Strict hand washing
- Use mechanical pipetting devices
- Use of appropriate gloves, face protectors, and laboratory clothing
- Well-defined housekeeping procedures and schedules are important in reducing the risks.

Laboratory Practices

- Work surfaces must be decontaminated daily and immediately after spills
- All biological waste and contaminated equipment should be decontaminated or inactivated before disposal or reuse
- Hypodermic needles and syringes should be used carefully. Use needle-locking syringes or units
- Contaminated broken glass also is a potential hazard, which must be decontaminated and disposed off carefully
- Safety devices that prevent the escape of aerosols into laboratory environment, including biological safety cabinets should be used.

DENTAL HEALTH CARE HAZARDS

Dentists and dental health professionals comprise a sizable group at risk for multiple occupational exposures. Unacceptable hazards and exposures including excessive amounts of mercury and waste anesthetic gases in the environment have been found in a number of dental offices and clinics.

Chemical Agents

During routine practice of dentistry, dentists and dental personnel are at risk for multiple exposures to chemical agents. Although benign for most dental patients, prolonged or repeated exposures may lead to adverse health effects to the dental staff. Acute exposures from chemical releases in the workplace are also a matter of concern. Dental personnel can inadvertently inhale waste anesthetic gases, the long-term exposure to which has been associated with a variety of deleterious health effects. Finally, a number of health consequences may result after exposure to certain disinfectants, sterilants, and photographic materials.

Waste Anesthetic Gases

Administration of inhalation anesthesia in dental operations has resulted in considerable exposure of dental personnel to waste anesthetic agents. These gases include nitrous oxide, halothane, enflurane, and others. Reported effects in humans include decrements in motor, perceptual,

and cognitive skills, liver disease, cancer, spontaneous abortion, and birth defects in offspring.

Exposure to waste anesthetic gases occurs primarily from leakage of gases from anesthetic system, poor fit of the mask on patients, and improper work practices. To provide a safer workplace for those at risk for exposure to waste anesthetic gases, the following preventive measures should be implemented:

- Use effective scavenging equipment and monitoring devices
- Regularly inspect anesthetic administration equipment from leaks
- Direct waste gas away from windows, ventilators, air-conditioning inlets, or other areas that might allow gases back into the office
- Maintain adequate ventilation
- Minimize conversation with patients
- Check for snug fit of facemask
- Maintain and service equipment regularly.

Mineral Dusts (Airborne Particulates)

Clinical dental procedures, such as high-speed grinding of silica-containing composite restoratives, the contouring of fused porcelain, and the polishing of plastics and metals with silica- or metallic oxide-containing materials, are routine in the dental work environment.

Asbestos has been used chiefly as a binder in periodontal dressings and as a lining material for casting rings and crucibles. Airborne asbestos is known to cause pulmonary fibrosis (i.e. asbestosis), lung cancer, and mesothelioma of the pleura and peritoneum.

CONSTRUCTION WORKERS

Construction workers build, repair, renovate, modify, and demolish structures of all sorts and in industrialized nations, where construction is ranked amongst the most dangerous occupation; large numbers of teenagers are employed for these jobs. These workers are more like nomads moving wherever the construction boom is. They also tend to live in make shift houses/*jhuggis* and their children also tend to play near construction sites and are thus exposed to the same hazards as the workers.⁴⁶

Construction is often done in extreme heat or cold, in windy, rainy, smoggy, or foggy weather, or at night. Health care facilities are limited for such workers, and even those who desire health care, episodic employment, frequent changes of employer, and continuous changes in work site exposures and ambient conditions limit the clinician's or the researcher's ability to trace the individuals work history or exposures to hazards.⁴⁷ Because of these factors, many of which are unique to construction, limited data exist on the extent or effect of toxic exposure in the construction industry.

Lead Toxicity

High-risk activities associated with lead dust and fumes amongst bridge and structural steel workers: abrasive blasting, sanding, burning, cutting or welding on steel structures coated with lead paint, and the use of containment enclosures at these sites could result in high lead concentrations, and hence toxicity.

There are various mechanisms by which lead interferes with normal function. These include binding and interfering with the function of many proteins of the sulfhydryl group. Some of these changes may occur at extremely low concentrations of lead. For instance, protoporphyrinogen synthetase, an enzyme is extremely sensitive to lead.⁴⁸ Other enzymes affected are guanine hydroxylase, ferrochelatase, and 5'-pyrimidine nucleotidase.⁴⁹ Lead affects the central nervous system, and may accumulate in the kidney leading to Fanconi's syndrome.⁵⁰ Chronic lead poisoning is associated with gouty nephropathy and renal failure in adults.

PAPER AND PULP INDUSTRY

A whole range of acute and chronic lung diseases and a variety of annoyance symptoms (including headaches, nausea, eyes and throat irritation) are common in workers of paper and pulp industry. Odorous pulp mill air emissions are probably responsible for annoyance reactions. However, hydrogen sulfide, mercaptans, and organic sulfides are capable of producing respiratory tract and mucous membrane irritation at lower exposure levels.

The occupational health status of pulp mill workers has been studied for a variety of endpoints, including cancer, pulmonary function, skin diseases, and hearing impairment. Community studies of chronic respiratory disease (in particular, bronchitis) near pulp mills have typically shown excesses in relationship to smoking and mill employment, but not to residents living in proximity to the mills.⁵¹

Cancer mortality patterns among pulp mill workers have been examined in a number of cohort studies—yielding proportional mortality ratios and standardized mortality ratios and in case control studies and tumor registry-based standardized incidence ratio studies.⁵²

Finally, a variety of cutaneous hazards also exist in pulp mills, including wet work and botanical allergent, phototoxic chemicals (e.g. anthraquinone) used in delignification, and cutaneous irritants used in slimicides.⁵³

EMERGING INFECTIOUS DISEASES

The classification of new pathogenic agents has been accompanied by the discovery that infectious agents are associated with a number of diseases that have not been classically considered infectious. Many malignancies result

from chronic infections, including lymphoma, and nasopharyngeal carcinoma (Epstein Bar virus), human T-cell leukemia/lymphoma virus-1, liver cancer (hepatitis B and C), cervical carcinoma (human papilloma virus), stomach cancer (*Helicobacter pylori*), and Kaposi's sarcoma (HHV-8).

Categories of Emerging Infections

New Infections

HIV originated in central Africa and spread occurred through heterosexual transmission of the infection. In contrast, the epidemics of the United States and Western Europe began predominantly as infection of male heterosexuals and were rapidly followed by its spread among parenteral drug users, with relatively limited spread into the remainder of the population. In India, the proliferation of the HIV epidemic has followed the major truck routes, with truck drivers acquiring the infection via their contact with the prostitutes, followed by transmission to prostitutes in their communities as well as transmission within the communities in which they live.⁵⁴

Remerging Diseases

Many infectious diseases are characterized by epidemic occurrence with substantial variation in incidence over months, years, or decades. Seasonality occurs when the variation is annual and is found in infections caused by influenza, enteroviral, malaria, tick-borne, and numerous others. There are multiple reasons for emergence or re-emergence of these infections, which include:

Ecological Factors

A number of diverse ecological factors may be important in the emergence of infectious diseases, and they have been enlisted in the beginning of the chapter. One of the more frequent examples involves changes that result in closer proximity between humans and vectors or animal hosts of zoonotic infections.

Climatic changes have a variety of effects on infectious disease transmission.

- In sub-Saharan Africa, epidemic transmission of meningococcal meningitis occurs during the dry season.⁵⁵
- Malaria transmission is more intense in rainy season because of proliferation of anopheline mosquitoes. The *Plasmodium* parasites are limited to temperatures of greater than 16°C, and the incubation period of the mosquito is shortened as the temperature rises to 27°C. During the twentieth century, the earth's mean temperature has risen by 0.5°C.

Even earthquakes can have an important effect on infectious disease transmission, as demonstrated by a large outbreak of coccidioidomycosis in Ventura County, California, after an earthquake that occurred in 1994.⁵⁶ The earthquake allowed the fungus to be carried by dust

clouds into an area that normally has very little coccidiodomycosis.

Microbial Adaptation

- Isolates of *S. aureus* resistant to the antistaphylococcal penicillins (e.g. methicillin) have spread throughout the world and are frequent in some regions. Other organisms for which drug resistance has become an important problem include *Plasmodium falciparum*, *Plasmodium vivax*, *Mycobacterium tuberculosis*, *Streptococcus pneumoniae*, and *Enterococcus faecium*.
- Organisms may also acquire new virulence factors by acquisition of the gene from other organisms or by mutation of existing genes. Probable examples of this include toxic shock production by *S. aureus* or *Streptococcus pyogenes*. HIV most likely adapted to humans from another primate host and is even able to adapt to different cell types within an individual human host because of its rapid mutation rate.

Human Behavior

- The plague epidemic of the Middle Ages resulted in part from the crowded substandard living conditions that brought people in close proximity with rats and with each other.
- In the last half of the twentieth century, the sexual revolution in the United States and elsewhere, with its concomitant increase in numbers of sexual partners, led to increased frequencies of a number of sexually transmitted infections, including *Chlamydia trachomatis*, HPV, HSV, and HIV.
- Human diets play an important role. Enteric and systemic pathogens that are commonly transmitted by food include *E. coli*, *Campylobacter jejuni*, *Shigella* sp., *Salmonella* sp., *Trichinella spiralis*, and numerous others.
- The epidemic of transmissible neurodegenerative disease in the United Kingdom most likely resulted because cows fed on the remains of other cows who had died from bovine spongiform encephalopathy (BSE), resulting in a high prevalence of BSE in cattle; then, people were rarely infected after ingestion of meat from these cattle.

Breakdown in Public Health

- The decreased mortality from infectious diseases in developed countries during the twentieth century has resulted far more from improved hygiene and public health measures than from the use of antimicrobial agents.
- The substantial increases in frequency and morbidity from pertussis that occurred in Europe and North America when the fear of vaccine side effects resulted in low immunization rates in entire populations.
- Revolution and war in many countries have led to a high number of refugees living in conditions of poor

hygiene, resulting in a high incidence of cholera and other enterically transmitted infections.

- The dismantling of the tuberculosis control program in the United States has played an important role in the current resurgence of tuberculosis.

Eventually environment continues to affect the welfare and health of individuals and populations into the twenty first century. Politics and economics will either continue to cloud science in the debate on environmental pollution and the interrelated health of humans and ecosystems or will help to clarify the facts and provide answers to pollution problems.

Multidisciplinary research will better define the interdependent relationship between environment and health. Finally, better economic modeling inclusive of natural capital and "silent" ecosystem markets will be critical to reinvesting in the environment.

Another important issue which has changed the dimension as well as horizon of medical problems is globalization. Hence, it is pertinent that we mention how globalization impacts human health.

- The globalization of trade is particularly relevant for health services that have become a commodity that can be traded in distinct ways. First, health services can be provided across borders. Examples include a range of telemedicine tools, such as teleradiology and teleradiology as well as medical consultation through traditional and electronic channels. Second, patients can travel abroad to receive health care or use certain facilities.⁵⁷ Other countries, including developing ones such as Cuba and India, openly advertise to attract foreign patients to their clinics and hospitals.⁵⁸
- Globalization has had large effects on international travel, with serious consequences for global health. The liberalization of the airline industry in many countries has made air travel affordable for more and more people around the world, which has led to a dramatic increase in the amount of global air travel. Sutherst⁵⁹ estimated that about one million people travel internationally every day and a similar number travel between developed and developing countries each week. Far-reaching air travel, aided by improvements in aircraft technology that allow longer non-stop flights, facilitates the spread of communicable diseases. It is entirely possible that a person in the early stages of an infectious disease could be halfway around the world in 12 to 15 hours and thus function as a vector for that disease, aiding its spread, perhaps into vulnerable and nonimmune populations. The recent epidemic of severe acute respiratory syndrome (SARS) is the best contemporary example of the rapid spread of a hitherto unknown and virulent viral pathogen through travel of infected humans⁶⁰
- Another example is the global spread of antibiotic-resistant *Pneumococcus* that was first identified in Spain

in the early 1980s and rapidly jumped to South Africa and the USA before spreading to all other parts of the world.⁶¹ Each year, approximately two million children die in developing countries as a result of lower respiratory infections, mostly pneumonia. The exact origin of this *Pneumococcus* strain is still unknown but is likely to come from the Far East⁶²

- Giving basically everyone who is interested access to the full sequences of human pathogen genomes, and the ongoing trend towards open access of published research⁶³ and even ongoing research activities for new drugs⁶⁴ poses a serious dilemma with important implications for global health. Should the full sequence of the anthrax bacillus or smallpox virus and other virulent pathogens be published if this data could be used to develop biological weapons?

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Anticipatory Guidance in Pediatric Oral Health

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INTRODUCTION

To ensure a smooth transition from one stage in the growth and development of a child to the next, parents and care givers can take specific action. The health care in the first few years of a child's life, the formative years, is very essential to the long-term health of that child. Health professionals can educate and train parents to monitor the overall health of the child and can guide them through these critical years. Oral health is a vital part of overall infant health. All individuals with whom a child interacts play an important role in the overall health and development of the child, including the child's family, dentists, pediatricians, and other health professionals. These providers can work together towards a common goal of improving the child's oral health and, in turn, general health. To achieve this goal health professionals should provide to parents, anticipatory guidance, which would help them better care for their children's health because anticipatory guidance, much as the name implies, anticipates oral issues and diseases and incorporates a preventive regimen into the child's health care. To achieve effective anticipatory guidance, providers must have guidelines on which to base prevention and early treatment strategies. The oral health of children in developed and developing countries has significantly improved over the years, but high-risk groups into which prevention and intervention strategies have not been extended still exist, including families with low-income or without health insurance, minority groups, and children with special health care needs, because of a lack of pediatric dentists in some areas, no access to affordable dental care, and a lack of the parent's knowledge about when and why to see a dental professional.

The American Association of Pediatric Dentistry (AAPD) puts special emphasis on anticipatory guidance in pediatric oral health. The risk-benefit ratios and cost-effectiveness of preventive procedures in developing

countries indicate that anticipating and preventing health problems are more economical for both the individual and the government. Countries other than the United States that have guidelines similar to those of the AAPD have reduced the prevalence of many oral diseases, especially dental caries.¹ This reduction is very important because even in a developed country like the US dental caries is the most common childhood disease and 5 times more common than asthma.²

Anticipatory Guidance for the Health Professional

The AAPD and the American Dental Association (ADA) recommend that a child should first visit the dentist within six months of eruption of the first tooth and no later than 12 months of age.⁴ After that, a child should visit a dentist every 6 months or according to the individual need of the child. The reason for the first-year dental visit is for the parent to receive oral anticipatory guidance and to establish a "dental home", which identifies a child with a dentist in a familiar and safe health-supervision relationship and is similar to that of a "medical home."⁵ The medical home is where a child's parent receives prevention instructions, counseling and anticipatory guidance, and where a child receives medical care such as immunizations. A medical home can also provide an oral health exam and referral to a dentist, which can result in a dental home for the child at an early age, a practice that the AAPD recommends.³ A dental home can provide orodental anticipatory guidance for parents of a child as young as the age of 1 and provide access to preventive and emergency services.

The concept of dental home is new and though no empirical data have been gathered. Table 1 shows the ideal characteristics of a dental home.⁵ In addition scientific evidence supports the reasons for the child's first visit within the first year. For example, *Streptococcus mutans* has been detected as early as 6 months of age in preeruptate

Table 1: Ideal characteristics and practical advantages of a dental home

<i>Characteristic</i>	<i>Description</i>	<i>Practical advantages</i>
Accessible	<ul style="list-style-type: none"> Care provided in the child's community All insurance accepted and changes in coverage accommodated 	<ul style="list-style-type: none"> Source of care is close to home and accessible to family Minimal hassle encountered with payment Office ready for treatment in emergency situations Office nonbiased in dealing with children with special health care needs Dentist knows community needs and resources (like fluoride in water)
Family centered	<ul style="list-style-type: none"> Recognition of centeredness of family Unbiased complete information is shared on an ongoing basis 	<ul style="list-style-type: none"> Low parent child anxiety improves care Care protocols are comfortable to family (behavior management) Appropriate role of parents in home care is established
Continuous	<ul style="list-style-type: none"> Same primary care provider from infancy through adolescence Assistance provided with transitions (for example, to school) 	<ul style="list-style-type: none"> Appropriate recall intervals are based on child's needs Continuity of care is better owing to the recall system Coordination of complex dental treatment is possible (traumatic injury) Liaison with medical providers for CSHCN is improved (congenital heart disease)
Comprehensive	<ul style="list-style-type: none"> Health care available 24 hours a day 7 days a week Preventive, primary and tertiary care provided Information centralized 	<ul style="list-style-type: none"> Emergency access is ensured Care manager and primary care dentist are in the same place
Coordinated	<ul style="list-style-type: none"> Families linked to support education and community services 	<ul style="list-style-type: none"> Records centralized School, workshop, therapy linkages established and known (cleft palate care)
Compassionate	<ul style="list-style-type: none"> Expressed and demonstrated concern for child 	<ul style="list-style-type: none"> Dentist-child relationship is established Family relationship is established Children less anxious owing to familiarity
Culturally competent	<ul style="list-style-type: none"> Cultural background recognized, valued and respected 	<ul style="list-style-type: none"> Mechanism is established for communication of ongoing care Specialized resources are known and proven if needed Staff may speak different languages and know dental terminology

Adapted from: The Dental Home – A Primary Care Oral Health Concept, Arthur J. Nowak; Paul S. Casamassimo JADA Vol. 133, Jan 2002.

children; the mother was the source of the infection.⁶ This first visit is therefore an opportunity for the dentist to instruct the parent on oral health practices for the child. Such a home could be a foundation on which a lifetime of preventive dental education and care can be built.

In the United States 66 percent of children ages 2 to 4 years old from families with annual incomes of less than \$10,000 had not had a dental visit the preceding year.⁷ The AAPD suggests that if pediatricians learned about and promoted oral health of infants and children pediatricians could educate parents and children and work in partnership with oral health professionals. As part of routine oral-supervision visits pediatricians can incorporate interview questions, risk assessment, screening and anticipatory guidance.³ These interview questions address dietary practices, fluoride exposure, oral hygiene, utilization of dental services, number and location of mother's

fillings and other dental work. The pediatrician can then provide to the dentist a good baseline on the risk of oral disease in the child and help the dentist better educate the parents in the dental home.

The pediatrician should begin a dental risk assessment by the age of 6 months though all children are not at equal risk of developing dental problems. Tables 2 to 5 shows the risk factors and protective factors for four common diseases of childhood, i.e. dental caries, periodontal disease, malocclusion, and injury and these could be a guide on which prevention strategies can be based.¹⁴ Oral screenings and examinations will reveal if tooth eruption and loss are on schedule. Although variations in tooth eruption and loss can be normal, these variations may also indicate oral health problems. For example, delayed tooth eruption can be due to certain syndromes, developmental defects of teeth, cysts, or tumors. Screening also assesses

tooth irregularities and alignment of teeth and will help find problems early and prevent any further harm to the dentition. In addition, the pediatrician can assess the parent's administration of oral hygiene practices and demonstrate

proper practices to the parent, such as the correct plaque removal technique with an appropriate-sized toothbrush. This visit can also address tooth decay, malocclusions, oral injuries, and other risk factors for each child.

Table 2: Risk assessment for different childhood dental conditions—dental caries

<i>Risk factors</i>	<i>Protective factors</i>
<p><i>All ages</i></p> <ul style="list-style-type: none"> • Inadequate oral hygiene • Poor family oral health • Poverty • Frequent snacking • Special carbohydrate diet • Frequent intake of sugared medications • Reduced saliva flow from medication or irradiation • Variations in tooth enamel; deep pits and fissures; anatomically susceptible areas • Special health needs • Previous caries experience • Gastric reflux • High mutans streptococci count 	<ul style="list-style-type: none"> • Optimal systemic and/or topical fluoride • Good oral hygiene • Access to care and good oral hygiene • Access to care • Reduction in snacking frequency • Preventive intervention to minimize effects • Alternative medications or preventive intervention to minimize effects • Saliva substitutes • Sealants (if possible) or observation • Preventive intervention to minimize effects • Increased frequency of supervision visits • Management of condition • Reduction of mutans streptococci
<p><i>Early childhood</i></p> <ul style="list-style-type: none"> • Bottle use at night while sleeping or when awake at will • High parental levels of bacteria (<i>S. mutans</i>) • History of baby bottle tooth decay 	<ul style="list-style-type: none"> • Prevention of bottle habit and weaning from bottle at 12 months • Good parental oral health and hygiene • Increased frequency of supervision visits
<p><i>Infancy</i></p> <ul style="list-style-type: none"> • Bottle use at night while sleeping or when awake at will • High parental levels of bacteria (<i>S. mutans</i>) • History of baby bottle tooth decay 	<ul style="list-style-type: none"> • Prevention of bottle habit and weaning from bottle at 12 months • Good parental oral health and hygiene

Table 3: Risk assessment for childhood dental conditions—periodontal disease

<i>Risk factors</i>	<i>Protective factors</i>
<p><i>All ages</i></p> <ul style="list-style-type: none"> • Inadequate oral hygiene • Unrestored caries • Poor family oral health • Poverty • Special health needs • Nutritional deficiency • Infectious disease • Medications • Metabolic disease • Neoplastic disease • Genetic predisposition • Poor quality fillings • Mouth breathing • Injury 	<ul style="list-style-type: none"> • Good oral hygiene • Restoration of carious lesions • Access to care and good oral hygiene • Access to care • Preventive intervention to minimize effects • Healthy eating habits • Treatment of disease or preventive intervention to minimize effects • Preventive intervention to minimize effects • Treatment of disease • Treatment of disease or preventive intervention to minimize effects • Preventive intervention to minimize effects • Properly contoured and finished restorations • Management of condition • Use of age appropriate safety measures and treatment of injury
<p><i>Early childhood</i></p> <ul style="list-style-type: none"> • Malpositioned and crowded teeth 	<ul style="list-style-type: none"> • Good oral hygiene
<p><i>Infancy</i></p>	
<p>None</p>	<p>None</p>

Table 4: Risk assessment for different childhood dental conditions—malocclusion

<i>Risk factors</i>	<i>Protective factors</i>
<i>All ages</i>	<ul style="list-style-type: none"> • Early intervention • Early intervention • Early intervention • Use of age appropriate safety measures • Dental intervention as part of medical care • Early intervention • Dental intervention as part of medical care • Dental intervention as part of medical care
<ul style="list-style-type: none"> • Congenital absence of teeth • Variations in development (tooth eruption delays and malpositioned teeth) • Conditions associated with malocclusion (e.g. cleft lip/palate) • Injury • Acquired condition from systemic condition or it's therapy • Family tendency toward malocclusion • Musculoskeletal conditions (e.g. cerebral palsy) • Skeletal growth disorders (e.g. renal disease) 	
<i>Early childhood</i>	<ul style="list-style-type: none"> • Elimination of habit • Early therapy • Early intervention for caries
<ul style="list-style-type: none"> • Non-nutritive sucking habits • Muscular imbalances • Loss of space due to caries 	
<i>Infancy</i>	
None	

Table 5: Risk assessment for different childhood dental conditions—injuries

<i>Risk factors</i>	<i>Protective factors</i>
<i>All ages</i>	<ul style="list-style-type: none"> • Referral for counseling • Referral for counseling • Referral for counseling • Referral for appropriate therapy • Use of age appropriate safety measures
<ul style="list-style-type: none"> • Substance abuse in family • Child abuse or neglect • Multiple family problems • Lack of protective reflexes 	
<i>Early childhood</i>	<ul style="list-style-type: none"> • Orthodontic care • Referral for appropriate therapy • Adjustment of medications • Management of condition
<ul style="list-style-type: none"> • Failure to use safety measures appropriate for child (like car safety seats, stair gates, safety belts) • Protruding front teeth • Poor coordination • Over medication • Hyperactivity 	
<i>Infancy</i>	
<ul style="list-style-type: none"> • Failure to use safety measures appropriate for infant (like car safety seats, stair gates, safety belts) 	<ul style="list-style-type: none"> • Use of age appropriate safety measures

The pediatrician can screen a child and refer the child to a dentist, who can establish a dental home for the child. An oral examination by a dentist includes a complete clinical oral assessment and appropriate diagnostic testing to assess oral growth and development and/or pathology. During the exam the dentist will also assess the child's exposure to topical and systemic fluoride, counsel parents about fluoride, and prescribe systemic fluoride supplements, if indicated. In this visit the dentist will also assess the appropriateness of feeding practices and provide anticipatory guidance. If stains or deposits are present, the dentist or dental hygienist may remove them and schedule another appointment if the child needs further treatment. The first visit will also help familiarize the child

to a dental office and can make the child more receptive to dental care.³

Recommendations

Anticipatory guidance can identify and prevent problems because dentists can treat many oral diseases and conditions if they are identified early in their development. The AAPD recommends that all primary health care professionals who serve mothers and infants should provide parent/caregiver education on the etiology and prevention of early childhood caries (ECC). Oral health counseling is especially important for the mother. Therefore, materials on the infectious and transmissible nature of bacteria that cause ECC and methods of oral health risk assessment,

anticipatory guidance, and early intervention should be in the curriculum of all medical, nursing and allied health professional programs.³

By six months of age every infant should receive an oral health risk assessment from a dentist or pediatrician.³ This risk assessment should include the use of the caries assessment tool (CAT), shown in Table 6, to determine the patient's risk of developing ECC, education on infant oral health, and should evaluate and optimize fluoride exposure. This should all be part of establishing a dental home for the child, and the dentist can use this information to determine a timetable for future appointments for the child.

The pediatrician should advise parents or caregivers to establish a dental home for infants by 12 months of age;⁴ in this visit the dentist should record thorough dental and medical histories of mothers/caregivers and infants and perform a thorough oral exam.

Besides doing the risk assessment the pediatrician can also work with the child's dentist and help plan comprehensive care and appropriate interventions as necessary. For example, if the pediatrician notices a lot of decay in a child he can make the necessary referral for restoration and also provide a background on the child's medical health to help dentist plan treatment accordingly.

Anticipatory Guidance and Pediatricians and Dentists

The AAPD has recommendations for pediatricians and dentists on educating parents on the oral developmental changes of their children and parental care for them at every stage. Included here are recommendations for expectant mothers, parents of infants and young children, which can be in a dental home environment (Table 7).

Pregnant Women, New Mothers or Intimate Care Givers

Pregnancy is a good stage for physicians to instill appropriate oral hygiene practices in expectant mothers. Physicians should advise them to brush their teeth thoroughly twice a day with fluoridated toothpaste and spit out the excess after brushing and to floss daily. The residual toothpaste helps prevent tooth decay. Expectant mothers should rinse every night with an alcohol-free over-the-counter fluoridated mouth rinse. They should have a dental visit for an exam and restoration of all active decay as soon as feasible. The physician should also educate the mother about hormonal changes during pregnancy, which can increase a woman's risk for gingivitis.

Table 6: AAPD caries risk assessment tool: (AAPD reference manual 2002–2003)

<i>Caries risk indicators</i>	<i>Low risk</i>	<i>Moderate risk</i>	<i>High risk</i>
Clinical conditions	<ul style="list-style-type: none"> • No carious teeth in past 24 months • No enamel demineralization • No visible plaque or gingivitis 	<ul style="list-style-type: none"> • Carious teeth in past 24 months • One area of enamel demineralization • Gingivitis 	<ul style="list-style-type: none"> • Carious teeth in past 12 months • More than 1 area of enamel demineralization • Visible plaque on anterior (front) teeth • Radiographic enamel caries • High titers of mutans streptococci • Wearing dental or orthodontic appliances
Environmental characteristics	<ul style="list-style-type: none"> • Optimal systemic and topical fluoride exposure • Consumption of simple sugars or foods strongly associated with caries initiation primarily at meal-times • High caregiver socioeconomic status • Regular use of dental care in an established dental home 	<ul style="list-style-type: none"> • Suboptimal systemic with optimal topical fluoride exposure • Occasional (i.e. 1-2) between meal exposures to simple sugars or foods strongly associated with caries • Midlevel caregiver socioeconomic status (i.e. eligible for school lunch program or SCHIP) • Irregular use of dental services 	<ul style="list-style-type: none"> • Enamel hypoplasia • Suboptimal topical fluoride exposure • Frequent (i.e. 3 or more) between meal exposures to simple sugars or foods strongly associated with caries • Low-level caregiver socioeconomic status (i.e. eligible for Medicaid) • No usual source of dental care • Active caries present in the mother • Children with special health care needs • Conditions impairing saliva composition and flow
General health conditions			

Table 7: AAPD recommended anticipatory guidance for parents*Pregnant women, new mothers or intimate care givers*

- Brush teeth twice a day with fluoridated toothpaste and floss daily
- Spit excess toothpaste after brushing and do not rinse
- Rinse every night with alcohol free OTC fluoride mouth rinse
- Have a dental visit for an exam and restoration of all active decay ASAP
- Educate mother about hormonal changes during pregnancy that can increase a woman's risk for gingivitis

Parents of infants

- Make an appointment for the infant's first dental visit within 6 months of eruption of the first tooth and no later than 12 months of age
- After initial dental visit make future appointments based on the schedule suggested by the dentist, based on the infant's individual needs
- Clean infant's gums with a clean damp cloth or an infant toothbrush with a small head using plain water after each feeding
- Brush infant's teeth as soon as the first tooth erupts usually at the age of 6-10 months twice a day using a soft bristled tooth brush designed for infants
- Give infant nothing to eat or drink after brushing at night, except water
- For infants at increased risk of tooth decay consult a dentist or physician about brushing with fluoridated toothpaste
- Become familiar with the normal appearance of the infant's teeth and gums so problems can be identified if they occur (check once a month)
- Give the infant 6 months or older fluoride supplements but only as recommended by a dentist or physician (based on water fluoride level)
- In case infant has sore gums caused by tooth eruption give infant a clean teething ring, cool spoon or cold wet wash cloth or even rub his gums with a clean finger

Parents of young children

- If the child has not yet been for a dental visit make an appointment for the first dental visit
- After initial dental visit make future appointments based on the schedule suggested by the dentist, based on the infant's individual needs
- For children under age 2 brush the teeth with plain water twice a day
- For children with increased risk of tooth decay consult a dentist or a physician about brushing teeth with a fluoridated toothpaste
- For children ages 2 and above brush twice a day with no more than a pea sized amount of fluoridated toothpaste and make him spit but not rinse
- Young children cannot clean teeth without parental help so they need to be helped as brushing requires fine motor skills (around 7-8 years)
- Become familiar with the normal appearance of the infant's teeth and gums so problems can be identified if they occur (check once a month)
- Give the child fluoride supplements but only as recommended by a dentist or physician based on the level of risk and that of fluoride in the drinking water
- Discuss with a dentist or other qualified health professional the need to apply fluoride topically
- Discuss with a dentist or other qualified health professional the need to apply dental sealants
- In case infant has sore gums caused by tooth eruption give infant a clean teething ring, cool spoon or cold wet wash cloth or even rub his gums with a clean finger

Parents of Infants

Table 7 lists recommendations for pediatricians to give to parents of infants. The pediatrician should educate parents about making an appointment for the infant's first

dental visit within 6 months of eruption of the first tooth and no later than 12 months of age. The dentist then develops a schedule for future appointments based on the infant's individual needs and susceptibility to disease. Visits

might be more frequent for special needs patients. Parents should clean the infant's gums with a clean damp cloth or an infant toothbrush with a small head using plain water after each feeding. They should brush infant's teeth twice a day as soon as the first tooth erupts, usually at the age of 6 to 10 months, using a soft bristled toothbrush designed for infants. An infant should be given nothing to eat or drink after brushing at night, except water, and parents should consult a dentist about brushing with fluoridated toothpaste for an infant who is at increased risk for tooth decay. But parents should be warned not to let the child ingest the toothpaste as this may become an unintentional source of systemic fluoride leading to overdose toxicities. A dentist in a dental home can instill this information in parents; it can go a long way toward good oral health and health practices of the child. Parents should be familiar with the normal appearance of the infant's teeth and gums so they can identify problems if they occur. The dentist can teach the parent through pictures and example, the appearance of the normal versus diseased teeth and gums and should advise parents to assess the infant's oral tissue about once a month. Giving the infant 6 months or older fluoride supplements based on the level of risk and amount of fluoride in the child's drinking water, the physician or dentist may recommend fluoride supplements for the infant who is six months or older. If the infant has sore gums caused by tooth eruption, parents may give infant a clean teething ring, cool spoon, or cold wet washcloth or can even rub infant's gums with a clean finger.

Parents of Young Children

Just like parents of infants, parents of young children should have made the initial dental appointment for their child and should make future appointments based on the schedule the dentist suggested, according to the infant's individual needs and susceptibility to disease. Visits might be more frequent for special needs patients. For children under age 2 the parent should brush their teeth with plain water twice a day after breakfast and before bed, and for those with increased risk of tooth decay, the parent should consult a dentist or a physician about brushing teeth with a small pea sized amount of fluoridated toothpaste. Brushing after breakfast and before bed removes food debris that may remain on teeth after meals and contribute to tooth decay. Parents can brush teeth of children more than 2 years of age twice a day with no more than a pea sized amount of fluoridated toothpaste and make them spit without rinsing as described earlier. Parents should understand that brushing requires good fine motor skill and that young children cannot clean teeth without parental help. After children acquire these fine motor skills, typically at ages of 7 to 8 years (an age at which they can tie their own shoe laces), they can clean their own teeth with parental supervision. Again parents

should be familiar with the normal appearance of the teeth and gums and should perform home oral exams about once a month. The physician should inform parents that they should ask the dentist about the need for fluoride supplements for their child, which the dentist can prescribe based on level of risk and amount of fluoride in the drinking water. In addition, parents of young children can discuss with a dentist the need to apply fluoride topically (like varnishes, gels, foams), which renews the high levels of fluoride in the outer layer of tooth enamel. Topical applications maybe especially effective in children with a high risk of tooth decay such as those who have a history of tooth decay, who are not exposed to fluoridated water, who snack frequently on foods containing sugar, or who have medical problems that decrease their resistance to tooth decay. Also, in a dental home, the parents can discuss with a dentist or other qualified health professional the need to apply dental sealants (thin plastic coatings that are applied to pits and fissures on chewing surfaces of teeth). Sealants create a physical barrier against dental plaque, and this barrier prevents tooth decay. Dental sealants should be applied shortly after the posterior teeth erupt. The pediatrician can also instruct the parent on treatment of sore gums from tooth eruption: give the child a clean teething ring, cool spoon, or cold wet washcloth or rub the gums with a clean finger.

Advantages of Anticipatory Guidance in Specific Dental Conditions

Dental Caries

A transmissible oral infection, dental caries is the most common childhood disease and is five times more common than asthma.² Cariogenic bacteria in the mouth produce acids to breakdown food debris on the teeth. These acids cause tooth mineral loss. Prolonged attack that exceeds the individual's capacity of healing can cause irreversible decay and eventual tooth loss.

More than 6 percent of 1-year-old, 22 percent of 2-year-old, 35 percent of 3-year-old 49 percent of 4-year-old in a Head start program in arizona had clinical tooth decay.³ The third National Health and Nutrition Examination Survey (NHANES), 1988-1994, indicates that 8 percent of 2-year-old in the United States had at least 1 decayed or filled tooth and by age five 40 percent of children did. Children as young as 1 experience untreated tooth decay, and among children ages 6 to 8, 72 percent of American Indian/Alaskan Native, 50 percent Hispanic and 34 percent African-American children experienced untreated tooth decay.³ This vast number with tooth decay clearly indicates the need for preventive action and a need for more aggressive measures in a country like India where access to health care and the dentist-to-population ratio is very low.

Early childhood caries (ECC) may occur in infants or children with prolonged exposure to beverages high in sugar like soda, fruit juices, milk, or formula from a bottle or a cup, prolonged breastfeeding, frequent snacking on foods high in sugar, and pacifiers coated with sweeteners. Volume and composition of saliva and blockage of salivary flow also affects ECC. The younger the age at which decay begins the greater will be the risk of future decay. ECC can affect a lot of teeth and cause severe loss of function and harm to the child's dentition. Good oral hygiene, use of fluorides and dental sealants, good dietary habits, and chemical and physical reduction of plaque can all be achieved with early intervention to prevent ECC.

CARIES PREVENTION THROUGH ANTICIPATORY GUIDANCE

Pregnant Women, New Mothers or Other Intimate Care Givers

The AAPD has recommendations for dietary practices in pregnant or new mothers, infants and children.³ The recommendations suggest that the pediatrician educate the parents about the diet for their children and themselves and that the dentist reinforce these healthy practices. The pediatrician and dentist should advise these women to eat healthy foods and to avoid snacking in between. Healthy meals should include fruits, vegetables, grain products, and dairy products. The foods containing sugar should be eaten at mealtimes only and in limited amounts. This education will help parents develop good oral health practices, which they will pass on to their children.

Physicians should advise pregnant women to choose fruit rather than fruit juice for their recommended daily fruit intake and avoid carbonated beverages during pregnancy and at least for the first 30 months after delivery. Pediatricians should encourage these women to drink fluoridated water, and should inform them about the transmission of bacteria that cause tooth decay from the parent to child and that parents should not share utensils or clean the pacifier or bottle with saliva.

Parents of Infants

The pediatrician should advise mothers to breastfeed the infant for approximately the first 6 to 12 months of life.³ To prevent the transmission of bacteria that cause tooth decay via saliva from mother to child, parents should not share utensils with the child, test the temperature of the bottle with the mouth, or clean a pacifier or bottle nipple with saliva, practices many parents adopt that are not hygienic. The infant should never be put to sleep with a bottle or sippy cup in the mouth, and never allowed frequent or prolonged feeds with beverages high in sugar. These practices are the primary cause of early tooth decay

because parents use them to pacify and to induce sleep in the infant. Pediatricians should tell parents to hold infant while feeding and never to prop the bottle using pillows or other objects to hold the bottle. This propping can injure the unattended infant and prolonged propping and feeding can cause ECC. Some parents also add cereal to a bottle of the infant but pediatricians and dentists should discourage this practice because it will cause sugary foods to pool around teeth increasing the risk for decay. Parents can introduce a small cup when the infant can sit up without support, and the infant should be weaned from the bottle when he starts to eat more solid foods and made to drink from a cup. Parents should not introduce juice into an infant's diet before age 6 months and limit it to 4-6 oz per day. Infants 6 months and older should receive age-appropriate healthy foods as recommended by their pediatrician and avoid snacking between meals. Foods containing sugar should be served to infants at mealtimes only and in limited amounts.³ Pediatricians should have the knowledge or be able to do the required referral for good nutrition and dietary counseling to support oral and general health of the child (Table 8).

Parents of Young Children

The pediatrician should reiterate the following guidelines for young children. To avoid transmission of bacteria that cause tooth decay from parent via saliva to child, parents should not share utensils or clean a pacifier or bottle nipple with saliva. Parents should encourage a child to drink from a cup and to wean them from the bottle at 12-14 months and should not put a child to sleep with a bottle or sippy cup or allow frequent or prolonged feeds for reasons mentioned earlier. Parents should provide age appropriate healthy planned foods and prohibit snacking in between meals. A good healthy meal should contain fruits, vegetables, grains and dairy products. Child should eat fruit rather than drink fruit juice and be served the juice in a cup limiting it to 4 to 6 oz per day. Beverages between meals should be fluoridated water and milk rather than juices and sodas.

Fluorides

The primary factor in reducing the prevalence of cavities among the children in the United States has been the widespread availability of fluoride. According to the CDC, frequent exposure to small amounts of fluoride each day is the best way to reduce the risk of developing tooth decay.⁸ Systemic fluorides only help during the tooth-forming years (ages 6 months–19 years) they enhance resistance to later acid demineralization. They can be delivered in the form of fluoridated water or fluoride supplements available as tablets, drops, or liquids and reach the child's teeth through the digestive and circulatory systems. Fluoridated

Table 8: AAPD recommended anticipatory guidance for parents on good nutrition*Pregnant women, new mothers or intimate care givers*

- Eat healthy foods during planned meals and snacks and avoid snacking in between
- Include fruits, vegetables, grains and dairy products
- Foods containing sugar should be eaten at mealtimes only and in limited amounts
- Choose fruit rather than fruit juice for recommended daily fruit intake
- Avoid carbonated beverages during pregnancy and at least for the first 30 months after delivery
- Drinking of fluoridated water
- Once infant is born avoid transmission of bacteria that cause tooth decay from the parent, like avoid sharing utensils or cleaning pacifier or bottle with saliva

Parents of infants

- Breastfeed the infant for approximately the first 6 months of life can be continued for 12 months
- Prevent transmission of bacteria that cause tooth decay via saliva, avoid sharing utensils, testing the temperature of the bottle with the mouth or cleaning a pacifier or bottle nipple with saliva
- Do not put infant to sleep with bottle or sippy cup or allow frequent or prolonged feeds with beverages high in sugar
- Hold infant while feeding, never prop the bottle using pillows or other objects to hold the bottle
- Never add cereal to a bottle this will cause sugary foods to pool around teeth
- Introduce a small cup when the infant can sit up without support
- Wean the infant from the bottle when he starts to eat more solid foods and drink from a cup
- Do not introduce juice into an infant's diet before age 6 months and limit to 4-6 oz per day
- For infants 6 months and older, serve age appropriate healthy foods and avoid snacking between meals
- Serve foods containing sugar at mealtimes only and limit amount

Parents of young children

- To avoid transmission of bacteria that cause tooth decay from parent via saliva to child avoid sharing utensils, or cleaning a pacifier or bottle nipple with saliva
- Continue to encourage a child to drink from a cup wean from bottle at 12-14 months
- Do not put a child to sleep with a bottle or sippy cup or allow frequent or prolonged feeds
- Allow age appropriate healthy planned foods and avoid snacking in between
- Serve fruits, vegetables, grains and dairy products
- Encourage child to eat fruit rather than drink fruit juice
- Serve the child juice in a cup and limit to 4-6 oz per day
- If child drinks beverages between meals encourage drinking water and milk rather than juices and sodas
- Drink fluoridated water

water is the best way to get systemic fluorides to a child. Fluoride supplements are recommended only when a child's ingestion of fluoride is less than optimal. Table 9 shows the recommended doses for fluoride supplements based on age of child and level of fluoride in the drinking water.⁹ Early referral to a dentist in a dental home can address fluoride issues. The dentist will know the community, and the fluoride content in the water in the community and will be able to prescribe the ideal dosage for the child if necessary.⁵ Topical fluorides are most important in the prevention of tooth decay because they reach teeth directly and are more effective than the small doses in foods, water and fluoridated toothpastes. In a child's

dental home the dentist would know the child and the family and this beneficial relationship would help the dentist treat the individual needs of the child and would also improve compliance in both the parents and the child. The dentist can also professionally apply topical fluorides like varnishes, gels, or foams. These are especially effective in children who are at high risk of dental caries due to lack of fluoridated water, who have a history of caries, who snack frequently on high-sugar foods or have a medical condition. The dentist in a dental home would know all this due to regular appointments, and knowledge of the general health of the family. Pit and fissure sealants are also advantageous in caries prevention especially in

Table 9: Fluoride supplementation guidelines*Fluoride ion level in drinking water in ppm #*

AGE	< 0.3 ppm	0.3-0.6 ppm	> 0.6 ppm
Newborn – 6 months	None	None	None
6 months – 3 years	0.25 mg/day*	None	None
3–6 years	0.50 mg/day	0.25 mg/day	None
6–16 years	1.0 mg/day	0.50 mg/day	None

#1.0 ppm = 1 mg/L.

*2.2 mg of sodium fluoride contains 1 mg fluoride ion

newly erupted primary and permanent molars with deep pits and fissures, and can be professionally applied by the dentist.¹⁰

ANOMALIES IN THE NUMBER OF TEETH

Many tooth-number anomalies, if recognized early, can help the dentist diagnose more serious general health problems. These anomalies can be markers of certain congenital problems and syndromes and maybe unrecognized in a medical exam. For example hyperdontia (more than the normal number of teeth) indicated by delayed tooth loss in a radiographic and clinical exam. Extra teeth need to be identified and removed early to facilitate eruption of the underlying normal teeth. Hypodontia (less than the normal number of teeth) or anodontia (the complete absence of teeth) are indicators of syndromes like ectodermal dysplasia, which affects a lot of other systems as well. In these cases, the pediatrician and the dentist in the dental home can work as a team to care for these patients.

Anomalies in the Development of Teeth

Hypoplasia, hypocalcification, fluorosis, amelogenesis, and dentinogenesis imperfecta appear as abnormal whitish-to-gray or even brownish discolorations of teeth. The tooth surfaces appear rough and tend to retain more plaque. Teeth that have not developed normally also tend to break or chip easily and are more susceptible to carious breakdown. These conditions need early dental treatment to avoid further loss of tooth structure, and anticipatory guidance can help parents get these children timely dental treatment.

Soft Tissue Conditions

Many soft tissue conditions need early identification and treatment and include viral, bacterial and fungal infections, some of which could be indications of more serious health conditions. These soft tissue conditions include primary herpetic stomatitis, and candidiases, which can be an indication of HIV infection for example. Congenital

cysts and tumors should be excised and treated early, but eruption cysts maybe due to newly erupting teeth that do not need treatment usually but need to be observed. Other conditions like mucocoeles, which are caused by injury to minor salivary glands and result in mucous retention in oral tissues, are typically on the lower lip, and may need early excision. Other lesions that are benign but may need excision include fibromas and papillomas; they can occur anywhere in the mouth. Ankyloglossia also known as tongue tie, is characterized by an abnormally short lingual frenum. If it interferes with speech, then it may require frenectomy as early as possible so that speech problems don't become permanent. Ulcers sometimes occur in young children, due to trauma from a sharp tooth, for example, or could be due to infections, systemic deficiencies, or immune deficiencies. If these conditions remain undetected they may result in bigger problems. Regularly scheduled dental visits in a dental home would allow the dentist to recognize and to treat these problems before they become serious health issues. This can best be accomplished if the pediatrician and the dentists work as a team with a common goal of improving the oral and, in turn, the general health of the child.

Habits

Thumb or digit sucking is a natural reflex for infants. This non-nutritive sucking provides the infant with emotional benefits. Many parents allow a pacifier, and a dentist or a pediatrician can instruct parents in its appropriate use. Until the age of 3, non-nutritive sucking does not cause dental problems, but beyond that it can lead to misalignment of primary teeth. It can cause anterior open bites, movement of the upper front teeth (incisors), and constriction of the maxilla. All of these problems resolve if the sucking habit is discontinued before the permanent teeth erupt. Anticipatory guidance can help parents avoid or curtail this habit in their children. Interventions include talking with the child, using reminder therapy, rewarding the child (positive reinforcement), or, if needed, physically interrupting the habit.

Injuries

Infants and young children commonly tend to injure themselves around the head, face and mouth. Injuries to primary teeth are common in children 18 to 30 months of age because they are still unsteady on their feet.³ These injuries could also be a result of child abuse and neglect.

Parents need to closely supervise infants when they are on chairs, furniture, or any high areas from where they are likely to fall and injure themselves Table 10. Locking doors and using safety gates at the top and bottom of stairs are beneficial with an infant in the house. Pediatricians should advise parents that infants and children be placed in appropriate child safety seats in a motor vehicle and

Table 10: AAPD recommended anticipatory guidance for parents on injury prevention

- Closely supervise infants on furniture, chairs or any high areas
- Lock doors and use safety gates at the top and bottom of stairs
- Place infants and children in appropriate child safety seats in a motor vehicle

Supervise children in playgrounds make sure they play on developmentally appropriate equipment

- Avoid use of infant walkers
- Make children wear helmets when riding on bicycles or tri-cycles
- Wait until children have developed basic motor skills before allowing them to participate in organized sports
- Do not place infant in a shopping cart, instead use stroller or front pack or backpack
- Provide infant's caregiver with a dentist's emergency phone contact and ensure that they are familiar with how to handle oral health emergencies.

not place an infant in a shopping cart, but in a stroller or frontpack or backpack. Parents should not put infants in infant walkers. All of this advice should be a part of follow-up visits, given by pediatricians or dentists, based on the age and activities of the child. Interview questions about different stages in the child's development can help the pediatrician to determine which practices the parents are following and to encourage the parents to institute new practices if needed. Children need parental supervision on playgrounds and should play on developmentally appropriate equipment.³ Children should wear helmets when riding bicycles or tricycles. Before children participate in organized sports, they need to have acquired basic motor skills, which they develop at about 7 to 8 years of age. It is important to provide the infant's or child's parents with a dentist's emergency phone number and ensure that they are familiar with how to handle oral health emergencies. Trauma in children could also be from abuse or neglect. Health professionals must report suspected child abuse or neglect.

Management of Oral Injuries

Pediatricians and dentists should educate parents in advance on the management of children with injuries. They need to know how critical the time is between injury and getting care for the child, how any delay could result in damage that could become permanent. In case of a tooth avulsion, the parents should be informed that they need to find the tooth, hold it by the crown only, rinse it under cold water, and not to scrub it. The tooth needs to be reinserted in the socket making sure it is placed facing

the right way, or, if that is not possible the tooth should be put in cold milk or cold water, and the child should see the dentist immediately. A dental home can help parents in dental emergencies get immediate care for their child and thereby avoid problems like tooth loss and disfigurement.

Children with Special Health Care Needs

Children with special needs are another important group that deserves mention in this chapter. Infants and children with special health care needs maybe at increased risk for developing oral conditions like delayed tooth eruption, malocclusion, dental anomalies, trauma, infections, and soft-tissue enlargements (gingival enlargements). All of these conditions are attributed to several congenital syndromes, medications, or inherent immune deficiencies and include Down's syndrome, Treacher-Collins syndrome, and ectodermal dysplasia. Several medications cause gingival enlargements; for example, dilantin and phenobarbital, which are prescribed for epilepsy, can cause gingival hyperplasia. It is very important for a general health professional to be aware of these conditions: children with these conditions may need dental referrals on a regular basis. Like all children, these children should have their first visit within 6 months of eruption of the first tooth or at 12 months of age. However, future visits may have to be more frequent, maybe at 2 to 3 month intervals. Dental treatments may require additional time to accommodate the child's condition, medications, behavior, and complexity of care. Most important, these children should receive oral health care from those who have experience with this population.

DISCUSSION

India with its population of 1027 million (2001 census), has 72 percent of the population living in a rural setting. The rural health infrastructure consists of subcenters (SCs), primary health centers (PHCs), and community health centers (CHCs). Although the country produces 7000 dentists per annum the dentist-to-population ratio is 1:30,000. There are no dentists or dental surgeons posted at the CHC and PHC levels. Therefore it is very important for the family physician and the pediatrician to be trained to include oral health care as part of the regular health check ups since they are the only health care professionals most of the population has contact with. Physicians must receive adequate resources and information to identify dental risk behavior and should educate parents and caregivers and give necessary referrals for dental treatment.

Dental diseases have been increasing both in prevalence and severity in India over the past few decades, and an urgent need to halt the rising trend of dental diseases in India has arisen.¹¹ Dental caries is a public health problem

with prevalence as high as 60 to 80 percent in Indian children, and is more common than asthma.¹³ Also, about 30 percent of the children suffer from misalignment of teeth and jaws, which interferes with proper functioning of the dento-facial apparatus.¹²

The aforementioned problems are due to the lack of awareness about dental diseases, a missing component of oral health in the present health care setting, inadequate knowledge of general physicians and health care workers about oral hygiene and the prevention of oro-dental problems.¹³ Without question, a health care professional in India should know basic oral health and implement anticipatory guidance for patients.

The incorporation into the Indian health system of the guidelines and recommendations discussed in this chapter will be economically favorable for a developing country like India, where resources are limited and are allocated need wise. It is by far more cost effective to implement prevention and health education than to treat diseases, especially oral diseases, which for a large part are preventable.¹⁵

Since children under the age of 3 years are more likely to see a physician or other health professional earlier and more frequently than a dentist, it is very important that this health professional be knowledgeable about oral health, can recognize oral conditions, and can give necessary referrals. This early coordinated intervention can reduce the prevalence of oral diseases nationwide and can benefit the nation as a whole.

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Behavioral Problems in Pediatric Patients

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Behavioral problems in pediatric patients are of growing concern in pediatric practice. Pediatrician comes across a gamut of behavioral problems in children in day-to-day practice. Some of them are nonspecific and some of them constitute specific behavioral disorders. Nonspecific problems are few difficulties such as irritability, restlessness, stubbornness, etc. encountered by parents and teachers but they do not amount to syndromal disorder. The unanswered question is how many of these children with nonspecific behavior difficulties go on to develop specific behavioral disorder. In this chapter, the first part will outline the common behavioral problems in the children followed by behavioral disorders in pediatric age group.

COMMON BEHAVIORAL PROBLEMS

Behavioral problems are common in younger children. Western data estimates that 3 to 8 percent of under-fives have moderate to severe behavioral problems¹. The main problems in pediatric patients are attention-seeking and dependency, argumentative relations with other children, overactivity and poor concentration, disobedience and hot tempers. Boys are more likely to be overactive, disobedient and girls are more likely to be fearful and miserable.

These common behavioral problems are issues of concern for parents and many parents consult pediatrician about them. These problems are minor if they are isolated without several associated behavioral difficulties, have been present for less than six months and cause only minimal impairment to the child's life and routines. These isolated behavioral problems respond very well to explanation, self help books or a brief behavioral intervention for a specific problem.

Many times these behavioral problems persist and are associated with other behavioral problems. Problems are more common in the presence of specific language delay or mental retardation,² and adverse social and family

factors such as marital discord, low parental warmth, high criticism and maternal depression. Predictors of persistence are more severe problems, several problems in the same child, low IQ, early onset and adverse social circumstances. Caspi et al (1996) in a landmark study delineated that behavioral phenotypes such as under controlled (impulsive, restless, distractible) and inhibited (shy, fearful, easily upset) types at the age of 3 years can be a risk factor for the future behavioral and psychiatric problems such as drug use, depressive disorder, antisocial behavior.³

Behavioral management principles are the mainstay of treatment for common behavioral problems. Individual counseling of the younger child has not been shown to be effective, and medication should be considered if the problems are persistent and severe enough to be considered as syndromal behavioral disorders. Otherwise medications are seldom required and usually the condition relapses on stopping.

Behavioral management principles state that most behavior is influenced by antecedent events and consequent responses. Altering these may change the frequency or intensity of the behavior. Parents are encouraged to reinforce the behavior they want to see more often and to extinguish unwanted behaviors. For most children positive attention from the parents by smiles, eye contact, hugs and praises is the most effective reinforcement and may be supplemented by stars, small treats and rewards. While behaviorally-based treatments have a high face validity and may seem like common sense, working out such programs can be surprisingly difficult and demanding if inadvertent reinforcement of unwanted behaviors is to be avoided.

BEHAVIORAL DISORDERS

Attention-deficit/hyperactivity disorder (ADHD), conduct disorder (CD), and oppositional defiant disorder (ODD)

are the various behavioral disorders seen in pediatric patients. As a group, these are the most common disorders of childhood and among the most researched areas of childhood psychopathology. There is also increasing recognition that these disorders continue into adulthood.⁴

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

The cardinal features for children with attention-deficit/hyperactivity disorder (ADHD) are excessive motor activity, inattention and impulsiveness.⁵ Compared with their peer group, these children are restless, fidgety, and boisterous when required to be still and quiet. This is true both in structured situations, such as the classroom, and in unstructured situations, such as the playground. They have difficulty attending to instructions in academic and social situations. They tend to look away when spoken to, require frequent repetition of directions or appear unable to comprehend the nuances of an instruction. At school, their work is characterized by careless errors, poor organization and forgetfulness. They lose things such as books, notes and assignments that are crucial to school work but they also lose possessions that are of obvious personal value. They are typically last to start a designated activity (often because they cannot find the necessary materials, forget to gather them together or have been daydreaming) and last to finish (because of staring off into space, failing to concentrate and being distracted). They shout out their replies, interrupt others and are reckless and accident-prone. On the other hand, they may not speak when they are supposed to.

The characteristics of ADHD are variable both within and among individual children.⁵ It is rare to find a person who exhibits every characteristic of hyperactivity to a comparable extent. It has been seen that children with ADHD can have varied symptoms which are context-dependent varying with the demands of the situation in school and at home. Parents frequently comment that it is the marked variability day-to-day, hour-by-hour and minute-by-minute that is the most salient feature of these children. The profile of these children changes with age and development. Hyperactivity remains the prominent feature in preschool years with inattention becoming more salient once child confronts the demands of the classroom. By the time children reach adolescence, the motor activity seems to diminish, and inattention and impulsiveness become most impairing and are particularly noticeable in social situations.

Children with ADHD experience serious social, academic and psychological impairment at every stage of development. In comparison to their normally developing peers, children with ADHD have poor school performance and are more likely to have a diagnosis of a learning disability.⁶ Poor school performance results in low self-esteem, peer rejection and emotional problems

which can lead to school dropout, risk of delinquency and substance abuse. They are rejected by peers and adults and treated in a controlling and negative fashion by them. Their parents experience considerable stress and feelings of incompetence as parents which can cause frustration, emotional problems and depression in them. Children with ADHD are more likely than their unaffected peers to live in families that are disrupted by poverty, characterized by material discord and parental psychopathology and to have siblings who are at risk for the development of psychopathology.⁵

Various subtypes of ADHD have been distinguished, based on phenomenology, pervasiveness of symptoms, response to treatment and patterns of comorbidity but most of them remain less well established and speculative except the subtypes based on symptom profile. A distinction between hyperactive-impulsive, inattentive and combined hyperactive-impulsive and inattentive subtypes is made,⁷ although the true significance of this distinction is unknown. The inattentive and combined subtypes are about equally prevalent among school-age children and are more common than the hyperactive-impulsive subtype which is more common in very young children. Many children with the hyperactive-impulsive subtype have combined subtype on follow-up.

Many children with ADHD meet the criteria for another psychiatric disorder. In general, ODD is observed in 35 to 50 percent of cases, conduct disorder in 25 percent, depressive disorder in 15 to 20 percent and anxiety disorder in 20 to 25 percent. Learning disability occurs in 15 to 40 percent of children, particularly among those with inattentive symptoms, and language impairment in about 15 to 75 percent of children. In fact over 50 percent of children with ADHD meet criteria for two comorbid conditions.^{5,8}

Originally, ADHD was thought to be a transient phenomenon because of the tendency for symptoms, especially restlessness, to diminish as children grow and reach adolescence. Inattention and impulsiveness are more persistent manifestations and it is now clear that the disorder persists into adolescence in half or more of affected persons, and into adulthood in half or more of adolescent cases.⁶ Poor outcome in adolescence and young adulthood is more likely when the affected child experiences stressful life circumstances, such as those that are commonly associated with poverty, overcrowding, negative expressed emotion in the parent-child relationship, and parental psychopathology. Prognosis is also worse when the ADHD symptoms are severe, and predominantly hyperactive-impulsive in nature and when the child exhibits early conduct, language or learning disorder. Nevertheless, the poor outcome of children with ADHD is not simply a function of these early associated impairments; ADHD increases the risk of a poor outcome, even when due allowance is made for the associated risk factors.^{9,10}

The prevalence of ADHD depends to a great extent on various factors such as diagnostic measures used, sampling method, number of informants used, etc. Overall the prevalence varies from 2 to 10 percent in school-age children with boys having higher rates than girls (2-4:1). In general prevalence declines with age, but follow-up studies support that ADHD persists into adolescence and adulthood.⁶

Attention-deficit/hyperactivity disorder (ADHD) is an etiologically heterogeneous disorder that can be caused by a range of biological, psychological and social conditions that act individually or together to increase the risk of ADHD. Much of the available evidence points to the importance of abnormal higher order cognitive functions caused by dysfunction in catecholamine (dopamine, adrenaline and noradrenaline) metabolism and neurotransmission in the prefrontal cortex and associated subcortical structures. Deficits in these processes are common among children with ADHD and are thought to be the proximal cause of their poorly regulated everyday behavior and impaired performance on laboratory tasks.¹¹ Relatives of individuals with ADHD having increased risk for ADHD, a markedly higher concordance of ADHD for monozygotic (79%) than dizygotic (32%) twins, biological parents of ADHD individuals more likely to exhibit ADHD or related disorders than are adoptive parents offer strong evidence of genetic susceptibility to ADHD.⁵ It is now established that certain alleles of the genes coding for the dopamine D4 receptor (7-repeat-allele) and the dopamine transporter (10-repeat-allele) occur more frequently in children with ADHD than in healthy controls.¹²

A range of psychological and neurobiological risk factors are associated with ADHD, including maternal stress during pregnancy, poor quality or disrupted early care giving as may be seen in children in institutions foster care, fetal exposure resulting from the mother's use of alcohol, drugs or cigarettes, the adverse effects of perinatal obstetrical complications or prematurity, traumatic brain injury, iron deficiency and exposure to environmental toxins such as zinc or lead. These risk factors probably interact among themselves and with genetic risks, making the specific role of any single factor difficult to assess accurately the etiology of ADHD.^{4,5}

To diagnose ADHD, the clinician should obtain information from the child's parents, the child and the child's classroom teacher. Behavior rating scales provide a valuable, simple and inexpensive means to collect descriptions of child behavior from various informants. During the assessment, the presence of a concurrent disorder and the relationship of the symptoms of a comorbid disorder and ADHD should be assessed. Children with ADHD are able to suppress their inattention, restlessness and impulsiveness to a great extent in novel and highly structured situations, such as those afforded by the typical visit to the clinic. Nevertheless, the interview

of the child may be useful for identifying comorbid disorders, assessing the relationship of symptoms to anxiety or academic demands, monitoring treatment, and establishing the report that is required to sustain a prolonged intervention. Because many children meet ADHD criteria almost exclusively on the basis of behavioral difficulties within the school context, it is essential to assess the presence of learning difficulties and language problems, the nature of the educational experience and the quantity of the child's relationships with peers and teachers. Intelligence test (IQ) and educational assessment to rule out mental retardation and learning difficulties are required whenever the child has poor school performance and difficulties in reading, writing and arithmetic. As there is no diagnostic test for ADHD, specific blood test, EEG and neuroimaging techniques are reserved for individual cases having high suspicion of organicity, dysmorphic features, and regression in milestones and should not be done on a regular basis. Recently there has been an alteration in the diagnostic criteria for ADHD. According to new guidelines issued by the American Academy of Pediatrics (AAP, November 2011) the age range for the diagnosis and treatment of attention-deficit hyperactivity disorder (ADHD) has been expanded to children as young as 4 and as old as 18 in contrast to original age range of 6 to 12 years.

Currently the accepted approach to treatment involves long-term multimodal intervention in which various pharmacological and psychological treatments and combinations of treatment are used together with a supportive management strategy. The mainstay of treatment is stimulant medication with psychological therapy involving family. Special diet (Feingold diet, elimination diet, reduce sugar intake), dietary supplements, Omega-3 fatty acids, and electroencephalographic (EEG) neuro-feedback are also used as an alternative to medication with promising results in certain children but more adequate scientific data is required.

Psychostimulants including methylphenidate (short term and sustained release available in India), dexamphetamine and pemoline, have shown to be effective in the treatment of ADHD. Numerous placebo-controlled randomized control trials confirm the substantial short-term benefits of stimulants.¹³ Although stimulants have proved effective, they have their limitations. They are thought by many to be prescribed too frequently and inappropriately and to be a public health risk in their own right because of their potential for undetected long term adverse events, for abuse and for the way that they can distract from 'genuine' treatments. Medication is not an acceptable treatment option for many children and families. Families are concerned about the biological or ethical implications of treating young children with drugs or about the potential for unknown long term risks of treatments. Lack of adherence limits the effectiveness of medication, as it does with

all medical treatments. Even though a beneficial impact of behavior, as rated by their teachers, may occur in about 70 percent of treated children, treatment normalizes the behavior of only about half of children and many disabilities remain. One of the most significant limitations of stimulant medication is the lack of evidence of its efficiency over prolonged periods of treatment.

Other drugs used in the management of ADHD and comorbid disorders include antidepressants, clonidine and its analogues, selegiline, newer atypical neuroleptics, and atomoxetine, a novel, nonstimulant therapy that has potential to fulfill some unmet treatment needs. Atomoxetine is a highly selective noradrenaline reuptake inhibitor that has been studied for use in the treatment of attention deficit/hyperactivity disorder (ADHD). Recent data from clinical trials show it to be well tolerated and effective in the treatment of ADHD in children, adolescents, and adults. Improvements are seen not only in core symptoms of ADHD, but also in broader social and family functioning and self esteem. Once-daily dosing of atomoxetine has been shown to be effective in providing continuous symptom relief. Atomoxetine does not appear to have abuse potential and is associated with a benign side effect profile. The development of atomoxetine represents an important advance in the pharmacological management of ADHD.¹⁴

Various psychological therapies have been used for ADHD, either as an alternative to medication or as a method of augmenting the effects of medication. Behavior parent training is the most commonly prescribed psychological intervention for ADHD predicated on the observation that parents of children with ADHD use overly controlling and inefficient parenting strategies and that adversity in the parent-child relationship is predictive of poor outcome.¹⁰ Parent-training programs (Table 1) use instruction, modeling and role-playing to teach parents to reinforce positive behavior, decrease the use of punitive strategies, and manage defiant, stubborn and inappropriate behavior effectively which improves the parents' child management skills, enhance their self-confidence, reduce family stress and mitigate oppositional behavior. However, parent training does not reduce the core symptoms of ADHD as effectively as does stimulant medication, nor does it appear to enhance the effectiveness of stimulants. Benefits tend not to persist beyond the period of treatment. Cognitive behavior therapy attempts to enhance self-control by teaching children self-instruction strategies. Social skills training targets the child's problems with peers and adults, typically in a group setting.

Overall, the evidence strongly supports the use of stimulant medications for treating the core symptoms of children with ADHD and, to a lesser degree, for improving functioning. Behavior therapy alone has only limited effect on symptoms or functioning of children with ADHD,

Table 1: Management tips for parents for children with ADHD

- *Basic techniques for attention enhancement*
 - Call the child by name
 - Make an eye contact with the child before talking to him/her
 - Use slight touch at times to gain child's attention
 - Keep the message short and clear
 - Be very crisp while talking to the child
 - Give single command at a time
 - Avoid detailed explanations
 - State the command positively
 - If possible give the child an option
- *Basic management for increasing organizational skills*
 - Encourage use of checklist
 - Encourage use of stopwatch to time self for completion of work
 - Making a time table
 - Organize everyday items. Have a place for everything, and keep everything in its place. This includes clothing, backpacks, and toys.
 - Use homework and notebook organizers. Use organizers for school material and supplies. Stress to your child the importance of writing down assignments and bringing home the necessary books.
- *Basic management for increasing compliance of instructions*
 - Set clear rules/discipline for home
 - Have prescribed consequences of misbehavior
 - Postpone the child's desire gradually starting from 2 minutes to 10 minutes to 20 minutes
 - Be clear and consistent. Children with ADHD need consistent rules they can understand and follow.
 - Give praise or rewards when rules are followed. Children with ADHD often receive and expect criticism. Look for good behavior, and praise it.
- *Basic management for channelizing energy positively*
 - Give frequent study breaks
 - Have a zero tolerance policy for hitting, pushing and yelling in your house or yard.
 - Encourage the child to participate in more sport activities (physical).

although combining behavior therapy with medication seems to improve functioning and may decrease the amount of (stimulant) medication needed.¹⁵

Conduct Disorders

Unlike most disorders, conduct disorders (CDs) are entirely defined in terms of the individual's relationship with other people and society. There is a persistent pattern of antisocial behavior whereby the individual repeatedly breaks social rules and carries out aggressive acts that disturb other people. This persistent tendency typically starts young and carries on until at least middle age. Thus a substantial proportion of children and adolescents with conduct disorder grow up to be antisocial adults, leading impoverished and destructive lifestyles; a significant minority will develop antisocial personality disorder

Table 2: Clinical features of conduct disorders
(Modified from ICD-10 DCR)¹⁷

<i>Conduct disorder (CD)</i>	<i>Oppositional defiant disorder (ODD)</i>
<ul style="list-style-type: none"> • Aggression to people and animals • Destruction to property • Deceitfulness or theft • Serious violation of rules 	<ul style="list-style-type: none"> • Unusually frequent or severe temper tantrums • Often argues with adults/actively refuses adults requests or defies rules • Often, apparently deliberately does things that annoy others • Often blames others for their own mistakes/misbehavior • Often angry/resentful/touchy • Often spiteful/vindictive

(psychopath). The personal impact and cost to society is high, since many domains of living are affected, many professionals and agencies get involved in managing the sequelae.¹⁶

Conduct disorders (CDs) comprise (Table 2) oppositional defiant disorder (ODD) which mainly affects younger children, and conduct disorder (CD) which affects older children and teenagers.¹⁷ In some children ODD is followed by features suggestive of CD. Approximately 90 percent of children with CD would also meet the criteria for ODD⁴. It is doubtful whether ODD differs substantially from CD in older children in any associated characteristics, and the value of designating it as a separate disorder is arguable. They are both variants of antisocial behavior although they differ on the intensity and severity (Table 2), so many clinicians call both as conduct disorders (CDs) and henceforth in the following text both will be discussed as CDs.

Although the Indian data is lacking, as per western data the rates for CD have been estimated to as low as 0.9 percent for school-age children but as high as 8.7 percent in adolescents. The overall prevalence of ODD varies across studies from 4 to 15 percent.⁴ Available evidence suggests that the juvenile crimes have risen and specific studies of CDs across cohorts also suggest a rise over the last 40 years. CD is common in boys at all ages, but the ratio of boys to girls depends on the type. In childhood, for oppositionality, boys outnumber girls by around 4:1. In adolescence the ratio narrows to around 2:1.

Major differences are found between early and adolescent onset CD. Those with an early onset display defiant and aggressive behavior before the age of 8, but it typically begins around 3 years of age. They go on to increasingly antisocial behaviors as they grow older. However, not all young children with this early onset pattern progress to more severe difficulties later in childhood. Only about half persist; the remainder improves. Compared to the adolescent onset group, the early onset children at three years show a more difficult temperament (restlessness,

inattention, negativity, irritability, etc.). At school age this group has cognitive, language and motor deficit, reading difficulties, adverse family contexts and poor parenting. By 18 years they have fewer friends and feel socially alienated, victimized, and are callous and suspicious. They continue behaving antisocially as adults. This pattern of antisocial behavior has been described as early onset-lifetime persistent.

Common by about 3 to 1 are the adolescent onset group who have not shown significant antisocial behavior earlier in their lives. Moreover by their early twenties they have reduced their level of antisocial behavior to less than half the level of the early onset groups. This group has been described as adolescence-limited, although they may not completely stop in adulthood and further studies will answer this question. The overall rate of arrests and convictions is somewhat lower than the childhood onset type, there are more girls (about 2:1 instead of 4:1 for childhood onset). Their behavior tends to be less aggressive and violent, less impulsive, they have fewer cognitive and neuropsychological deficits, more mood symptoms, tend to come from less dysfunctional family environments, and tend to be more adaptive socially. Crucially, the adolescent onset groups are more likely to stop offending in early adulthood than the early onset groups. There is only a small group of individuals who commence persistent antisocial activity in adulthood, less than 10 percent of the total.¹⁶

The outlook in children with CDs is determined by the frequency and intensity of antisocial behaviors, the variety of types, the number of settings in which they occur, and their persistence. The main settings where antisocial behavior in children and adolescents is manifested are home, school, and in public. There are many children who are perceived to be mildly or moderately antisocial at home but well behaved at school, and vice versa. However, for more severe antisocial behavior, there are usually manifestations both at home and at school. Concerns about antisocial behavior in public occur more commonly in adolescents and often lead to legal problems.

The duration of symptoms is another important consideration. Many children go through phases of becoming more defiant and argumentative for a few weeks or months. Sometimes this may be a reaction to a change in circumstances such as setting into a new school, or losing a friend or loved one. Only when difficult behavior has been present for 6 months or more, then it is likely to indicate substantial problems.

Making a diagnosis of conduct disorder is usually straightforward since parents readily volunteer the symptoms, although it is essential to obtain an independent report from school so as not to overlook behavior in that context. Sometimes the diagnosis may be inappropriate since antisocial behavior may arise

as a part of other disorders such as autism or mania, or may not be severe enough to warrant a diagnosis. More commonly the diagnosis is correct but comorbid conditions such as mood disorders are missed which are more common in adolescent onset group. Observation of parent-child interaction is invaluable which can be done when the family is seen together at the initial stage of the consultation. Individual session with the child is important as it may reveal some evasiveness about the difficult behavior, home environment and mood symptoms but appreciation of the child's strengths and demonstration of understanding by the clinician can go a long way in building trust. Physical examination should be carried out, looking for dysmorphic features, usually most evident in the face and hands. No medical tests are usually necessary, although chromosomal examination should be undertaken if dysmorphic features are found with EEG and neuroimaging techniques undertaken if there is a history of head injury, loss of consciousness or epilepsy. Cognitive assessment with an IQ test and assessment for learning difficulties is desirable if academic performance is sub-average.

As for any psychiatric disorders, both genetic and environmental risk factors contribute (Table 3). Whilst in the last 20 years genetic factors and nonshared (unique) environment have become recognized as major determinants for most disorders, for conduct disorder

family style, particularly parenting is much more of a major cause, together with temperament factors including hyperactivity and IQ.¹⁶

Protective factors in children who do well despite adverse risk factors have been studied. These so-called 'resilient' children, however, have been shown to have lower levels of risk factors. Protective factors are mostly the opposite end of the spectrum of the same risk factor, thus for example good parenting and high IQ are protective. Nevertheless there are factors which are associated with resilience independent of known adverse influences. These include a good relationship with at least one adult, who does not necessarily have to be the parent; a sense of pride and self-esteem; and skills or competencies.

Engagement of the family is particularly important in treatment for this group of children and families as dropout from treatment is high, at around 30 to 40 percent. Careful assessment of parental functioning is especially important in conduct disorders as it is such a major determinant of the problem, and such as effective and rewarding means of treatment. Parenting interventions may need to go beyond skill development to address more distal factors which prevent change. For example, drug or alcohol abuse in both parent, maternal depression, and a violent relationship with the partner are all common which need to be addressed. There is no evidence that in-patient admissions lead to gains that are maintained after the child is returned to their family, so this costly course of action is not recommended. A multimodal approach is likely to get larger changes.

Proven psychological interventions in CDs include those which singly or in combination address:^{4,16,18,19}

- Parenting skills
- Family functioning
- Child interpersonal skills
- Difficulties at school
- Peer group influences

Programs designed to improve parenting skills and the quality of the parent-child relationship have been found in randomized controlled trials to be effective for children up to about 10 years old.^{16,19} They address the parenting practices identified in search as contributing to conduct problems. Typically, they include 5 elements:

- Promoting play and a positive relationship
- Praise and rewards for sociable behavior
- Clear rules and clear commands
- Consistent and calm consequences for unwanted behavior
- Recognizing the child's day to prevent trouble.

Treatment can be given individually to the parent and child, which enables live feedback in light of the parent's progress and the child's response. Alternatively, group treatments with parents alone have been shown to be equally effective. Trials show that behavioral parenting programmers are

Table 3: Risk factors for conduct disorders (CDs)^{4,16}

Genetic

- Genetic influences – in early onset with comorbid hyperactivity
- XYY karyotype – higher rate of criminal behavior

Child characteristics

- Difficult temperament
- Hyperactivity/ADHD
- Social skill deficits, low self esteem
- Faulty thinking style/distorted cognitive attributional bias
- Physical and sexual abuse
- Low IQs, deficits in executive control functions, autonomic arousal

Family environment

- Coercive parenting styles
- Harsh, erratic discipline
- Lack of warmth, critical/hostile
- Poor supervision
- Marital discord/broken homes

Psychiatric problems in parents

- Depression, drug use, psychoses
- Criminality of father

Environment beyond the family

- Poorly organized unfriendly schools
- Deviant peer influences, rejection by peers
- Alcohol and drug use
- Overcrowding, poor housing, poor neighborhoods

effective in reducing child antisocial behavior in the short term, there is little loss of effect at 1 or 3 years follow up. Parenting skills interventions are chiefly used with younger children, although there is evidence for their successful use with delinquent boys.

Multisystematic therapy¹⁸ and treatment foster care²⁰ aim to change a range of difficulties which impede effective functioning of teenagers with conduct disorder. Multisystematic therapy was developed by Henggeler and colleagues in the USA. The young person's and family's needs are assessed in their own context at home and in their relations with other systems such as school and peers. Following the assessment, often methods of intervention are used to address difficulties and promote strengths. Treatment foster care is another way to improve the quality of encouragement and supervision that teenagers with conduct disorder receive. The young person lives with a foster family specially trained in effective techniques; sometimes it is ordered as an alternative to jail. While the young person is living with the specially trained foster cares, the families of origin are trained in effective methods. Outcome studies following return to the birth family show useful reductions in rates of reoffending.

Most of the programs to improve child interpersonal skills derive from cognitive behavior therapy²¹ which helps young persons to:

- Slow down impulsive responses to challenging situations by stopping and thinking
- Recognize their own level of physiological arousal, and their own emotional state
- Recognize and define problems, develop several alternatives responses and choose the best alternative based on anticipation of consequences
- Reinforce themselves for use of this approach.

Difficulties at school can be divided into learning problems and disruptive behavior. There are proven programmers to deal with specific learning problems. There are several schemes for improving classroom behavior, which vary from those which stress improved communication and those which work on behavioral principles are part of a multimodal package. Many of these schemes have been shown to improve classroom behavior, and some specifically target children with conduct disorder. At the level of the individual teacher with a particularly disruptive child, two or three sessions spent imparting and refining basic behavioral management techniques can lead to substantial improvement in classroom behavior and learning.

A few interventions have aimed to reduce the bad influence of deviant peers. However, a number attempt this through group work with other conduct disordered youths. But outcome studies showed a worsening of antisocial behavior. In modern treatments therefore, either youths are seen individually where an element is to try to steer them away from deviant peers, or the work is in small groups (say 3-5 youths) where the therapist can control the

content of sessions. Some interventions place youths with conduct disorder in groups with well-functioning youths, and this has led to favorable outcomes.

There is no convincing evidence that medication has any specific effects on conduct disorder. Extreme irritability just might be part of a manic illness and so respond to lithium, anticonvulsant or mood stabilizing drugs, but in the absence of other features confirming the diagnosis of a manic illness medication should not be given. Neuroleptics can, unsurprisingly, have a sedative effect and are not infrequently used for challenging behaviors in children and adolescents with mental retardation, but several studies show that if psychological management is better, this usage declines or stops. Where there is comorbid hyperactivity in addition to conduct disorder, several studies attest to a large reduction in antisocial behavior with medication, both at home and at school. However, the impact on long-term outcome is unstudied.

Overall, much is known about the causes of conduct disorder, and there are many effective interventions available. The challenge is to make these universally available, and to deliver them with quality and fidelity so the life changes of the young people improve.

Also there are various sociocultural factors that influence the diagnosis and management of the behavioral disorders. It is important to note that manifestation of them can be very culture specific. However, our most of the diagnosis and management plans are based on western studies done on western populations. This becomes one of the limitations of the treatment processes practiced in India. Further, on one hand western world is often accused of over diagnosis and overmedication of ADHD and behavioral disorders, and on the other side in India, the problem of under diagnosis remains to be a huge concern. This problem is due to various factors like lack of awareness, lack of good culture sensitive assessment tools, limited child and adolescent mental health services, etc. Both of these concerns indicate conducting more Indian research to understand the behavioral disorders in children and also to develop productive therapy modules which are culture specific and hence more beneficiary and cost effective in our Indian scenario.

KEY POINTS

- Behavioral problems are common in children and behavior management principles are effective in their management.
- ADHD and conduct disorders present as challenging behavioral disorders in pediatric age group and have substantial risk for poor outcome in adolescence and adulthood.
- Multimodal treatment including a variety of pharmacological and psychological interventions have been found to provide success over the short term, and

increasingly data indicate that treatment effects can be maintained over more extended period of time.

- Indian studies are needed to understand complexities of behavioral problems and behavioral disorders in pediatric age group and to develop culture specific and cost effective interventions.

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Psychosocial Aspects of Chronic Diseases

Roma Kumar

Learning that a child has a life-threatening illness and adjusting to the demands of treatment are amongst the most distressing experiences that a family can face. Although family therapists and psychologists often treat families with seriously ill children, there has been little rigorous family research in this area. Both children and adults with medical illnesses have benefited from twentieth century advances in medicine, and clearly still more advances loom on the horizon of this century. Children who, in the past, might have died or had their physical functioning severely comprised by their illness are now living into adulthood. As more children survive childhood diseases they have a potentially better quality of life than ever before. The leading consequence is that attending to children's physical care also requires attending to their psychological well-being. Mental health professionals have been increasingly sought out by families and physicians to help chronically ill children and their families with illness related problems optimize psychological functioning throughout life.

Illnesses and their treatments change, both within the course of illness and over time. Indeed, in most childhood chronic illnesses, substantial progress has been made in recent decades in treatment and cure. These changes have affected the type of care that families provide, and often the meaning of the illness for the child and family. In childhood diseases, illnesses that were once fatal are now curable. Thus childhood cancer has become more akin to chronic disease (rather than terminal illness) as treatment spans several years and survival becomes a strong possibility for particular illnesses.

Changes in treatment and survival alter the developmental framework for understanding family adjustment. With early onset and treatment lasting many years, childhood chronic disorders affects the family system during its early childrearing years and results in a population of

survivors who are still young children. Specific issues for families at this stage include

- Other infant or preschool children,
- Normal developmental behaviors (high level of activity, fearfulness) accentuated by treatment,
- Discipline of ill preschoolers, and
- Parents balancing childrearing and employment demands.

The long-term impact of surviving an illness that killed peers but that is largely inaccessible to conscious memory is an unknown and interesting question. Furthermore, although children may recall little of the experience, the long-term memory of the child's illness and its legacy in the family is likely to persist.

The concept of "psychological problems" is broad and comprises a large number of possible components. There exists a wide variety of theoretically based instruments intended to tap various aspects of the human psyche. Anxiety and depression are among the most common psychological problems that are discussed and studied in relation with disability.

The proportion of children affected by chronic illness is relatively high, approximately 10 to 12 percent. For these children, there is no available cure and the best that medical care can currently offer is relief from symptoms and the opportunity to participate in normal life as far as possible. Epidemiological work suggests that many of the children experience relatively few restrictions on everyday life, but about 1 to 2 percent of the total population of sick children have more severe conditions.¹

Chronic illness has been defined as, "a disorder with a protracted course that can be fatal or associated with a relatively normal life span despite impaired physical or mental functioning. Such an illness frequently shows a period of acute exacerbations requiring intensive medical

attention.” Chronic illness or disease differs from acute illness in that,¹ it is treatable yet not curable, thus needs management for long periods of time, and therefore,² the responsibility for the management of the illness is shared with and/or transferred to the child and family. Illnesses such as asthma, insulin dependent diabetes mellitus (IDDM), congenital heart disease, juvenile rheumatoid arthritis, sickle cell disease, hemophilia, cystic fibrosis, cancer, and AIDS fit this definition of chronic illness. Although these conditions have distinct biological processes, there are numerous commonalities with respect to the psychosocial impact on the child.

Historically, clinical psychology has focused on pathologies perceived to be within individuals, with intervention geared toward remediation after the onset of psychopathology. More recent developments have modified this orientation to include prevention and increase involvement with individuals whose problems do not necessarily involve psychopathology or in situations in which an orientation that is broader than an intra-individual focus is warranted. In childhood chronic disease, psychological problems can become a primary handicap, although for most of these children diagnosable psychological disturbances are not found. It is not uncommon, however, to see mild-to-moderate levels of distress or psychopathology somewhere within the family system. Psychological distress appears to be related to several variables, including the nature and course of the illness; individual coping resources; family structure and function; and medical, psychosocial, and educational resources. In many medical settings, children with chronic health problems are referred to psychologists because of concomitant cognitive impairments that require assessment and the integration of recommendations with other health care professionals. Although developmental, educational, social and family issues are often explored, the involvement of psychologists in this process has frequently been limited to cognitive assessment or to the management of behavior problems. In terms of assessment, intervention, and research, psychologists' roles with chronically ill children can be expanded.

In this chapter we discuss the issues critical to understanding the psychology of chronic medical illness – definitions and prevalence, models for understanding the interaction of illness and psychological adjustment, psychological risk factors, causes of adjustment problems and psychological disorders as well as strategies of prevention and intervention. Understanding the interaction of the medical illness and psychological factors can form the basis of an intervention plan that can affect the course and outcome of the illness and maximize the well-being of a child with chronic medical illness.

Chronic diseases share the following characteristics:

- They have a biological, psychological or cognitive basis
- They last, or are virtually certain to last, for more than one year
- They are associated with one or more of the following sequel:
 - Limitation of function, activities or social role in comparison with healthy, same-age peers in the areas of physical, cognitive, emotional and social functioning, as well as growth and development
 - Dependency on one or more of the following to compensate for or minimise limitation of function, activities or social role: medications, special diet, medical technology, assistive device, personal assistance
 - A need for medical care or related services, psychological services or educational services over and above the usual for the child's age, or for special ongoing treatments, interventions or accommodations at home or school ²

PSYCHOLOGICAL IMPLICATIONS OF LIVING WITH CHRONIC DISORDERS

- Stress and anxiety
- Depression and low mood
- Fear of dying/ breathless/ exacerbation
- Panic
- Altered body image
- Altered role in family
- Loss of control and independence
- Lifestyle changes
- Alteration of relationships
- Low self-esteem/sense of worthlessness
- Denial
- Anger
- Loss of dignity
- Frustration
- Guilt
- Loss of intimacy
- Irritability and impatience

Expression of emotion is closely linked with dyspnea and some patients may avoid emotion as an adaptive coping mechanism. This may result in patients living in an 'emotional straight jacket', which may then predispose to or compound existing anxiety and depression.

Impaired physical and social dimensions of daily living often result in a sedentary lifestyle with progressive dyspnea and fatigue. This in turn leads to social isolation and an inability to participate in many activities of daily living.

PSYCHOLOGICAL RISK FACTORS RELATED TO ILLNESS

The coping ability and adjustment of the chronically ill child or adolescent depend on multiple factors. These include risk factors related to the illness itself and resistance factors related to the individual. Although there is no one-to-one relationship between any particular risk factor and a particular outcome, the areas of influence include:

- *The degree to which the illness impairs functioning:* Functional disability seems to increase the risk of psychological problems, but the relationship is complicated by other factors. For example, it has been suggested that visibility of illness may contribute to improved psychological functioning because the inability to hide or deny the condition may compel the child to adjust and accept his status;
- *Involvement of the brain:* Behavior, social and cognitive problems have been consistently associated with conditions or treatments affecting the brain. In some instances, insults to the brain, as when a stroke or tumor occurs, can lead to impairments in cognitive functioning that can cause learning problems or social skills deficits;
- *The nature of the illness:* the severity and the course of the illness, and the direct threat to life influence psychological concerns and outcome. For example, cystic fibrosis impairs lung functioning and decreases later life expectancy. Thus, fear of death may increase over time in concert with the change in illness status. For a child with cancer, in spite of a possible 70 to 90 percent rate of remission for some forms of cancer, the terror of death at diagnosis is more likely to occur than for someone diagnosed with IDDM;
- *The type of medical procedures and hospital/non-hospital required experience:* Direct interventions—painful or benign—and where they occur vary widely. Sickle cell disease may require ongoing lifestyle changes with intermittent hospital admission for painful crises. This illness biography impacts a child differently than a lifetime routine of self-administered insulin injections by a child with IDDM or the surgery and concentrated 14-month treatment for a child with bone cancer;
- *The interference with nonillness related aspects of life:* An illness can easily spill over into or consume other areas of life. A child with acute lymphocytic leukemia may need chemotherapy and related treatment for three years. This treatment necessitates sporadic school absence that is likely to affect social and academic skills development. These academic and social risks are different than those for the child with juvenile arthritis, for example, who must have a modified school athletic program;
- *Family functioning:* Both the way the family functions and the effect of the illness on the family influence the child. Parents, siblings, grandparents, and extended family members are prone to particular expected reactions to illness that in turn impact the child. Parents' emotional well-being and style of coping directly affect the child, either due to the child's modeling of parents' reactions, or because the parents' functioning changes the family environment. Marital stress and family functioning can be either helped or hurt when a child has a chronic illness, but illness alone does not automatically cause long lasting family trauma. The consensus is that a child does best when a family is cohesive, flexible, and supportive, the mother is coping well, and communication is open and clear;
- *The individual characteristics and internal resources of the child:* Preillness personality, functioning, and coping ability interact with the illness related situation to affect the level of distress for the child. Anxiety and learning disorders, attention-deficit/hyperactivity disorder, etc. exist in the general population as does poor family functioning, abuse and neglect—all of which can be components in the child's life irrespective of, but affecting, the illness picture. Unfortunately, most findings in this area are gathered after an illness, making preventive conclusions difficult;
- *Demographic variables such as age, sex, and social class:* The general influences of non illness risk factors also have bearing on adjustment, psychiatric, or behavioral problems. For example, "the risk of emotional problems in the general population increases with age, the emotional well-being of boys with a chronic physical illness is usually more affected than girls," but not always, and the risk is greater for those with a chronic illness as well as a disability;
- *External resources and support systems:* Adequate outside support can have a positive effect on the child and family's adjustment and is related to personal, financial and geographic factors. Social support typically includes available interpersonal networks and is seen as either protecting individuals from the detrimental affects of stressful life events or enhancing life regardless of life stress. There is also a dynamic interaction between the individual and the actual supports. However, the individual's perception or interpretation of the availability, size, and utility of these systems or individuals influences their effectiveness. An at-home single mother with more than one child may require and accept different kinds of help than a working couple with one child, newly relocated to another part of the country and feeling distant from family. Therefore providing support requires an understanding of an individual's preferred style, what is deemed supportive, and how it is most successfully accessed.

INCIDENCE AND CAUSE OF PSYCHOSOCIAL ADJUSTMENT PROBLEMS AND PSYCHIATRIC DISORDERS

The general consensus of the limited literature is that chronically ill children are at risk for psychological problems. There is, however, little agreement as to the incidence or cause. Estimates range from 9 to 37 percent, compared to 5 to 15 percent in the general population. Problems that do exist are most likely a normal response to illness-related issues and experiences rather than an indication of serious disturbance. This is not to say their significance should be ignored, only that they should be put in the correct context.

Definitive epidemiological statistics and results of intervention programs are difficult to report due to: existing resistance or denial of the problem from medical staff, the small numbers of children available with any one illness, the flaws inherent in collecting data from children with different illnesses, the lack of adequate comparative control groups, and the problem in accurately defining appropriate adjustment for these children. Because chronic illness itself is not likely to cause serious psychiatric disturbance, distinguishing between symptoms characteristic of a more systemic problem, such as depression or anxiety, and those resulting from the illness and situation, such as the stress of hospitalization or separation from parents, is of key importance. It is not unusual for children hospitalized for long periods of time to develop sleep, eating, or behavior problems due to constant waking by staff, physical restriction from intravenous lines, unappealing food, and to experience feelings of frustration and lack of control. A 5-year-old girl with leukemia may throw tantrum due to anxiety about being separated from her parents while receiving radiation treatments. These situations are instances of reactions precipitated by particular illness-related events. On the other hand, a preadolescent with hemophilia may be noncompliant with medical appointments and guidelines for curtailed physical activity as a result of conduct or learning problems unrelated to, but interfering with, the illness.

The most common psychological problems and areas of concern for mental health professionals are:

- *Internalizing problems:* anxiety, depression, fear, hopelessness, helplessness, loss of control, frustration
 - *Externalizing problems:* aggression, noncompliance, withdrawal
 - *Somatic complaints:* pain and impaired functioning
 - *Self-concept issues:* poor self-image, low self-esteem, changed or negative identity
 - *Social and educational difficulties:* academic and learning problems, decreased or deficient social competence
- particular problems that vary by illness are associated across different illnesses but for different reasons. For example, cognitive deficits are a possible complication

for children with leukemia who have had cranial radiation and for children with sickle cell disease if they have had strokes. As medicine and mental health services help more children, more are physically and emotionally healthier. A review of 60 studies of children ages 4 to 18 who had various chronic medical problems concluded that children with cancer were no more depressed than other children.⁴ Thus outcome research may show even smaller differences and more accurately delineate etiology and identify successful treatment. In fact most recently, cancer patient survivors were found to be functioning as well as, if not better than, their healthy counterparts on measures of aggression, antisocial behavior, and substance abuse.

MODELS FOR UNDERSTANDING THE INTERACTION OF ILLNESS AND ADJUSTMENT

Various models have been proposed for explaining and directing research on psychosocial adjustment, but most are generally constructed around concepts of stress and coping. Different theoretical frameworks describe the source of stress as:

- Emanating from the illness itself, as when a child with asthma has a flair up of breathing problems or must be hospitalized for a procedure; or from life stress and the environment, such as when a child changes schools or has parents who are divorcing;
- Derived from the interaction between specific illness risk factors (e.g. functional handicap and existing mental health problems) and protective or resistance factors (e.g. parental adjustment and problem solving ability).

One way to understand adjustment is by looking at the relationship between the source of the stress or threat and an individual's personal appraisal of stress. The basic stress and coping model posits that stress can be objective (e.g. shots hurt) or subjective (e.g. being afraid of shots). Successful coping strategies can be either problem-focused, addressing the objective source, or emotion-focused, directed at the subjective affective response.⁵ Active problem-focused coping efforts on the part of the child have proven to be more effective than avoidant coping or self-blame for concrete illness related medical needs. Research has yet to tailor treatment protocols due to an incomplete understanding of variables that influence treatment outcome. Age, gender, cognitive ability, and personality style are some factors that have been shown to independently or interdependently act on illness to impact outcome. For example, one study showed that girls with migraine headaches "profited more from (behavioral-psychophysiologic treatment) than boys, and those with a shorter history of migraine evidenced greater headache reduction as a result of treatment".⁶

Also unclear are the processes responsible for change. For example, a family-based intervention has been shown

to improve metabolic control of adolescents with diabetes but not family functioning, so the family-specific mechanism responsible for the change is not apparent. Thus successful functioning is dependent on isolating salient variables which affect treatment outcomes and refining interventions.

MANAGEMENT OF ILLNESS RELATED ISSUES: PREVENTION AND INTERVENTION

Due to the variability in illness type, degree of physical impairment, and the individual characteristics of the child's situation, identifying interventions requires careful assessment. Ideally, even though an understanding of the psychological issues is reached according to their medical origin, particular consideration should also be given to the individual and family variables that will influence intervention outcome.

The medical model for understanding illness prevails when a child's problems originate from a medical illness and the case is identified via the medical system. Prescribing an intervention can best be done by understanding the concrete medical/illness basis for the problem and its consequent psychological problem. For example, a child on chemotherapy with periodic low white blood cell counts may have restricted social activities. Psychologically, the child can feel he has no control over his body or illness, feel isolated, and therefore be angry and withdrawn. Intervention must target the source of the problem (perhaps with education or instruction on infection precautions) in addition to the resulting feelings and behaviors (perhaps by encouraging viable options for maintaining contact with classmates).

When, Why, and How to Intervene?

Planning an intervention is a complex process. The first step is to decide on a target problem and which aspect of the problem to attack. At first glance, a problem may seem straightforward, yet closer inspection usually reveals the interconnected, multidetermined nature of medically related psychosocial problems. For example, fluctuating insulin levels in a child with IDDM are most obviously related to inadequate insulin management. The cause of the poor management, however, is less obvious. Possible explanations include: improper technique, poor understanding of the disease, lack of parental supervision of a child who is self-administering insulin, and a child or parent's anger or denial.

The goals of preventive and targeted intervention include:

- "Mastery of anxiety and fears related to the illness and its management;
- A developmentally appropriate understanding of the illness;
- Compliance with treatment regimens;

- Integration of the illness into family life, including a balance between the needs of other family members;
- Successful adaptation to the important systems, such as the hospital, school and peers.⁷

Types of Interventions

Various interventions have been used with the child and/or those individuals in the home or school environments to meet the psychological demands imposed by the illness. Listed below are some of the most prevalent interventions.

Education: The importance of education about a disease – its cause, course, treatment, and long term effects – is often overlooked. But understanding of this information is influenced by the patient's age, cognitive ability, and psychological style. Children, like adults, vary as to the amount and type of information that is useful. Educating a child and family is not an all-or-nothing, single event. Accurate, honest information is the standard, but it must be transmitted in language appropriate to a child's age, when he/she is ready, and perhaps repeated at different times and in different formats. This also means refraining from making unrealistic promises such as "this won't hurt." A long-term view of education is also important. It is incorrect to assume that a child diagnosed with leukemia at 3 years of age, treated until age 6, who has relapsed at age 8 will know all there is to know based on experience alone. Misconceptions and inadequate and inaccurate information likely coexist and are confused with a more mature conceptualization. As children age, new issues become relevant. Genetic concerns with respect to marriage and pregnancy, for example, may emerge for the young adult with cystic fibrosis who is exploring intimate relationships. Education about appropriate parent-child interactions can decrease parents' overprotective tendencies and the child's adoption of the "sick" role. Illness information and guidance about interacting with the health care system and staff also can empower children and parents to be useful advocates and care partners.

Cognitive-behavioral strategies: Cognitive and behavioral techniques can help a child or teen identify the source of stress, change how it is perceived, and/or teach new behaviors. The goal of this approach is to reduce the impact of the stress, and to change feelings and consequent experiences. Cognitive components can include exploration of the link between thoughts and actions and training in more helpful ways of thinking about problems or symptoms. Behavioral components can include: breathing exercises, filmed modeling, systematic desensitization, behavioral rehearsal, positive reinforcement, distraction, and hypnosis-related techniques such as progressive muscle relaxation, focused attention and guided imagery. Play and art can also be utilized to improve mastery of medically-related behaviors or in conjunction with role play, imagery and relaxation strategies. Rehearsing bone

marrow aspirations or teaching self injection for IDDM via realistic dolls can gradually improve technique, shape compliance, and decrease fear.

Social skills training: Given that problematic peer relations can impact later psychosocial development, improving social functioning can have a protective effect. Interpersonal skill deficits can result from

- Lack of specific abilities
- Lack of opportunity
- Emotional or cognitive factors that interfere with performance. Effective training can result in improved self-esteem, confidence, and social competence. The components of social skills training programs vary, but typically should involve:
 - *Behavioral training:* this can include modeling, rehearsal, corrective feedback, and reinforcement
 - *Skill instruction:* direction and teaching for specific skills such as starting conversations, joining games, increasing peer acceptance
 - *Problem-solving:* skill training has been shown to be enhanced by training the cognitive processes needed for implementing learned skills. Teaching a child to learn to assess, negotiate, and plan action in social situations improves implementation and generalization of skills.

Remediation and Rehabilitation

Physical and academic remediation and rehabilitation for functional deficits can have a tremendous impact on psychological functioning. Early intervention in these areas allows children to be active, rather than passive participants in their illness management, and provides concrete, sequential feedback of improvement. Both the concrete progress and inherent message communicated by remediation and rehabilitation can counterbalance feelings of helplessness and hopelessness that often result from the vague, slow, long-term, sometimes static trajectory of medical improvement.

Family Therapy and Group Work

Given the interactive relationship between the child's illness and family and friends, working within a larger context can be helpful. Family work is often included in the management of the chronic illness with life-long duration, such as asthma and diabetes, where the family members can exert a positive effect on illness management. It can also be helpful for ventilation of feelings and clarification of misinformation by children and their siblings. Illness-related groups for children and adolescents with either similar or mixed illnesses can offer support through reality testing and shared problem solving. Going one step further, interventions done in school with respect to school re-entry or socialization can be considered as group work.

A child's social skills can be enhanced when work done individually is augmented with work done in the actual setting with peers. Providing guidance for handling school absence, physical difference, or answering questions can ease or eliminate teasing or isolation and improve peer relations.⁷

Examples of Implementation

The following two areas of concern typify issues that present to mental health professionals. The issue of school re-entry illustrates the use of intervention to minimize the immediate school-related problems secondary to a chronic illness and the prevention of later social and academic problems. Pain management represents a common acute problem, which if inadequately treated, can complicate medical treatment and lead to future adjustment and psychological difficulties.

School Integration or Re-entry

In easing the integration or return to school for the chronically ill child most efforts focus on all fronts: assisting the staff, classmates, and the child. The staff is helped by being educated about the illness and any necessary modifications that need to be made, such as a shortened day, restriction of foods or activities, and possible academic difficulties. The staff should also be guided as to how to explain the child's illness to the class. Consideration should be given to what the child and family want shared, what vocabulary to use, and if and how the child wants to participate in any teaching or transmitting of information. School staff should also be alerted to possible problem areas, such as upcoming treatments that could interfere with a standardized testing timetable, or a hospital admission that will prevent attendance at an important school dance. Academic concerns should be identified; either those that predate the illness or are newly caused by the illness. The child herself can be helped before returning to school by learning and practicing strategies to help her deal with potentially awkward peer interactions. Problem solving, role playing (perhaps related to explanations about the illness), and assertiveness training for possible teasing can be helpful. Having staff and/or the child talk directly to peers and having a child present a healthy and positive attitude can demystify misconceptions and increase acceptance.

Pain Management

Given that pain is multidetermined, resulting from the interaction of physical and psychological components, interventions focus on two areas. Pain perception is addressed by teaching the child, 1) "to regulate or modify his or her perception of pain through self-regulatory methods such as hypnosis, guided imagery, relaxation, and bio-feedback," and, 2) improving pain behavior through "the

manipulation and modification of environmental events that maintain pain behaviors.”

Assessment of a child who is referred for pain management entails gathering information from observers – parents, medical staff – as well as from the child. The child might be asked to describe the pain and to rate it by means of an objective scale. Unrealistic information and fears might need to be addressed and corrected through education. Other helpful strategies to develop a revised stress and coping cycle might include: relaxation techniques to train a new response when pain starts; doll play to help the child localize the pain, externalize feelings, and practice positive coping strategies; and self-hypnosis using patient-generated guided imagery. The parents can be educated about expected levels of pain to prevent them from overreacting to their child’s pain and they may be enlisted as coaches to assist the child in following through with a particular regimen of pain control. Decreased pain and anticipatory anxiety, increased sense of control and mastery, and enhanced ability to engage in normal activities resulting in prevention of later social sequel would indicate success.

OUTLOOK FOR THE FUTURE

Understanding how families change and develop has lagged far behind individual development. Families change over time although most family research has looked at them at only one point. Consistent with the notion that individuals, families, health care systems, and diseases interact over time, the need for prospective investigation of all these variables is crucial. Although the entire system is the overarching interest, understanding individuals, dyads, and triads within families is also important. Research at a family level of analysis can focus on either the entire family system or on individuals and subsystems conceptualized within a systems framework. That is, an individual’s responses, or sibling relationships can be seen as part of the larger system, which is consistent with family research. At times, incorporation of well-validated, accepted measures of individuals and couples may be preferable to less well-articulated and developed “family” measures. Studying one subsystem of the family is legitimate, so long as one specifies why the question fits with the larger understanding of the family.

There is an urgent need for consideration of developmental (children, parents, family) variables. Children of all ages have chronic diseases and the experience may be expected to vary by developmental stage. There are also

issues that are specific to children and childhood illness that have not been addressed in empirical studies. These include

- the locus of responsibility for medical compliance (parent vs patient),
- developmental ability to comprehend the illness and intricacies of treatment,
- school issues,
- relatively rapid developmental changes, and
- the impact of developmental stage on siblings.

Just as families change over time and evolve, so too do the course of our knowledge and the treatment of diseases. Advances in medical technology and changes in treatment regimens can change the impact of a disease dramatically. These changes demand current research that looks at the nature of the illness at present and makes many older studies obsolete.

The physical and psychological future for children and teens with chronic illness appears brighter than ever. With attention to their emotional needs, targeted interventions with a mental health professional, and guidance to parents, children’s adjustment and quality of life can be maximized. While awaiting medical cures or undergoing existing treatments, mental health care can help children and teens feel confident, effectively manage stress, adapt to their particular illness and grow to be independent, socially competent adults.

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CHAPTER 201

Drugs in Psychiatric Disorders

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Child psychiatry is one of the upcoming and emerging superspecialties in the field of pediatric care in India. With the increase in awareness and early recognition of emotional and behavioral problems in children, the use of psychotropic drugs (those prescribed specifically to alter the behavioral or emotional state) in children has been on the rise across the world. The expansion of pharmacotherapy has been prompted, in part, by introduction of safer medications with better risk benefit ratio. Drug treatment represents a powerful way of altering the behavioral and mental states of children.

Approximately 7–15 percent of children and adolescents meet criteria for clinical psychiatric disorders.^{1,2} Problems of mental health and behavior in children are a multi-disciplinary problem and optimal approach is multi-modal treatment approach. The treatment should stress multi-modal intervention of which pharmacotherapy is only one part of the treatment, and should also address co-morbid psychiatric disorders.^{3,4} Medication has an important place in child psychiatric treatment, and expertise in the theoretical and practical aspects of drug use should be available in all child and adolescent mental health services (CAMHS). This chapter focuses on the pharmacological basis and use of psychotropic drugs in the management of various psychiatric disorders in children.

ASSESSMENT AND EVALUATION

A detailed multidisciplinary assessment is the stepping stone of any intervention. An ideal assessment of children should consider the total bio-psychosocial perspective and include a detailed neuro developmental history (Table 1). A thorough physical evaluation of the child is necessary to rule out organic (medical and neurological) conditions. Once the diagnosis has been established it should be re-assessed longitudinally to ensure accuracy, and for the development of any co-morbid conditions over time.

Table 1: Assessment and evaluation

Goals

- To determine a psychiatric diagnosis or target symptoms for which drug treatment might be indicated
- To identify and establish baseline measures for therapeutic targets
- To establish therapeutic contact and rapport with the child and the family

History

- Reasons for child's referral and current difficulties
- Target symptoms – frequency, duration, severity, precipitating, predisposing and maintaining factors
- H/o problems during antenatal, postnatal period, infancy and early childhood
- Language, social, cognitive, sensory, motor, physical and emotional development
- Temperament
- Sexual development and behavior
- Peer, siblings and family relationships
- Family and community background
- Strengths, abilities and areas of weakness
- Interests, hobbies, talents and vocations
- Exposure to traumatic or unusual circumstances
- Educational and vocational potential
- Present and past use of psychotropic and non-psychotropic medications, response to treatment and family's attitude towards intervention
- H/o substance abuse by the patient as certain medication can have a devastating interaction with illicit drugs
- Family h/o mental illness, suicide, substance use, neurological illness and specifically their response to psychotropic medication

APPROACH TO DRUG TREATMENT OF PSYCHIATRIC DISORDERS

One method to conceptualize treatment is to consider pharmacotherapy for core symptoms such as hyperactivity, inattention, self-injurious behavior, aggressive behavior,

sleep problems or the other approach is to consider it as a disorder as a whole such as depression, obsessive compulsive disorder, psychosis, etc. Periodic assessment and reevaluation is required to make a decision to go either for the symptom based approach or for the disorder based approach.

FACTORS ASSOCIATED WITH DRUG THERAPY AND RESPONSE IN CHILDREN

Neurodevelopmental factors: Various neurodevelopment factors may alter the response of children to drugs that have proven efficacy in adulthood.⁴ Parasympathetic and sympathetic modulation, varying hepatic metabolism, increase ketosteroid levels, different hormonal milieu and incomplete maturation of the neurotransmitter system may affect the drug response as the child grows. Therefore as child matures, treatment plans need to be revisited and adapted to changing individual.

Pharmacokinetic and pharmacodynamic factors: Very less is known about pharmacokinetics and pharmacodynamics of psychotropic drugs in children, than in adults. Age, sex, weight, disease state, absorption, distribution, metabolism and excretion may all alter the drug response in children. As mentioned above, neurodevelopmental factors are important to be considered.

Drug interactions: Simultaneous administration of psychiatric drugs and other drugs for physical ailments can have serious adverse reactions if ignored. Knowledge of these interactions of psychotropic drugs with drugs such as antibiotics, antihistaminics and anticonvulsants are important in children. Polypharmacy is to be avoided unless it is absolutely necessary with close monitoring and revisiting at regular intervals.

Lack of research in children: Very few psychotropic drugs are exclusively used for specific conditions in children such as atomoxetine and stimulants for attention deficit hyperactivity disorder (ADHD), as most of the psychotropic drugs are developed and researched in adults. This may be due to various ethical and consent issues, which has deprived children with psychiatric disorders with many drug options. Simultaneously, short and long-term side effects including developmental impact are not known in children for most of the psychotropic medicines. Also except for few psychotropic drugs, most are not available as child friendly preparation, which interferes with the compliance in children.

Other factors: Inadequate assessment with rapid jump to drug treatment, presence of co-morbidity (presence of more than one disorder simultaneously), drug treatment as the only treatment, inadequate understanding of psychosocial factors, and lack of trained child mental health professionals are the other factors which contribute to drug therapy and response in children on a longer term.

ETHICAL ISSUES

The main purpose of professional ethics in relation to pediatric psychopharmacology is that children are treated upon in a safe, effective and fair manner so that they or the society are benefited from such treatment with no or minimal adverse effects on the children.^{5,6} Psychopharmacology with children and adolescents has to face an inherent paradox: on one hand, it is unethical to use treatment procedures without scientifically proved efficacy; and on the other hand, there are ethical problems to examine the efficacy of treatment methods scientifically. This contradiction has been called the “inherent paradox of clinical trials in psychiatry”.

Few issues, which should be considered while treating children with psychotropic drugs, are:

- Only children with impairing psychiatric symptoms or disorders should be treated with medication.
- Medication should be chosen in a manner that it affects the maximum possible target symptoms.
- Medication should be initiated at the lowest possible dose and dose titration should be gradual in general.
- Medication chosen should not improve one symptom and worsen others.
- The children should not suffer from undue side-effects of psychotropic drugs.
- Children should not be exposed to new unapproved medication unless justified, and with consent from parents.
- Any drug treatment for psychiatric disorders should not be thought of as indefinite. It must be determined, from time to time, whether it is necessary to continue medication.
- Adequate information about the need for medication, and for symptoms it is being prescribed, how it is to be administered and for how long, what improvement to expect, side effects, and other treatment options available, impact of treatment on child psychiatric disorder and his life should be discussed with parents.
- An attempt should be made to include children in the process of management and they should be told about their psychiatric problems and treatment and medication in an age appropriate manner. This will go a long way in increasing their willingness and compliance for treatment.

DRUG TREATMENT OF SPECIFIC DISORDERS

In recent years, the emphasis on evidence based practice has led to a more rational evaluation of the use of drugs in child psychiatry with more evidence existing for disorders such as attention deficit hyperactivity disorder (ADHD) and obsessive compulsive disorder (OCD). Table 2 illustrates the conditions where drug treatment plays a significant role along with the first line commonly prescribed

Table 2: Treatment of specific disorders where drugs play a significant role

<i>Disorder</i>	<i>Commonly used (First line)</i>	<i>Dosage</i>	<i>Alternative (Second line)</i>	<i>Others (Third line)</i>
ADHD	Stimulants Methylphenidate Dexmethylphenidate Lisdexamfetamine	0.5–1.5 mg/kg	Tricyclic antidepressants TCA's (imipramine) Alpha-agonists (clonidine, guanfacine)	Antipsychotics Selegiline Buspirone Venlafaxine Modafinil Bupropion
Tourette's syndrome	Atypical Antipsychotics Risperidone Clonidine	1.0–1.5 mg/kg 0.25–2 mg/day 50–300 mcg/day	Typical antipsychotics (haloperidol, pimozide) Selective Serotonin Reuptake Inhibitors (SSRIs) TCA's (imipramine)	Tetrabenazine Anticonvulsants Botulinum toxins Benzodiazepines
Obsessive compulsive disorder (OCD)	SSRI's* Fluoxetine Sertraline Paroxetine Fluvoxamine Citalopram Escitalopram	20–60 mg/day 50–200 mg/day 20–60 mg/day 50–200 mg/day 20–60 mg/day 5–20 mg/day	Clomipramine ²² (50–200 mg/day)	Benzodiazepines Buspirone Atypical Antipsychotics (risperidone)
Psychosis/schizophrenia	Atypical Antipsychotics Risperidone, Aripiprazole Olanzapine Quetiapine Paliperidone	1–6 mg/day 5–20 mg/day 5–20 mg/day 50–500 mg/day 3–12 mg/day	Typical antipsychotics (haloperidol)	Clozapine for treatment resistance ²¹
Depression	SSRIs* Fluoxetine Sertraline Paroxetine Citalopram Escitalopram	20–40 mg/day 100–200 mg/day 20–40 mg/day 20–40 mg/day 10–20 mg/day	Tricyclic antidepressants (imipramine) Atypical antidepressants (venlafaxine, mirtazapine, bupropion)	Mood stabilizers (lithium sodium valproate) Atypical antipsychotics (olanzapine)
Bipolar disorders	Mood stabilizers Lithium Sodium valproate Carbamazepine Oxcarbamazepine Atypical Antipsychotics Olanzapine Risperidone Quetiapine Aripiprazole	600–1200 mg/day (0.4–1.0 mEq/L)* 500–2000 mg/d (50–100 mg/L)* 300–1200 mg/d (5–10 mg/L)* 300–1200 mg/d 5–20 mg/day 1–6 mg/day 100–600 mg/day 5–20 mg/day	Benzodiazepines (lorazepam, clonazepam) Anticonvulsants (lamotrigine)	Other anticonvulsants (topiramate) SSRIs (if depression persists) * Blood levels

*Warning: All SSRI's except fluoxetine carry risk of increasing suicidal behavior and require frequent monitoring

drugs with their dosages.^{4,7-12} Beside first line drugs, there are second line and third line drugs (Table 2) which need to be prescribed when the first line drugs fail to give adequate response or need to be stopped due to undue side effects.

There are certain psychiatric disorders in children and adolescents^{4,7,9,10,13-18} where the medication may not play a significant role and where drugs are used to ameliorate certain specific target symptoms (Table 3).

Table 3: Treatment of specific disorders where drugs play a less significant role

<i>Disorder</i>	<i>Target symptoms</i>	<i>Drugs used commonly</i>	<i>Other drugs used</i>
Autistic spectrum disorder (ASD)	Aggression Hyperactivity Self-injurious behavior Stereotype behavior Social deficit	Atypical antipsychotics (risperidone, aripiprazole) SSRIs (fluoxetine) Clonidine	Buspirone Benzodiazepine Naltrexone Mood stabilizers Donepezil
Mental retardation (MR)	Behavioral problems Aggression Hyperactivity Emotional problems Depression Anxiety	Atypical antipsychotics Clonidine Stimulants SSRIs	Buspirone Benzodiazepine Mood stabilizers
Conduct disorders	Aggression	Atypical antipsychotics Mood stabilizers	Buspirone Benzodiazepine
Anxiety disorders	Separation anxiety Fear/phobias Social anxiety Selective mutism Generalized anxiety Panic attacks	SSRIs Fluoxetine Sertraline Paroxetine Fluvoxamine Citalopram	Buspirone Benzodiazepine Tricyclic antidepressants Atypical antidepressants
Enuresis	Bed wetting	Desmopressin	Imipramine Amitriptyline Carbamazepine
Sleep disorders	Insomnia Night terror Nightmare Night walking Hypersomnia	Benzodiazepine Melatonin Zolpidem Zalapelon Stimulants (methylphenidate) Modafinil	Tricyclic antidepressants Atypical antidepressants
Eating disorders	Binge eating	SSRIs	Topiramate

MAIN CLASSES OF DRUGS USED IN PSYCHIATRIC DISORDER

Stimulant drugs including methylphenidate (only one available in India), and dexamphetamine, are widely used world-wide and are effective in the treatment of attention deficit hyperactivity disorder (ADHD).

Despite the extensive clinical and pharmacological knowledge about stimulants, the basis for their efficacy in ADHD remains unclear. Stimulants act by releasing monoamines from nerve terminals in the brain. Noradrenaline and dopamine are the most important mediators but serotonin release also occurs. They increase intrasynaptic concentration of dopamine by blocking the dopamine transporter and by displacement of monoamines from synaptic vesicles. The core behavioral response in child with ADHD seems to be an improved ability to 'inhibit', and therefore enhance persistence in motor and cognitive functions.

The different stimulants have slightly different half-lives and this is important in clinical practice. Methylphenidate has the most rapid onset of action (1–3 hrs) and

shortest half-life (2–3 hrs) so that the clinical effect wears off after 4–6 hrs. Long-acting preparations (available in India now) are appealing for whom the standard formulations act briefly, those who experience severe rebound hyperactivity, or in whom frequent dosage is impractical.⁷ There is little evidence for the development of tolerance in children taking stimulants for treatment of ADHD.

Although the stimulants are safe, dose-dependent side effects may occur, and are similar for all stimulants. The most common are reduced appetite, stomach ache, headache, jitteriness, delayed sleep onset, increased blood pressure and pulse, and dysphoria which usually wear off or may be reduced by lowering the dose or switching to alternative drug. There is little evidence that stimulants produce a decrease in the seizure threshold or drug addiction results from the prescription of the stimulants for ADHD.⁴ Growth retardation resulting from long-term stimulant use is actually small and it can be minimized by using drug free periods if given for long-term. The results of the Multimodal Therapy of ADHD (MTA) study

revealed a more persistent effect of stimulants on decreasing growth velocity than have most previous studies, particularly when children were on higher and more consistently administered doses.²⁵ The effects diminished by the third year of treatment, but no compensatory rebound effects were found. However, diminished growth was in the range of 1 to 2 cm. An uncommon additional significant adverse effect of stimulants is the occurrence of hallucinations and other psychotic symptoms. Although concerns have been raised about the rare occurrence of sudden cardiac death among children using stimulant medications, sudden death in children on stimulant medication is extremely rare, and evidence is conflicting as to whether stimulant medications increase the risk of sudden death. It is important to expand the history to include specific cardiac symptoms, Wolf-Parkinson-White syndrome, sudden death in the family, hypertrophic cardiomyopathy, and long QT syndrome, and if present, baseline ECG should be done before starting stimulants.

There is abundant evidence for the short-term beneficial effects of stimulants for the treatment of ADHD. Stimulants not only improve the core symptoms but also have a wide variety of effects on academic, behavioral, social and cognitive domains. Greater hyperactivity, inattention, clumsiness and absence of emotional disorder predicts a greater response to methylphenidate.⁸ The MTA (multimodal treatment study of children with ADHD), New York-Montreal long-term ADHD treatment study and Preschool ADHD treatment study (PATS) provide strong support for the role of medication in treating children with ADHD across all age group.^{23,25} The findings from the MTA study suggested that more than 70 percent of children and youth with ADHD respond to one of the stimulant medications at an optimal dose when a systematic trial is used. Because stimulants might produce positive but suboptimal effects at a low dose in some children and youth, titration to maximum doses that control symptoms without adverse effects is recommended. Stimulants can be effectively titrated over a 3 to 7 days period. Although they are being used in preschool children but methylphenidate is not recommended to be used before the age of 6 years and only dexamphetamine has been recommended to be used before the age of 6 years.¹⁹ The presence of comorbid conditions such as anxiety disorders, tics and autism may alter the response to stimulant medication and requires cautious treatment. Evidence suggests that the rate of metabolizing stimulant medication is slower in children 4 to 5 years of age, so they should be given a lower dose to start, and the dose can be increased in smaller increments. Maximum doses have not been adequately studied.

Because norepinephrine-reuptake inhibitors and α 2-adrenergic agonists are newer, the evidence base that supports them—although adequate for FDA approval—is considerably smaller than that for stimulants. Only 2 medications have evidence to support their use as

adjunctive therapy with stimulant medications sufficient to achieve FDA approval: extended-release guanfacine and extended-release clonidine. Other medications have been used in combination off-label, but there is currently only anecdotal evidence for their safety or efficacy, so their use cannot be recommended at this time.²⁴

A few medications have shown benefit for challenging or repetitive behaviors, and the clearest evidence favors atypical antipsychotics risperidone and aripiprazole. Significant adverse-effect profiles, however, make it clear that although these drugs are efficacious, caution is warranted regarding their use in patients without severe impairments or risk of injury.

The recent Research Units on Pediatric Psychopharmacology (RUPP) study on the treatment of the behavioral problems of children with autism is the largest published study undertaken to try to identify pharmacotherapeutic agents that can be useful for these often severely disruptive children. The results showed a significant reduction in irritability score in children who were prescribed atypical antipsychotic risperidone as compared to placebo group.²⁶ Insufficient evidence is available to judge the potential benefit or adverse effects of all other medical interventions currently used to treat autism.²⁷

The selection of the specific SSRI in treating depression should be based on the optimum combination of safety and efficacy data. The patient and family should be informed about the possible adverse effects (clinicians may use a checklist) including possible switch to mania or the development of behavioral activation or suicidal behavior. Once the antidepressant is started, and if tolerated, the clinician should ensure an adequate trial up to the maximum dose and duration.²⁸

The Treatment for Adolescents with Depression Study (TADS) was a randomized controlled trial that evaluated the effectiveness of fluoxetine hydrochloride therapy, cognitive behavior therapy (CBT), and their combination in adolescents with major depressive disorder. The study concluded that in adolescents with moderate to severe depression, treatment with fluoxetine alone or in combination with CBT accelerates the response. Adding CBT to medication enhances the safety of medication. Taking benefits and harms into account, combined treatment appears superior to either monotherapy as a treatment for major depression in adolescents.²⁹

The Pediatric OCD Treatment (POTS) Study, a balanced, masked randomized controlled trial conducted in 3 academic centers in the United States randomly assigned participants to receive CBT (Cognitive behavior therapy) alone, sertraline alone, combined CBT and sertraline, or pill placebo for 12 weeks. The results showed better response with combined treatment with CBT along with pharmacotherapy. Hence, children and adolescents with OCD should begin treatment with the combination of CBT plus a selective serotonin reuptake inhibitor or CBT alone.³⁰

Table 4: Other classes of drugs to treat psychiatric disorders

Drug	Mechanism of action	Actions	Side effects	Pharmacokinetics	Primary indications	Possible indications
Benzodiazepines						
Lorazepam	Enhancement of inhibitory effect of GABA acting GABA-A receptors	Sedative Anxiolytic Anticonvulsant	Confusion Amnesia Tolerance Dependence Impaired coordination	Well-absorbed orally Inactivated by hepatic metabolism Half-lives varies	Sedation	Acute aggression Anxiety disorders
Antidepressants						
Tricyclic (Imipramine)	Norepinephrine, serotonin, dopamine reuptake inhibitors	Antidepressants Anxiolytic Sedative	Tricyclic-sedation, dry mouth, constipation, giddiness, cardiotoxicity	Well-absorbed orally Half-lives varies b/w drugs and individuals	Depression Obsessive-compulsive disorder (OCD)	Anxiety disorders ADHD Autistic spectrum disorder (ASD) Nocturnal enuresis
Atypical (Mirtazapine)	Monoamine receptors antagonists		SSRIs-nausea, agitation, insomnia, headache Atypical-varies	Give rise to long-lived active metabolites Clinical response 2-4 weeks		
Mood stabilizers						
Sodium valproate	Uncertain weak GABA-enhancing and Na-channel blocking action	Antiepileptic Antimanic Sedative	Nausea, somnolence Weight gain, hepatotoxicity	Well absorbed orally Half-life 12-15 hours		Aggression Kleine-Levin syndrome (KLS)
Carbamazepine	Na-channel blocking action	Antiepileptic Antimanic Sedative	Nausea, dizziness, tics Leukopenia and hepatotoxicity at high plasma levels	Well-absorbed orally Half-lives varies 12-60 hrs, tending to decrease because of induction of metabolizing enzymes	Mania Bipolar disorder	
Lithium	Uncertain second messenger systems	Antimanic	Nausea, tremor, polyuria, ataxia, confusion	Renal excretion Monitoring of plasma concentration		Autistic spectrum disorder (ASD) ADHD Aggression sadation
Antipsychotics						
Typical (Haloperidol)	Dopamine receptor antagonist	Sedation Antipsychotic	Extrapyramidal side effects Sedation, weight gain, Hyperprolactinemia	Well-absorbed orally Inactivated by hepatic metabolism Half-lives varies	Psychosis Tourette's/ Tic disorder	Autistic spectrum disorder (ASD)
Atypical (Risperidone)	Serotonin and glutamate receptors modulation		Metabolic side effects			
Clonidine	Partial agonist at alpha-2 adrenoceptor	Sedation ↓ sympathetic activity	Hypotension, sedation, dry mouth, bradycardia	Well-absorbed orally Plasma half-life 12 hours but pharmacological effect 2-4 hours	ADHD Tics/ Tourette's disorder	Nocturnal enuresis
Atomoxetine	Selective norepinephrine reuptake inhibitor	↑ concentration ↓ impulsivity	Somnolence, decrease appetite, fatigue, dry mouth	Well-absorbed orally Plasma half-life 5 hours	ADHD	

Beside stimulants, various other classes of drugs^{4,7,9-15,20,23} are used to treat psychiatric disorders in children and adolescents (Table 4).

CONCLUSION

Prescribing habits for treatment of psychiatric disorders in children and adolescents continue to be determined as much by dogma as by evidence. Treatment decisions can only be made on the basis of rigorous assessment and diagnostic evaluation. Routes into mental disorders can be developmental, genetic or environmental but etiology does not generally determine treatment in psychiatry. Clearly the final common pathway to behavioral, emotional or cognition dysfunction is through alteration in the brain function, and an effective part of treatment may be to use drugs which act on the brain. With better understanding of psychiatric disorders in children and adolescents, newer psychotropic drugs with better side-effect profile and higher degree of precision will be an asset to the clinician dealing with children and adolescents.

KEY POINTS

Drug therapy in children must take into account the child's environmental influences and should be part of an overall multimodal treatment plan that addresses the relevant individual, familial and cultural issues.

Drug therapy can be symptom based or disorder based but should be based on "Start Low, Go Slow".

Cautious, judicious drug therapy in children can make a difference to their suffering and assist them in the maintenance of their expected developmental trajectory.

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Child Abuse: An Unrecognized Problem

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CONCEPTS AND DEFINITIONS

Child abuse is one of the major problems affecting children today. Child abuse causes more physical and psychological morbidity than does most pediatric illnesses. It is not a new phenomenon. Lynch (1885) points out that the incidents of child abuse are referred to in literature dating back to the second century AD but still no exact statistics are available. Kempe and colleagues (1962) coined the term battered child syndrome. It led to increased interest in, and recognition of, what come to be known as non-accidental injury. Nowadays, the simple term child abuse is generally preferred. This covers not only physical abuse but also sexual, emotional abuse and neglect. Child abuse affects children of all ages.

Though this problem of child abuse of children in India is increasing, it has failed to draw the attention of pediatricians, psychiatrists and sociologists in our country. The public and government also have not yet recognized it as a serious problem.

The study of child abuse and neglect has been hindered by the failure to establish a consensus regarding an objective operational definition of what constitutes abuse. Starr (1988) stated that there are four elements involved in defining child abuse:

- The intentionality of the act
- The impact of the act on the child
- Value judgments about the fact
- The cultural and societal standards upon which the act is evaluated.

At present, there is no single, specific definition on child abuse in India. The definition of child abuse can be gathered from a number of articles in the Constitutions of various countries.

But still child abuse has been defined medically as any interaction or lack of interaction between a child and his/

her caregiver which results in nonaccidental harm to the child's physical or developmental state. "Neglect" refers to denial of health or other basic needs, emotional deprivation or mistreatment or failure to provide proper parenting. It is now a broader concept applied to acts of omission and commission by parents and caretakers that harm or potentially harm children.

Incidence

There are wide variations in the reported incidence of child abuse and neglect. This is no doubt due in part to real difference in the incidence in different populations, but the variations are also due to definitions of what constitutes abuse and to the use of different methods of ascertainment. In the absence of public and government interest in the problem of child abuse no statistics have been compiled in India to indicate the incidence of abuse. Considering the poverty, illiteracy, and large size of families in India, it could be said that 5 to 15 per 1,000 children are abused by parents and employers in our country. In India, the 1991 census put the figure of child abuse at 16.5 million, i.e. 5.5 percent of the total child population. A study by Kewalramani (1990) in Rajasthan was focused on 167 children in the age range of 10 to 16 years. Of the 167 case studies, 124 were cases of physical abuse, 23 of sexual abuse and 103 of emotional abuse (the total is more than the case studies because many children were victims of multiple abuses). Further, of total cases studied, 61.7 percent were boys and 38.3 percent were girls. Incidents of physical and emotional abuses were more common among boys and sexual abuse among girls. In a 1999 report by the Tata Institute of Social Sciences, a study done in 1994 and 1995 with 150 minor-age girls in Mumbai, India showed that 58 of the girls surveyed had been sexually abused before age 10. Of this number, 50 had been abused by a family member or friend of the family.

Etiology

The etiological factors of child abuse and neglect are complex. Most experts believe that child abuse occurs as a result of the combined outcome of various factors that may occur both in the patients and in the child in conjunction with the environment.

Mac Millan (2000) summarizes the “risk indicators” that have been found to be associated with abuse. For physical abuse there are:

- Child factor
 - Male sex
- Parental factors
 - Young maternal age
 - Single-parent status
 - History of childhood experience of physical abuse
 - Spousal violence
 - Unplanned pregnancy or negative attitude toward pregnancy
 - History of substance abuse
 - Social isolation or lack of social support
- Social factors
 - Low socioeconomic status
 - Large family size

For sexual abuse known ‘risk indicators’ are:

- Child factor
 - Female sex
- Parental factors
 - Living in a family without a natural parent
 - Poor relationship between parents
 - Presence of a stepfather
 - Poor child-parent relations.

The above factors are just correlates of abuse, not necessarily causes. As their presence should alert us to the possibility of abuse and if several of them are present, to the probability of it (Flow chart 1).

Types of Child Abuse

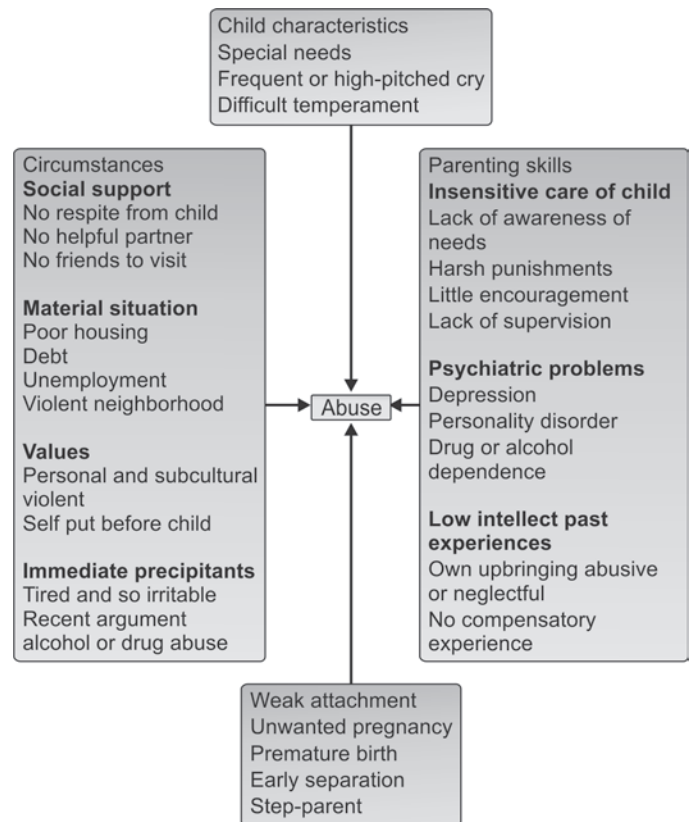
Four main types of child abuse occur—physical abuse, neglect, emotional abuse, and sexual abuse. More than one type of abuse may occur at any one time, and a child who has been subject to one form of abuse is more likely to suffer another in the future.

Physical Abuse

Physical abuse is still the prototype when we discuss about child abuse. Physical abuse occurs when an adult inflicts a physical injury on a child more severe than is culturally acceptable. It is sometimes more difficult than one might think to draw the line between acceptable and nonacceptable violence.

The cardinal feature of the clinical presentation of physical abuse is a physical injury for which the explanation provided is unsatisfactory. The common forms of nonaccidental injury result in multiple bruising, burns, abrasions,

Flow chart 1: Factors predisposing to abuse



bites, torn upper lip, bone fractures, subdural hematoma, and retinal hemorrhage, etc. Other forms of physical abuse include deliberate suffocation and poisoning.

Variants of Physical Abuse

Munchausen syndrome by proxy, also known as factitious illness by proxy, refers to a child being presented to doctors by a parent (almost always the mother) who has induced the illness. The mother brings the child to the hospital repeatedly for investigations. Forms of fabricated illness include respiratory arrests, apparent bleeding from a variety of orifices, poisoning, seizures, skin rashes, and fever, etc.

Shaken baby syndrome consists of intracranial damage (hemorrhage, shear) injuries created by violently shaking a child. Most victims are under 2 years of age. About 15 to 25 percent of identified victims die and most of the rest have neuromotor, visual and cognitive impairment.

Failure to thrive simply refers to less than expected weight gain. Until the later half of 20th century it was presumed that failure to thrive was always the result of an organic disorder. Only recently, we have come to know that a child's environment may be the cause of growth failure. This group comprises nonorganic failure to thrive. There is usually a background of prolonged neglect or physical abuse in these children.

Sexual Abuse

Sexual abuse may occur in the absence of other forms of abuse or neglect, and it may continue for long periods undetected. Girls are abused more often than boys. The abuse may consist of anything from fondling of the child's breasts or genitals to vaginal or anal intercourse. Another form of sexual abuse is the sexual exploitation of children in pornographic movies, videotapes and photographs. Approximately 85 percent of sexual abuse is committed by someone known to the child. The abuser may be parents, step-parents, other relatives and foster parents. Sexual abuse is equally prevalent in all socioeconomic classes whereas physical abuse and neglect may be more common in low socioeconomic classes. Incest is believed to be the most frequent child sexual abuse in India. Given the Indian attitude toward family loyalty, it is most difficult to prosecute.

Emotional or Psychological Abuse

The emotional and other psychological needs of many children are not adequately met in the families. Sometimes, it is very difficult to assess the severity of family failure to meet its children's needs so as to justify the use of the term emotional abuse, although extreme cases are easily identified. Elements include:

- Extreme hostility and criticism.
- Deprivation of attention.
- Rejection and withdrawal of affection.
- Threats of abandonment.
- Inappropriate stresses and demands.

Neglect

In contrast to persons who commit physical and sexual abuse, the perpetrators of neglect almost always are unaware that they mistreat their children. Neglect refers to an absence of appropriate care rather than positively inappropriate acts. Most areas of care may be involved:

- *Lack of physical care*—includes undernutrition, recurrent infection, unkempt dirty appearance, etc.
- *Lack of medical care*, with failure to bring the child for immunizations, failure to seek appropriate medical help for illnesses and accident.
- *Lack of enforced house routines*, rules and supervision, leads to an increased rate of accidents at all ages, including domestic and road traffic.
- *Lack of emotional warmth and availability*.
- *Lack of cognitive stimulation and encouragement in constructive pastimes*.

OUTCOME FOLLOWING CHILD ABUSE

It has been noted that less attention has been given to the consequences of child abuse. General statements cannot

be made about the outcome of child abuse. Many factors affect this, including the nature, severity, and duration of the abuse; the personality strengths and previous adjustment of the abused individual; the stability of the abused child's family and its ability to provide needed support to the child; and the treatment subsequently provided to the abused individual. What is known, however, suggests that there is no single pattern of emotional or behavioral difficulties that characterizes all abused children. To date only a few specific outcomes have been linked with specific patterns of abuse. This is partly due to wide overlap of types of abuse, so it is hard to study pure abuse of one type.

Consequences of Physical Abuse

Emotional Regulations

Four general patterns may be seen:

- Emotional blunting and lack of social responsiveness.
- Depressed affect with sad facial expressions, withdrawal and aimless play.
- Emotional lability, with sudden shifts from engagement and pleasure to withdrawal and anger.
- An angry emotional state with disorganized play and frequent outbursts in response to slight frustrations.

Formation of Attachments

Abusive parenting is associated with insecure attachments, which in turn often lead to later psychopathology in infant. Particularly common are the disorganized response, characterized by fear, disorientation, odd expression and freezing, etc.

Development of Self-concept

Abused children find it difficult to talk about themselves, and especially about their negative feelings. Measures show low self-worth and low self-competency ratings.

Physical Effects

A variety of physical consequences may result from child abuse. These include psychological short stature, non-organic failure to thrive, blindness, permanent mental retardation, cerebral palsy, physical injuries and death.

Symbolic and Social Development

Play is reduced in quantity, and its quality is impoverished, with an increase in routine, stereotyped activity. Abused children show less sensitivity to the emotions of others, more negative expectation of people and less trust in them.

Cognitive Development

Both language and nonverbal abilities are less well-developed than in nonabused controls.

Emotional and Behavioral Disorders

Acute psychiatric manifestations of child abuse have been shown in the Table 1. Increased incidence of various disorders like ADHD, aggression, PTSD, anxiety disorders, dissociative disorder, depression, substance abuse and suicide have been found in various studies.

CONSEQUENCES OF SEXUAL ABUSE

Negative effects to physical health specific to childhood sexual abuse include urinary tract problems, gynecological problems, elevated risk for sexually transmitted diseases (including AIDS), and elevated risk for pregnancy.

The medium and long-term psychiatric outcome for children who have been sexually abused frequently involves persisting dysfunction. These have been shown in Table 2.

The consequences of neglect and emotional abuse have been less well-studied, possibly because these forms of abuse often overlap with other types. However, it seems likely that these children will often fail to achieve their full potential for growth, and that they will show mild-to-moderate learning disabilities.

There are some factors, which may predict the outcome of child abuse to some extent but no conclusive studies are available regarding these factors (Table 4).

Diagnosis and Management

Divergences between the observed injury or condition and the history usually give a clue for determining whether abuse may have occurred. Without observable injuries or condition, history is the key component of diagnosis. A good evaluation starts with obtaining a thorough history

and completing a comprehensive physical examination of the child. Documentation of all injuries is crucial. Behavioral symptoms are generally nonspecific, consisting of indicators of stress (e.g. secondary enuresis, depression, aggression, deteriorating school performance). The management of children suffering from different types of abuses almost follows similar lines, except some investigation part (Table 3).

Table 2: Long-term manifestations of sexual abuse

Emotional

- Depression
- Panic disorders
- Phobias
- Somatization
- Hysteria

Interpersonal

- Pseudomaturity/regressive immaturity
- Overcompliance/aggressiveness
- Poor peer relations

Cognitive/perceptual

- Hallucinations
- Detailed knowledge about sex
- Inability to concentrate at school
- Learning disabilities
- Languages disabilities

Table 1: Acute psychiatric manifestations of child abuse

- Behavioral
 - Acting out
 - Aggressive
 - Delinquent
 - Hypersexual
 - Self-defeating
 - Acting in
 - Avoidant
 - Psychosomatic
- Emotional
 - Depressive
 - Anxious
 - Self-deprecating
 - Hypomanic
- Cognitive
 - Inattention
 - Memory dysfunction
 - Academic difficulties
- Interpersonal
 - Family dysfunction
 - Peer conflicts

Table 3: Signs and symptoms that arouse concern about physical abuse or neglect

Subnormal growth

- Weight, height, or both less than the 5th percentile for age
- Decreased velocity of growth

Head injuries

- Torn frenulum of upper or lower lip
- Bilateral black eyes with history of single blow or fall
- Retinal hemorrhage
- Intracranial trauma

Skin injuries

- Bruise or burn in shape of an object
- Bite marks, pinch marks, slap marks
- Bruises of various colors (cheek, buttocks, etc.)

Injuries of the gastrointestinal or genitourinary tract

- Recurrent vomiting or diarrhea witnessed only by parent
- Chronic abdominal or perineal pain with no identifiable cause

Bone injuries

- Rib fracture in the absence of major trauma such as a motor vehicle accident
- Multiple fractures in various stages of healing
- Complex skull fracture
- Metaphyseal long-bone fracture in an infant

Laboratory studies

- Impulsive or physiological inconsistent laboratory results
- Positive toxicologic tests in the absence of a known ingestion or medication

Table 4: Prediction of intervention success

<i>Factor</i>	<i>Better outcome</i>	<i>Worse outcome</i>
Parental	Acceptance of problems Compliance with treatment Normal personality Supportive partner No psychiatric disorder	Denial of problems Refusal to cooperate Personality problems Abusive partner Substance abuse Psychosis
Characteristics of abuse	Less severe injuries	Severe injuries
Interaction with child	Normal attachment Responsive care-giving	Disordered attachment Insensitive care-giving
Child	Healthy child	Special needs—physical or learning problems
	Resilient response to abuse	Extensive psychopathology
Circumstances	Good local childcare Informal networks	No facilities Social isolation
Professional intervention	Well-trained and resourced Therapeutic relationship	Few resources or skills Lack of engagement

Physician's Basic Responsibilities

The first step of involvement in suspected child abuse cases is to acknowledge that the problem exists. Some physicians refuse to believe that parents have injured their own children. Once the physician acknowledges that the abuse and neglect occur; he must maintain a high index of suspicion for cases of abuse and neglect. Usually parents themselves do not suggest abuse as a possible cause of their child's condition; therefore, the physician must constantly consider the diagnosis. However, many times the physical evidence is not conspicuous and a careful interview with the child and his parents will point out discrepancies between the history and observed condition. The physician then must make a medical judgment as to whether the physical signs and symptoms are plausibly explained by the history offered. The physician's consideration of abuse or neglect should not be biased by the socioeconomic, occupational or educational level of the parents.

The next step, probably one of the most difficult duties that the physician must take is to discuss with the parents that child abuse is in differential diagnosis of their child's problem. He must maintain his objectivity, control his hostility and be honest with the parents. It is when the physician confronts the parents with possible diagnosis that many parents are alienated from that physician. If handled properly the parents can be informed of the suspected diagnosis, will cooperate with the recommendations of the physician.

The physician's next responsibility is to protect the child. This may be done initially by admitting him in a hospital and contacting an agency that handles child protection matters in his community. Once the child is in hospital and is at least temporary protected from his

parents, an appropriate evaluation of the child's physical and development problem is necessary. Consultations from surgeons, ophthalmologists, orthopedists, psychiatrists, psychologists, and radiologists may be necessary as indicated to evaluate and document individual physical and psychological manifestations of the abuse. During this evaluation procedure everything should be documented in the medical chart.

The physician must be aware that his inputs into a case of suspected child maltreatment should be limited to that of a physician. Judges, social workers, NGOs involved in child protection issues all have their roles to play; the physician should not think that he can perform all the necessary functions because child abuse is a multidisciplinary approach. The physician may get caught up in the non-medical aspects of the case, forgetting the child's physical and psychological problems.

Physical Abuse

A physically abused child may be brought to medical attention when the injury persists or worsens. To diagnose physical abuse one requires having an understanding of child development and the biomechanics of injuries, and skills in eliciting an appropriate history. There are certain indicators that may increase the suspicion for physical abuse (Table 3).

Sexual Abuse

The diagnosis of sexual abuse is made most often by history. A high index of suspicion should be maintained. It is probably unusual for children to lie or fantasize about being sexually abused. All family doctors, pediatricians, and child psychologists should feel competent to make

general enquiries concerning the possibility of child sexual abuse by encouraging the child to talk about events that worry them and suggesting there might be problems the child may find it difficult to discuss. Anatomical dolls and drawings by the child are useful aids. Concerns about child sexual abuse should always be shared with other professionals.

Physical inspection of the external genitalia is a useful adjunct in gathering evidence of sexual abuse. Since many sexually abused children may have “normal” examination, so one cannot rule out abuse by examination only. Perhaps the only way to prove absolutely that sexual abuse occurred is to find sperm inside a young girl’s vagina. All other examinations are to detect scars, abnormalities, and pathogens that are highly suggestive of sexual abuse. Although visual inspection by an experienced physician can detect nearly all abnormalities, the use of colposcopy has greatly advanced the understanding and teaching of sexual abuse. Newer refinements include stereoscopic photography and recording of the colposcopic examination on videotape.

Apart from signs of physical injury in the genital area, or diagnosis of sexually acquired disease, sexual abuse may be suspected if the child shows one or more of the following—sexually seductive behavior, sexual knowledge inappropriate for his or her age, severe psychosomatic symptoms, especially nonepileptic seizures, severe acting-out behavior, especially running away, sexually precocious behavior, self-injurious or self-destructive behavior in the absence of other apparent stress, pregnancy in the early teen years.

Emotional Abuse

Emotional abuse is likely to be most evident when members are seen together as a unit. It will be noted that one or both of parents is openly critical of the child, with constant sarcasm and hostile comments. Parents should be seen separately to establish the reasons for such negative attitudes, and partly to determine whether they are suffering from any form of mental illness. Children over the age of 7 or 8 years should, with parental consent, also be seen alone. After sometime spent in discussion of neutral topics, they can be asked about parental behavior. In children of school age, the teacher may be a valuable source of information.

Neglect

To diagnose neglect requires the efforts of a multidisciplinary team. Most cases of neglect require some assessment as to whether and why minimum parenting goals have or have not been achieved. Results for the child, not the intents of the caregiver, are the ultimate criterion.

The child is likely to present to the family doctor or in the accident and emergency department for reasons other

than neglect, but to be noted to be poorly clothed, dirty, and failing to thrive. A dietary history may reveal the child is receiving an inadequate calorie intake and there will be catch-up growth in hospital when an adequate nutritional intake is provided. There will be poor weight gain in relation to height. Psychological investigation will reveal developmental retardation, often global, but possibly confined to language. There may be signs of other forms of abuse also.

A home visit will reveal low standards of cleanliness and inadequate protection and safeguards against accidents. There may be an absence of books, toys, and other play material.

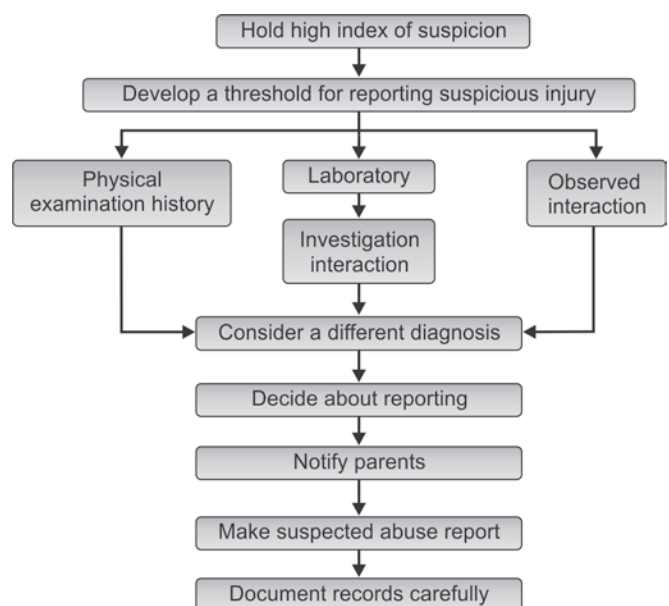
INTERVENTION

The management of established abuse is guided by three aims. The first is to prevent further abuse. The second is to mitigate the effects of what has already happened. The third is to meet the child’s emotional, social, and educational needs in the longer term, which may include deciding whether it is best for the child to live in their own family, making special educational provision and providing positive social experiences outside the home. Given the combination of factors that contribute to the development of child abuse, it seems clear that effective treatment must include multiple components (Flow chart 2).

Child and Parent Treatment

- Focus should be on multidimensional aspects of child abuse, rather than first in the abusive parent.
- Facilitating a more secure attachment between child and parent.

Flow chart 2: Steps in the management of child abuse



- Family-based therapy needs to improve the parent's developed self-image, reverse distortions of their child, interpret any link between the current abuse and the patient's own abuse history, and provide the parent with a positive model of raising children.
- Psychotherapy of the child should include creating a therapeutic environment, either in individual or group settings, which allow the child to master the trauma.
- Play therapy is useful in treatment of traumatized child.
- Pharmacotherapy can also improve the outcome of abused children, especially if they are manifesting symptoms of PTSD.

Propranolol, clonidine, guanfacine have been found to be effective in alleviating some symptoms like hyper-vigilance, hyperarousal and sleep disturbances, etc. Individual child and parental vulnerability, family dysfunction, and environmental stress variable all need to be addressed if the treatment is to be successful.

PREVENTION

Many approaches to the prevention of child abuse have been proposed, but the effectiveness of many of them has not been established by rigorous studies. Three types of child maltreatment primary prevention strategies are currently used. The first is competency enhancement, such as parent education programs. The second is preventing the onset of maltreating behaviors through, for instance, media campaigns, crisis hotlines, and community socialization programs for parents. The third is the targeting of high-risk groups, such as single, adolescent, parents of low socioeconomic status and those with complicated pregnancies and deliveries, to attend programs that increase parent-child contact and provide family support, such as visiting nurses or home visiting parent aides.

Educational efforts can play a great role as preventive approach to the problem of abuse. Also attention to social influences such as poverty, stress, and social isolation would be expected to reduce the development and perpetuation of abuse in the children.

CONCLUSION

Efforts directed at understanding, preventing, and interviewing in the area of child abuse remain at an early stage. In addition to the need to advocate for the improvement of environmental stressors, we urgently require the cessation of exposure of children to family violence, improved parenting, and child development education for parents and children. Child abuse is a multifaceted personal, familial, community, and societal phenomenon. At community level we require better welfare programs, legislation and administrative actions to curb this menace. The position can be further improved by the increased

cooperation between professionals and volunteers within the community, thus ensuring a much wider and comprehensive network of preventive, supportive and treatment options. Only with this multidisciplinary model we can ensure about the safety of our children.

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Adolescent Health Problems

Rajesh Mehta, Neena Raina, Gaurav Shah

ADOLESCENCE

The term adolescence derives from the Latin word, 'adolescere' meaning "to grow, to mature" and is defined globally as the period from 10 to 19 years of age (WHO/ UN definitions: Adolescents 10–19 years; Youth 15–24 years; Young People 10–24 years). This phase in human life is marked by a plethora of growth and developmental changes in the physical, mental, sexual and psychosocial domains. These changes are universal and conform usually to a predictable sequence and pattern, although there are variations in the velocity of growth and development between girls and boys and from person to person. Adolescents constitute about one-fifth of world's population and about 22 percent in the South-East Asia (SEA) region. Adolescents are full of life and energy and are an important asset for national development. Adolescence phase is full of opportunities as it is vulnerable to several risks, many of these related to health.

Adolescents are generally perceived to be healthy since the mortality in this age group is relatively low. However, adolescents do have health issues that have implications that are immediate as well as for later life. It is indeed crucial that society invests in keeping adolescents healthy so that they grow to their maximum potential and contribute to economic growth and development of the country. Preventing health problems among adolescents and responding to health problems as and when these arise deserves to be a priority for health sector. It is important to understand the main health problems during adolescence and their causative mechanisms in order to design appropriate services for adolescents.

ADOLESCENT HEALTH PROBLEMS

The problems faced by adolescents can be categorized in several ways. The problems can be mild in nature and

some of these are serious and may have life long consequences.

GENERAL HEALTH PROBLEMS AMONG ADOLESCENTS

The rapid physical and psychological changes in adolescents are accompanied by increased sensitivity and attention to bodily symptoms. Adolescents report some common symptoms that may not represent serious physical illness. Symptoms like headache, abdominal pain, backache, general weakness and vague body aches may reflect the anxiety due to the changes that the adolescent are going through. However, frequent headaches can also be a manifestation of depression in adolescents. Poor posture, during the phase of rapid height gain and in girls when they develop breasts, can also be a cause of backache. Poor dietary habits and choices can lead to accentuation or development of anemia that may be the cause of feeling of weakness or tiredness.

Many times these non-specific symptoms are used by adolescents to seek attention of parents and physicians since they find it difficult to communicate their actual concerns (like menstrual problems, concerns about nocturnal emission, delay in development of facial hair, sexual abuse, etc.). The physicians need to have the skills to build rapport, make the adolescent clients comfortable and seek out their actual underlying concerns. Timely recognition of the actual health concerns of the adolescents is important to address these in time for prevention of further risk behaviors and serious consequences.

PROBLEMS THAT ORIGINATE IN CHILDHOOD AND IMPACT HEALTH DURING ADOLESCENCE

- Adolescents/young people who survive repeated cycles of infections like diarrheal and respiratory diseases fail

to attain full adult growth and stature. Girls who do not achieve their full growth potential are at a greater risk of having complications during pregnancy and childbirth and give birth to low-birth-weight babies.

- Chronic under-nutrition during childhood, over and above the compromised fetal growth (low birth weight prevalence being about 30%) can result in stunted growth. Undernourished adolescents who become pregnant are further predisposed to malnutrition and micronutrient deficiencies. These factors can contribute to under-nutrition and health problems throughout the reproductive years giving birth to low birth weight babies thus completing an inter-generational vicious cycle of malnutrition.
- Perinatal asphyxia and infections of the central nervous system during neonatal period and childhood can lead to sequels like disorders of sight, hearing or speech that have a huge impact during adolescence. These affect not only performance but also self-esteem and personality of the adolescents.
- Neglect and differential access to food and care during infancy and childhood, child marriage, physical and sexual abuse can seriously affect the physical, mental and social well-being during adolescence.
- Diseases that start manifesting during childhood like thalassemia, juvenile diabetes, nephrotic syndrome, rheumatoid arthritis and epilepsy may continue during adolescence with additional psychosocial overlay and sometimes even worsening of the symptoms.

HEALTH PROBLEMS ORIGINATING DURING ADOLESCENCE WITH LIFELONG CONSEQUENCES

- Increased nutritional requirements put adolescents at the risk of under-nutrition and anemia that are likely to have life long consequences including compromised reproductive health outcomes for girls. On the under hand, excessive use of junk food that is rich in calories and fats along with decreased physical activity can lead to overweight and obesity that continues during adult life.
- Use of tobacco, alcohol, and other drugs and harmful substances many times starts during adolescence with substantial adverse effects like chronic lung or liver disease, and cancer manifest during adulthood or later. Most cases of addiction among adults actually start during adolescence.
- Use of alcohol and drugs impairs judgment and increases the risk-taking behavior of adolescents/young people like over-speeding and dangerous driving leading to accidental injury, violence and unprotected sexual relations. All of these may have health implications that are life long.
- Unsafe/unprotected sexual relations can cause unwanted pregnancy and sexually transmitted infections including HIV infection among adolescents/young people. Such infections and unwanted pregnancy and unsafe abortion with associated reproductive health risks can have serious consequences during adolescence as well as in later life. Adolescent pregnancy is associated with higher maternal, perinatal, neonatal and infant mortality. There are social implications of adolescent pregnancy on girls, especially in case of out of wedlock pregnancy, like interruption of schooling and truncated economic opportunities in addition to social rejection.
- Prevailing gender norms in many societies often lead to a lower status of women with a relative lack of physical, social and economic power. This makes adolescent girls and young women particularly vulnerable, among others, to (a) physical violence; (b) economically-coerced sex; (c) abuse at the workplace; and (d) trafficking and prostitution. This can be severely detrimental to their physical and mental health that continues life long.

Common Adolescent Health Problems

- *Pubertal health concerns and problems:* Anxiety and stress related to growing up issues; early and delayed puberty; musculo-skeletal conditions like kyphosis and scoliosis of spine; gynecological conditions like menstrual disorders, polycystic ovarian disorder syndrome, vaginal discharge; skin and hair conditions like acne, hair loss and hirsutism. Concerns about physical appearance are quite common.
- *Sexual health concerns and problems:* Concerns about sexual attraction and urge, nocturnal ejaculation, masturbation, premature ejaculation, sexual orientation and unsafe sexual engagement, STIs/HIV; sexual coercion and abuse
- *Reproductive health problems:* Early pregnancy (largely related to early marriage of girls) and childbirth related problems like increased risk of complications, higher maternal, neonatal and infant mortality, abortion related problems
- *Nutritional problems:* Under-nutrition, micronutrient deficiencies and anemia, eating disorders, overweight and obesity
- *Mental health problems:* Stress, anxiety, depression, obsessive and compulsive disorders, suicide, behavioral disorders
- *Substance use:* Tobacco, alcohol, drugs
- *Injuries and violence:* Sports injuries, road traffic injuries, burns, drowning, violence
- *Infectious diseases* that are not specific to this age like tuberculosis, malaria, kala azar

ADOLESCENT BEHAVIORS UNDERLIE THE HEALTH PROBLEMS

Many, if not all health problems in adolescents are behavior related. The critical adolescent behaviors and lifestyles that are related with health risks are:

- *Eating behavior:* What foods they prefer and eating patterns determines their nutrition status. Typical behavior of meal missing can lead to under nutrition and indulgence in junk food makes them prone to overweight and obesity.
- *Physical activity:* Low physical activity on account excessive TV watching, computer and video gaming puts them at risk of overweight and obesity.
- Unsafe sexual behavior makes them vulnerable to unwanted pregnancy and STIs, HIV/AIDS
- Use of tobacco, alcohol and drugs exposes them to several health risks in addition to social and medical consequences.
- Thrill seeking behavior like fast driving, heroism on play field, etc. makes them prone to injuries.

Clustering of Adolescent Behaviors and Health Problems

The adolescent health problems are inter-related and clustering is common. The adolescents who start using tobacco early are also known to initiate sexual engagement early. As mentioned earlier use of alcohol and drugs is associated with impaired judgment and makes them prone to take risks like fast driving leading to accidents and indulging in unsafe sex leading to unwanted pregnancy, unsafe abortion and STIs/HIV. Additionally, adolescent behaviors and health problems are determined by several underlying factors or determinants.

DETERMINANTS OF ADOLESCENT BEHAVIORS

The adolescent behaviors that underlie the adolescent health problems, in turn depend on intermediate and underlying factors called determinants. In the multi-factorial web there are well recognized “risk factors” for adolescent health and development. These are:

- *Psychosocial risk factors:* Lack of social support, isolation, low self-confidence, low self-esteem, high self-blame, misdirected peer pressure in absence of adequate knowledge, low learning ability, social dependence, cultural rootlessness or cultural confusion, lack of recreational, creative and working opportunities
- *Adolescent body image concerns:* Poor body image (how the adolescents perceive various features of their bodies) may be at the root of many “unexplained” behaviors and symptoms. The symptoms of poor body image may range from “stomach-ache”, headaches, and panic-attacks to menstrual disorders, anorexia and smoking (to lose weight!). The self-perception that a girl is overweight (even though her weight is

normal for her height) is the predominant reason for dieting and visits to the slimming centers rather than any actual increase in weight. Sometimes high-risk sexual behavior (to prove that one is attractive enough to the other gender, desire to prove physical strength and sexual powers) also arises due to body image concerns.

- *Physiological/biological risk factors:* Physiological immaturity of tissues (cervical and vaginal epithelium that increases vulnerability to contract STIs/HIV), endocrinal and other physiological changes
- *Behavioral risk factors:* Smoking, alcohol misuse, unhealthy eating habits, unsafe sex, substance use, thrill seeking, criminal/illegal activities
- *Situation/condition risk factors:* Poverty, low education/occupation, illiteracy, ignorance about sex and sexuality, stress, inadequate housing facilities, migration, discrimination due to sex, race, etc.

Role of Social Environment

Health-enhancing behavior and outcomes are primarily the responsibility of adolescents themselves. However, the knowledge, skills and opportunities they need to make healthy choices and to develop are influenced by the larger social, political, economic, and cultural context in which they grow and change. The key areas in the social environment include:

- *Relationships with the family and other adults:* Evidence¹ has shown that adolescents who have positive relationships (connectedness) with their parents and other adults (e.g. teachers) are less likely to initiate sex too early, less likely to use drugs and alcohol, and less likely to experience depression.
- *Influence of friends and peer groups:* Peer group has a special influence on adolescents. Friends are considered more important than parents and siblings at this age. Peer influence can be both positive, like in academics and sports, etc. as well as negative like substance use, over speeding, and unsafe sexual behavior.
- *Societal attitudes and norms:* Societal norms that value adolescents, their health and development will promote the healthy development of adolescents. On the other hand, social norms that value early marriage among adolescent girls, for example, serve as negative influences on their health outcomes as well as educational and economic opportunities.
- *Policies and legislation:* Policies and legislation that support adolescent health and development are very likely to significantly influence the healthy development of adolescents. For example, a reproductive health policy that allows adolescents, regardless of their marital status, to access contraceptive services,

¹ Broadening the horizon: Balancing protection and risk for adolescents, Geneva, World Health Organization, 2001.

will enable adolescents to protect themselves from early, unwanted pregnancies and sexually transmitted infections. Similarly legislation for safety while driving (use of helmet, seat belts) and restriction on tobacco selling and usage near the educational institution have a health promoting effect.

- *Mass media and entertainment:* The media can promote adolescent health and development by (1) providing accurate information on health and development issues; (2) communicating and mobilizing community support for promoting adolescent health and development; (3) giving space to positive role models and achievements of adolescents and young people, and (4) addressing aspects of the social environment and policies that have a negative impact on adolescent health and development. Access to and widespread use of social media like facebook, internet, email, etc. has become very popular among adolescents and young people and can be used to reach out to them.
- *Gender considerations in adolescent health and development:* Gender, as a concept, is used to describe those characteristics and roles of boys/men and girls/women, which are socially constructed in contrast to those, which are biologically determined. Thus, a gender approach places emphasis on the role of social factors in health. Adolescent boys are treated differently from adolescent girls. In most societies, boys are preferred to girls, and given more attention, opportunities and resources like less food and less care when they are sick and have less access to education and training that would enable them to improve their situation. It also leads to early marriage (and early motherhood) for girls. Their subordinate roles in relationships with men often means that they are not in a position to demand safe sex practices that would protect them from contracting the infections. Their lower social status and relative lack of physical, social and economic power often makes them more vulnerable, among others, to physical violence, sexual harassment, economically-coerced sex; abuse at the work place, and forced prostitution. On the other hand boys are more prone to morbidity and mortality due to injuries, accidents and violence because of the social expectations that they would indulge in outdoor activities much more than girls.

This understanding of multi-factorial determination of adolescent health and development is important to realize that many sectors have to contribute to prevention of adolescent health problems in collaboration with the health sector.

HEALTH SITUATION OF ADOLESCENTS IN THE SOUTH-EAST ASIA REGION

Based on the recent national demographic and health surveys (DHS) in the countries of the region the following picture emerges (graphics are provided at Annexure 1):

- *Mortality rates* among adolescents in the SEA region are generally lower than those observed in children or in older age groups. Globally, 97 percent of deaths among 10 to 24 year olds in 2004 occurred in low-income and middle-income countries, almost two-third of these in Sub-Saharan Africa and South-East Asia. In South-East Asia maternal causes of death (hemorrhage, sepsis, abortion complications) account for a higher proportion of deaths among females. Among males, injury-related deaths (traffic accidents, violence, fire-related injuries and drowning) account for a high proportion of deaths.²
- *Under-nutrition and anemia* are a public health concern in the adolescent age group in the region. Low BMI (<18.5) is reported from 24 percent (Maldives) to 47 percent (India) and anemia is prevalent in more than 50 percent of adolescents in several countries of the region. On the other hand, prevalence of overweight (BMI >25) among adolescents is gradually increasing, being 8 percent in Sri Lanka, 15 percent in Timor-Leste and 24 percent in Maldives.
- *Early childbearing* is a public health priority in several SEAR countries. Early pregnancy has higher chances of adverse reproductive health outcomes like high maternal mortality ratio and infant mortality rate. Adolescent women are two to five times more likely to die due to causes related to pregnancy and childbirth as compared to women in their twenties. Neonatal and infant mortality rates are higher among women aged <20 than among 20 to 29 year olds.

Considering that adolescent fertility remains high in some countries and is associated with higher maternal as well as infant mortality, this age group is significantly responsible for contributing to population momentum and a high MMR and IMR in the region.

- *Unmet needs for contraception* in married adolescents are high in Nepal, Maldives and India, with higher rates in women aged 15-19 than their older counterparts.
- *HIV prevalence among youth* (15–24 years) ranges from 0.01 to 1.32 percent; more than one-third of new HIV infections are reported in the age group 15-24 years.
- In many countries, prevalence of STIs is high in young people. In Bangladesh, more than 50 percent of the patients who sought treatment at formal facilities were young people. In Thailand, new STI cases reported among students have increased from 3 percent in 2000 to 10 percent by 2004.

² Global patterns of mortality in young people: a systematic analysis of population health data; George C Patton, Carolyn Coffey, Susan M Sawyer, Russell M Viner, Dagmar M Haller, Krishna Bose, Theo Vos, Jane Ferguson, Colin D Mathers; Lancet 2009;374:881–92.

Behaviors of Adolescents

- *Initiation of sexual activity* among adolescents could be as early as 13 years in some adolescents (Thailand 2004). Early sexual activity exposes adolescents to the risks of STIs and HIV in addition to the risk of unintended pregnancy.
- About 95 percent of new HIV infections in young people in Asia are in young sex workers, young men who have sex with men (MSMs) and young injecting drug users (IDUs). In Myanmar almost 53 percent of female sex workers aged 15-19 years were HIV positive in 2006. Of the total reported AIDS cases among IDUs in Indonesia, more than 40 percent were in the 15-24 year age groups.
- *Low condom use* characterizes a vast majority of sexual encounters among adolescents in the region. Condom use by sexually active male secondary students in Thailand with female sex workers was found to be 43 percent while it was less than 40 percent for all other partner types as well. In India, Bangladesh, Nepal and Sri Lanka not more than 52 percent of young males used condoms at the last high risk sex.
- *Drug and substance abuse* among adolescents is an emerging problem. The global youth tobacco survey (2003) showed a high prevalence of tobacco use in young people in SEAR. Injecting drug use among adolescents and young people has also increased in the region. In Maldives, the maximum number of cases of drug abuse was found in the age group of 16-24 years. In Nepal, half of the 50,000 injecting drug users were between 16 and 25 years.

Knowledge of Sexual and Reproductive Health Issues among Adolescents

- *The knowledge of contraceptives* among adolescents is high in the region, exceeding 90 percent among married adolescent females in almost all the countries but the contraceptive use rate is very low indeed.
- Though most young people have heard of HIV/AIDS, comprehensive knowledge of transmission and prevention is low and misconceptions are widespread. In India, 84.9 percent of youth had heard of HIV/AIDS, but only half of them were aware of two correct methods of prevention. In Myanmar, more than 90 percent of youth have heard of HIV/AIDS however only 18 percent of young women and 25 percent of young men knew two methods of HIV prevention. In Maldives, 34 percent of youth were not aware that a healthy-looking person could be HIV positive.
- *Awareness of STIs* and its symptoms is also generally low. In Sri Lanka 58 percent, in India 29 percent and in Timor-Leste 4 percent of adolescents were aware of STIs. Most young people do not perceive the risk for STIs and HIV.

- *Awareness of risk does not necessarily translate into safe behaviors.* In Indonesia, though 88 percent of young men were aware of condoms for HIV prevention, only 15 percent used a condom at the last commercial sex encounter. In India, 52 percent reported using a condom at the last casual sex while only 34 percent reported consistent condom use with all partners, despite quite high awareness about this preventive method. In Nepal, more than 90 percent youth knew where to get condoms, less than 10 percent used it with any partner. (DHS data from these countries)

IMPLICATIONS OF ADOLESCENT HEALTH SITUATION

Many of the health problems of adolescents described above are behavior dependent and are interrelated. Sexual behavior and gender relations, use of substances, dealing with conflicts and risks often have common roots. Preventive interventions for these behaviors are the same. Such interventions ensure positive personal growth and development. Healthy development of adolescents underlies prevention of adolescent health problems. Fortunately, the positive adolescent behaviors as well as the protective factors are also common and can be reinforced to keep the adolescents healthy and protected from health risks.

Provision of a safe and supportive environment that ensures sustained inputs for healthy and full development of adolescents is crucial. Several players in society like parents, families, teachers, society at large, and governments must contribute towards this.

A number of ministries and departments—health, education, social welfare, law and justice, etc.—need to work together and with civil society (including adolescents and their families) and community-based organizations to address the needs and problems of adolescents. The Ministry of Health must assume a central role for developing and sustaining a multi-sectoral response to promote adolescent health and development (Box 1).

National Response to Adolescent Health in South-East Asia Region

Although services, providers trained in reproductive health and HIV/AIDS and supplies may be available in the countries, adolescents and young people hesitate to use these services. At many places, the information and services needed by adolescents are not available or are not accessible. Health care providers have limited capacity to deal effectively and sensitively with adolescent clients. Biased and judgmental attitudes of providers, lack of privacy and confidentiality act as significant barriers to care-seeking behavior. Health care providers need capacity building to enable them to help a client who is 16 years and not six or 26 years old. The other common reasons for not using existing health services are lack of awareness,

Box 1: Why invest in adolescent health and development

Large number of adolescents: There are 1.2 billion adolescents worldwide; 350 million in South-East Asia; 1 in every 5 people in the world is an adolescent; 85 percent of adolescents live in developing countries.

Adolescents have been marginalized. They are generally considered healthy, thus there are very few programs for them.

Current health scenario (global situation)

- 300 million young people are smokers
- 16 million babies are born to adolescent girls each year (2008)
- There are about 2.6 million new HIV infections among young people per year (representing 50% of all new cases); 7000 young people are infected with HIV daily; about five young people are infected with HIV every minute
- There are more than 1,550,000 cases of tuberculosis each year among youth
- In addition to 100,000 suicides, there are 4 million suicide attempts by adolescents each year
- More than one million adolescents lose their lives—mostly through violence, pregnancy complications, and illnesses that are either preventable or treatable.

Impact on future health scenario

- Behavior formed in adolescence has implications for individual and public health. For example smoking in adolescence leads to 150 million tobacco-related deaths among adults, and early drinkers are four times more likely to develop alcohol dependency.
- *Economic reasons:* Healthy development of adolescents leads to improved productivity, and averts future health costs. Behaviors formed during adolescence have an impact on adult morbidity and mortality, which in turn has economic implications.

Human rights: Adolescents, through the Convention on the Rights of the Child have rights to a safe and supportive environment, information and skills, health services and counseling.

shyness or embarrassment, financial constraints, distance, and concern about the negative/unsympathetic attitude of health providers.

- A supportive policy environment is important to enhance access and coverage of the desired services for adolescents. Laws and policies in some countries remain indifferent to the sexual and reproductive health needs of adolescents. In some countries access to condoms, contraceptives, voluntary counseling and testing services and abortion services are restricted due to age (legally minors) and marital status. It is important to have clear policy guidelines within the existing legal framework to support access to services

by adolescents especially the ones below the legal age of consent. The national review of laws and policies for adolescent health review has been conducted Sri Lanka and Bangladesh, which revealed policy gaps that have been identified for advocacy with policy makers to redress the situation so that access by adolescents to the available services can be enhanced.

- Initial steps have been taken towards developing adolescent health programmes in several member countries in the region like India, Indonesia, Maldives, Myanmar, Nepal, Sri Lanka, Thailand and Timor Leste. However, national strategy on adolescent health has been developed only in Bangladesh, India, Indonesia, Myanmar, and Nepal. The main focus of programmes has been sexual and reproductive health, including HIV. Increased attention is needed to address unhealthy lifestyles, mental health and violence. One reason for inadequate attention to these issues may be that we do not have national level data on these.
- To improve the access for adolescent clients to services national standards for adolescent friendly health services have been developed in Bangladesh, India, Indonesia, Nepal, Thailand and Timor Leste.
- National adaptation of the global adolescent health training package has been carried out in several member states and they have started building capacity of the health care providers for delivering appropriate services in a sensitive and non-judgmental manner. Adolescent friendly health services are being rolled out in the countries in a phased manner.

India has done particularly well in institutionalizing adolescent friendly health services within the public health system under the National Rural Health Mission. Adolescent reproductive and sexual health strategy was launched in 2006 as one of the key technical strategies under the national reproductive and child health program (RCH II). All the thirty five states and union territories have planned various activities for operationalizing adolescent friendly health services at selected health facilities and through outreach services and school health programme. Capacity building package has been adapted from the WHO global packages.

In India, other Ministries are also contributing to adolescent health through several programs. Ministry of Women and Child Development has recently launched Rajiv Gandhi Scheme for empowering adolescent girls (Sabla scheme) under which nutrition supplementation, IFA supplementation, vocational skills building and reproductive health education. Education Ministry provides adolescent education programme in the schools to provide age appropriate health education and life skills development to class 9 and 11 students all over the country. Ministry of Youth and Sports has a countrywide programme to organize youth clubs that integrates cultural

activities, sports and health education for out of school adolescents/young people.

Professional associations like Indian Academy of Pediatrics and Federation of Gynecological Societies of India have worked closely with Ministry of Health to support Adolescent Reproductive and Sexual Health strategy under NHM/RCH-II. Their members in private sector are taking up the responsibility of offering friendly health services to adolescents as per the national standards.

However, much more needs to be done for ensuring coordination among various programmes in the government sector as well as collaboration with the private sector to reach out to maximum number of adolescents to keep them healthy.

SUMMARY

Twenty percent of world population belongs to 10-19 years age group (adolescents) who have a specific set of public health problems. The health of adolescents will determine whether the societies will ensure achieving their human potential for realizing the demographic bonus towards national development. Adolescents have to face a multitude of health problems like pubertal disorders and

concerns, nutritional problems, sexual and reproductive health problems, injuries and violence, mental health problems and substance use problems in addition to common communicable diseases that are endemic in the countries. Preventing these health problems and responding to the health problems through easily accessible adolescent friendly health services is an essential investment that health sector must undertake in order to ensure that adolescents/young people are able to contribute to the national development to their maximum potential. Countries need to develop a multi-sectoral response to promote adolescent health and development that underlies prevention of health problems.

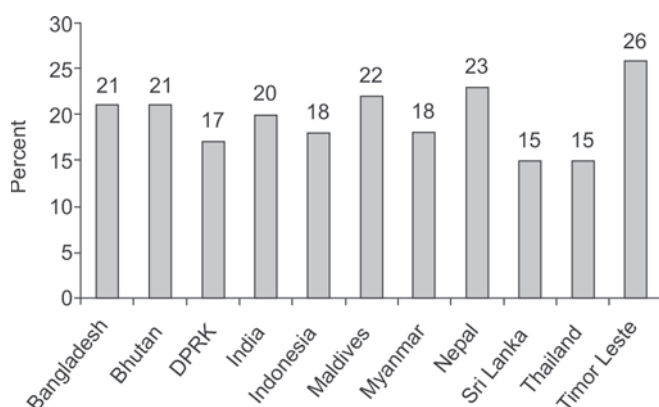
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ANNEXURE

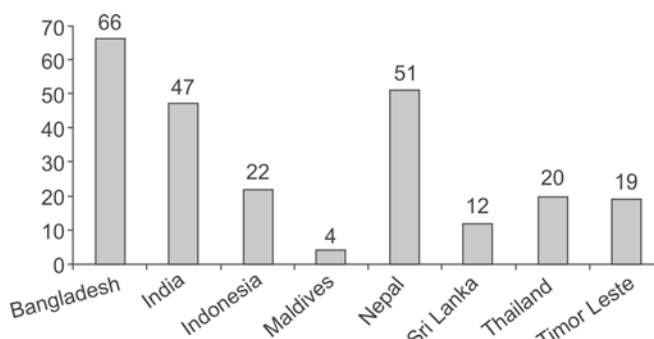
ADOLESCENT HEALTH SITUATION IN SOUTH-EAST ASIA REGION: SELECTED INDICATORS

1. Proportion of adolescents (10-19 years) in SEAR countries



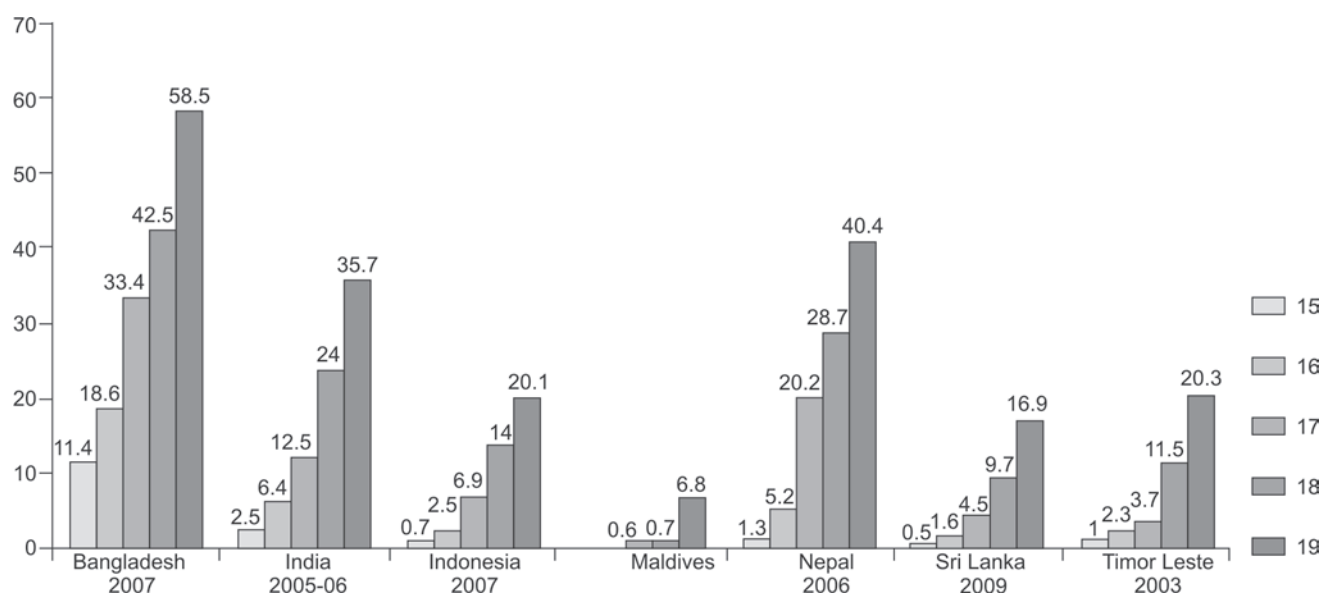
Source: Population Division of the Department of Economic and Social Affairs of the United Nations Secretariat, *World population prospects: The 2010 Revision*, <http://esa.un.org/unpd/wpp/index.htm>.

2. *Early marriage*: Percentage of women aged 20-24 years married by 18 years of age



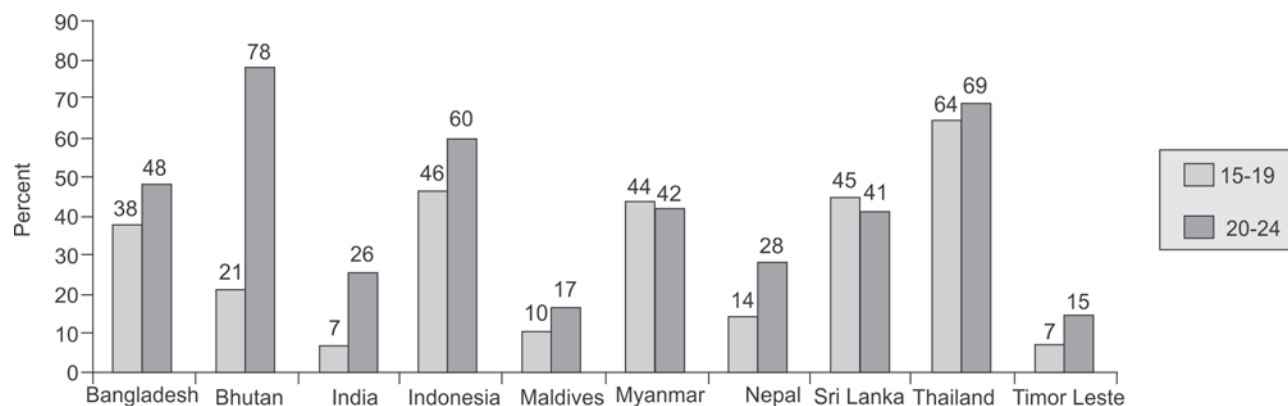
Sources: Bangladesh DHS 2007; India NFHS-3 2005-06; Indonesia DHS 2007; Maldives DHS 2009; Nepal DHS 2006; Sri Lanka DHS 2006; Thailand Multiple Indicator Cluster Survey 2005-06; Timor Leste DHS 2009-10.

3. *Early child bearing*: Percentage of married adolescents aged 15-19 years who have begun childbearing



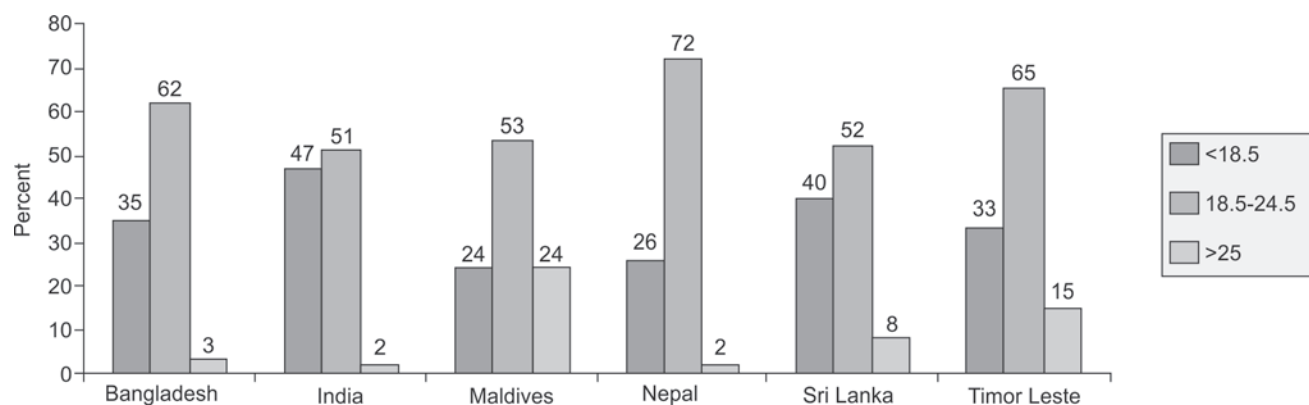
Sources: Bangladesh DHS 2007; India NFHS-3 2005-06; Indonesia DHS 2007; Nepal DHS 2006; Maldives 2009; Sri Lanka DHS 2005-06; Timor Leste DHS 2009.

4. *Low contraception use:* Contraceptive use (modern methods) among married 15 to 19-year-old and 20 to 24-year-old women



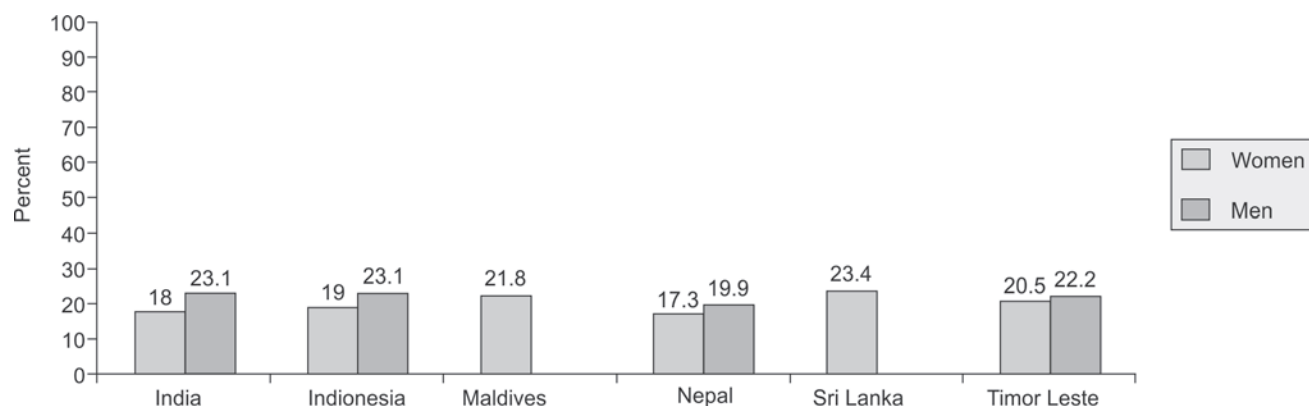
Sources: Bangladesh DHS 2007; Bhutan Living Standard Survey 2007; National Statistical Bureau, Royal Government of Bhutan (age group 20-29); India NFHS-3 2005-06; Indonesia DHS 2007; Nepal DHS 2006; Sri Lanka DHS 2006; Maldives DHS 2009; Myanmar Country Report on 2007 Fertility and Reproductive Health Survey, Union of Myanmar, Ministry of Immigration and Population, Department of Population and UNFPA; Timor Leste DHS 2009-10.

5. Nutritional status of adolescents aged 15-19 (BMI)



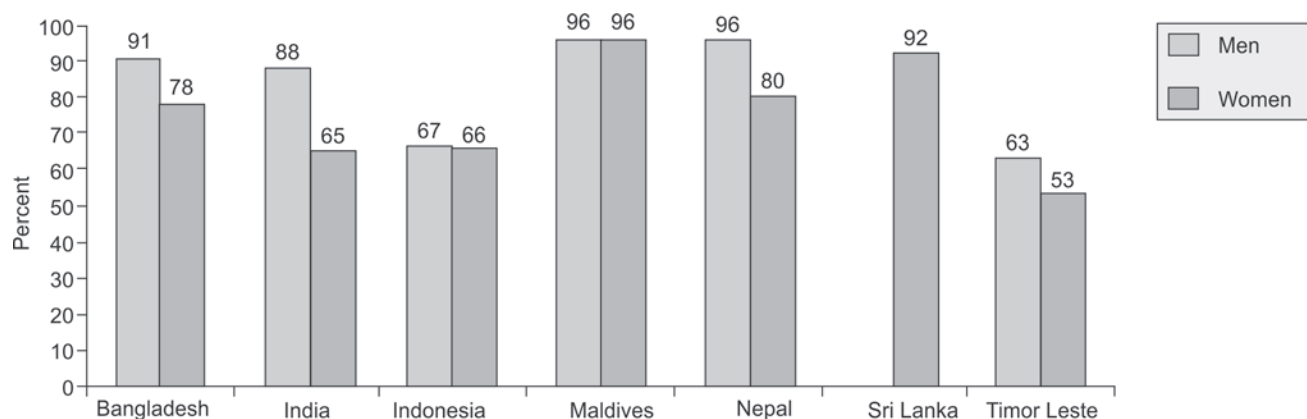
Sources: Bangladesh DHS 2007; India NFHS-3 2005-06; Nepal DHS 2006; Sri Lanka DHS 2006; Maldives DHS 2009; Timor Leste DHS 2009-10.

6. *Early sexual activity:* Median age at sexual debut among women
Ever married women and currently married men



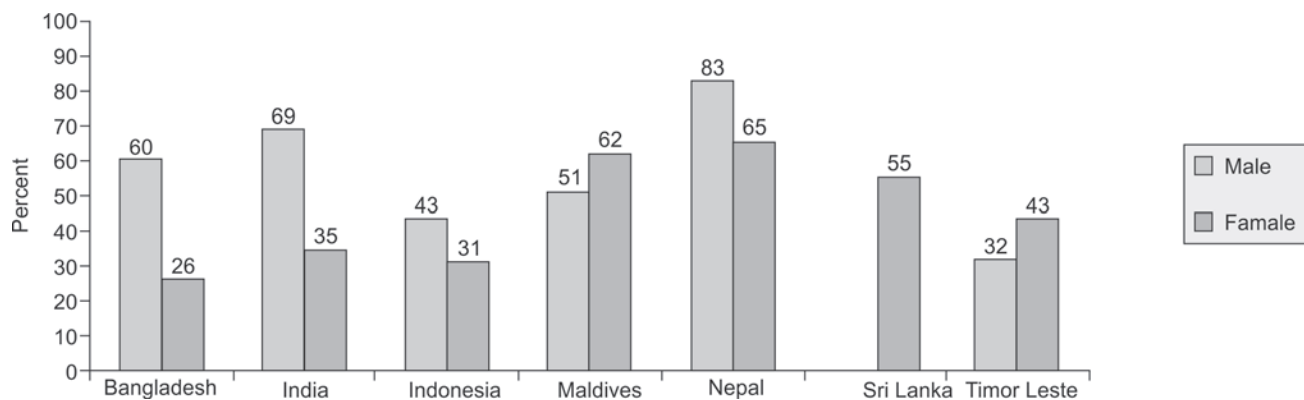
Sources: India NFHS-3 2005-06; Indonesia DHS 2007; Nepal DHS 2006; Sri Lanka DHS 2006; Maldives DHS 2009; Timor Leste DHS 2009-10.

7. *Knowledge about HIV:* Heard about HIV/AIDS among youth (15–24 years)



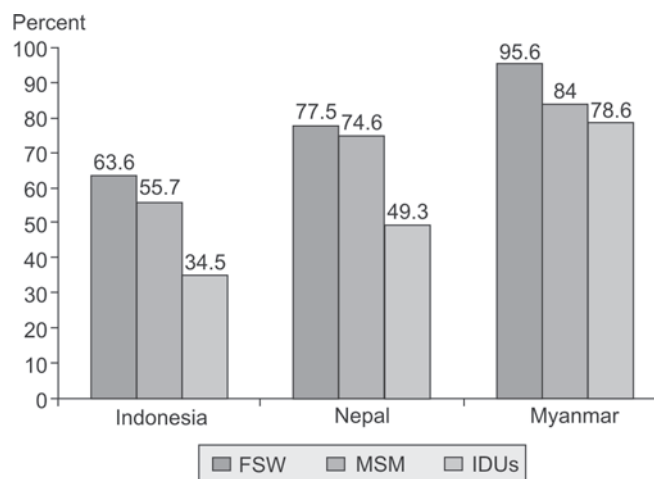
Sources: Bangladesh DHS 2007; Indonesia DHS 2007; India National Family Health Survey-3, 2005-06; Maldives DHS 2009; Nepal DHS 2006-07; Sri Lanka DHS 2006-07; Timor Leste DHS 2009-10.

8. Knowledge of youth (15-24 years) on at least two methods of HIV prevention



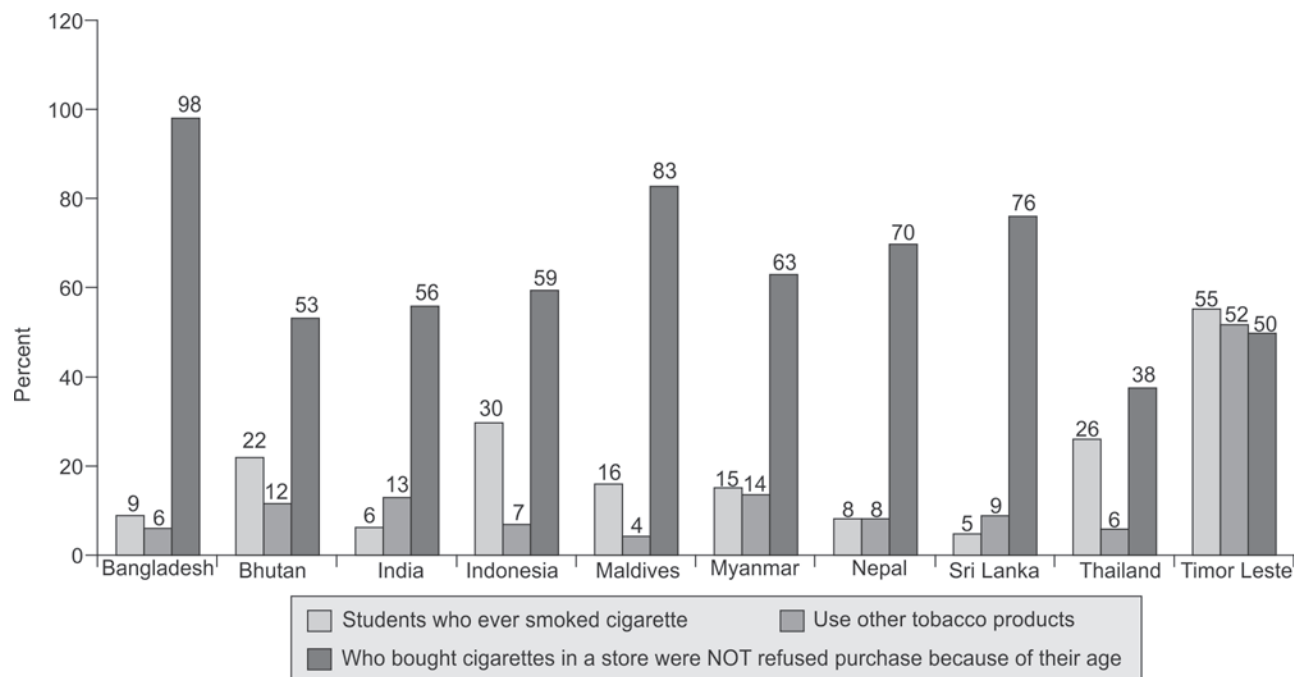
Sources: Bangladesh DHS 2007; India National Family Health Survey-3, 2005-06; Indonesia DHS 2007; Maldives DHS 2009; Nepal DHS 2006-07; Sri Lanka DHS 2006-07; Timor Leste DHS 2009-10.

9. Use of condom among the most-at-risk young people (<25 years) with their most recent clients



Sources: UNGASS Country Progress Reports of Indonesia, Nepal and Myanmar 2010

10. Tobacco use among adolescents (13-15 years) in SEAR



Source: Global Youth Tobacco Survey (GYTS)-2009

Mental Health Issues in Adolescents

CP Bansal, S Yamuna

INTRODUCTION

Adolescents are in a transition between the dependency of childhood and the autonomy and independence of adulthood. This transition is brought on by the hormonal changes of puberty. Adolescence is a period of mood swings with certain prolonged periods of sadness or elation depending on the environment in which he or she lives. The psychosocial evolution of adolescents predisposes them to mental health challenges which may result in mental illnesses in a few adolescents.

Very young adolescents are closer to parents but late adolescents not only move away from parents in search of autonomy and independence, but they also become closer to their peer group such as friends or with their intimate partners as in a relationship. Issues affecting their feelings, emotions and mood are usually unmasked, expressed, shared or discussed only with the group of people with whom they are comfortable.

Knowledge about mental health presentations in adolescents is very poor in the community that most behaviors in adolescents are either perceived as “difficult behaviors” with parental disapproval and reprimand or pushed aside as being part of the “storm and stress” of adolescence and is usually not addressed as the features are considered as part of the growth and development of the individual. It is now understood that such difficult behaviors are not part of normative development and thus it is essential to help these boys and girls with appropriate intervention to ease out their psychological upheavals.

Help seeking behavior among adolescents is also low because the adolescents are ignorant about the subtle differences between wellness and illness; adolescents do not unmask their mental health concerns unless they are comfortable with the attitude of the health care provider; adolescents are cooperative only in an environment where there is maintenance of privacy and confidentiality.

Adolescents are comfortable to take help from the health care providers who are able to evince that kind of comfort and confidentiality. Thus it becomes the duty of the primary care provider to take a proactive role in detecting symptoms of mental illness in the adolescents who reach them for primary health care needs.

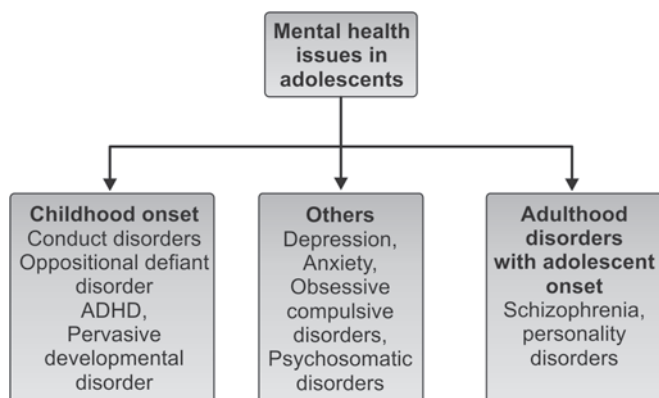
Depression in children and adolescents is associated with poor psychosocial functioning, high psychiatric comorbidity, and risk of recurrent episodes or onset of bipolar disorder. Depression during adolescence is associated with higher rates of smoking, alcohol abuse, unhealthy eating, and infrequent exercise and thus increasing the proneness of the adolescent to all lifestyle diseases. Thus depression during early adolescence has consequences for health and associated costs during young adulthood. Thus it is beneficial to inculcate the necessary skills to screen and treat depression among adolescents who reach us.

As pediatricians are well known to a growing child in view of familiarity, exploring the psychosocial aspects of the adolescents’ development through Home, education/employment, peer group activities, drugs, sexuality and suicide/depression (HEADSS) screening can be carried out with ease. If pediatricians can take the evaluation with an eye to detect difficulty in coping with the emotional demands of adolescence, early identification of mental health issues or illnesses would be feasible.

COMMON MENTAL HEALTH ISSUES IN ADOLESCENTS (FLOW CHART 1)

Mental Illnesses in adolescents can be classified as follows:

- Disorders of childhood may reach us during adolescence as they have not been addressed during childhood. Examples are conduct disorders, oppositional defiant disorders and attention deficit hyperkinetic

Flow chart 1: Common mental health issues in adolescents

disorders and pervasive developmental disorders which are not dealt with here.

- A few disorders can present during adolescence and thus contribute towards the morbidity and mortality of the adolescents. Depression, anxiety, obsessive compulsive disorders, psychosomatic disorders are a few disorders that deserve our active intervention during adolescence. If left untreated their course and prognosis can become troublesome at a later date.
- Disorders of mental health that happen in adults predominantly might have their onset during adolescence like schizophrenia, personality disorders etc. This group of disorders is also not dealt with here.

An attempt is being made to give an overview of the second class of disorders, their presentation, diagnosis and management in a way to stimulate the thoughts of the primary pediatrician:

- To recognize the manifestations of these illnesses from parents' account of their adolescents' behaviors
- To identify the conditions early during a casual interaction with an adolescent
- To spread messages in the community about the clinical features that should make parents, peers or teachers to suspect the illnesses in the adolescents they encounter
- To manage the illness with reasonable comfort until the help of a mental health professional is available.

With this objective in mind this chapter is aimed at addressing the common presenting features, clinical manifestations, diagnosis and early management of adolescent depression and anxiety disorders.

DEPRESSION IN ADOLESCENTS

Epidemiology of Depression in Adolescents

Prevalence of depression among adolescents is related to age, gender and social class. Very young adolescents have a lower prevalence and the number of adolescents with depression increases with age. Thus it ranges from

1 percent in very young adolescents to 25 percent among late teens depending on the other factors that increase the proneness to depression. Until the onset of puberty, depression among children is equally prevalent among boys and girls. With menarche girls are two to three times more likely to become depressed than boys. Depression is more common among lower socioeconomic status because of exposure to chronic environmental chaos and disquietness.

Families with members who have had depressive disorders have children who are more prone for depression during their lifetime. Though there is no definite cause for depression, biological factors, endocrine factors, social factors and structural factors in the brain seem to contribute to the features of depression. Environmental factors like socioeconomic status, level of family conflict, neglect or abuse, parental separation or divorce seem to play a significant role in the unfolding of depression in adolescents.

Major Depressive Disorder

It is easy to diagnose a major depressive disorder when it is acute in a child with no previous psychiatric illness. In children with anxiety disorders, or hyperactivity the onset can be insidious.

Clinical Features

Depression is characterized by the presence of the majority of the following symptoms for more than two weeks (DSM IV TR criteria). At least five of the following should be present associated with a change from the previous level of functioning:

- Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g. feels sad or empty or bored) or observation made by others (e.g. appears tearful). (In children and adolescents, this may be characterized as an irritable mood)
- Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (loss of interest to play or listen to music)
- Significant weight loss when not dieting or weight gain (e.g. a change of more than 5 percent of body weight in a month), or decrease or increase in appetite nearly every day
- Poor sleep/insomnia or excess sleep/hypersomnia nearly every day
- Psychomotor agitation or retardation nearly every day (Symptoms may take the form of restlessness, pacing, tapping fingers or feet, abruptly starting and stopping tasks, meaninglessly moving objects around, and more. Psychomotor agitation is frequently, though not exclusively, associated with agitated depression. Adolescents may be fidgeting their fingers frequently during consultation)

- Fatigue or loss of energy nearly every day
- Feelings of worthlessness or excessive or inappropriate guilt nearly every day
- Diminished ability to think or concentrate on academics, or indecisiveness, nearly every day
- Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

The symptoms are not due to the direct physiological effects of a substance (e.g. a drug of abuse, a medication) or a general medical condition (e.g. hypothyroidism).

The symptoms are not better accounted for by bereavement, i.e. after the loss of a loved one, the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.

The clinical features of depression can also be classified as affective, behavioral, cognitive and somatic symptoms:

- Affective or mood symptoms include depressed mood and feelings of worthlessness or guilt
- Behavioral symptoms include social withdrawal and agitation
- Cognitive symptoms or problems in thinking include difficulty with concentration or making decisions
- Somatic or physical symptoms include insomnia or hypersomnia (sleeping too much).

In prepubertal children the depression presents with more somatic symptoms; affective and behavioral symptoms are more common among adolescents. Adolescents also have cognitive symptoms with difficulty in focusing/concentration. In adolescents frank antisocial behavior can occur as a presenting feature. Feelings of restlessness, grouching, boredom, aggression, sulkiness, reluctance to cooperate with family expectations, withdrawal from social activities and a desire to leave home are common in adolescent depression. School difficulties, inattention to grooming, increased sensitivity to rejection in romantic relationships also signify depression in adolescents.

Feeling sad, bored, empty, low, down, blue, unhappy, feel like crying for no reason, are some of the words that are used by children and adolescents to convey sadness. Functional impairment due to depression extends to all areas of functioning including scholastic performance, peer interactions, and family relationships. Inputs from peers, teachers and significant others would help in the diagnosis of depression in adolescents.

Highly intelligent academically strong children can compensate for the mood disorder with increased attention

to academics. It is common for most children to have a fall in grades when affected by depression. Difficulty in concentration, lack of interest, lack of motivation, fatigue, sleepiness, depressive ruminations contribute to the fall in grades.

If features of depression are associated with hallucinations and delusions psychosis should be considered.

Depression rarely presents as a single entity. It is usually accompanied by other coexisting mental illnesses. Conduct disorder, oppositional defiant disorder, panic disorder, attention deficit hyperkinetic disorder, anxiety disorders, disruptive disorders, and substance use disorders are the usual comorbid disorders among adolescents. It is essential to identify the comorbid conditions as these conditions either alter the presenting features of depression or prolong the recovery phase of depression. If the conditions are not taken care of, the recovery can be different from the expected course.

INVESTIGATIONS

No lab investigation can help in making a diagnosis of depressive disorder. But it may help us in identifying other disorders like hypothyroidism, anemia, etc.

DIFFERENTIAL DIAGNOSIS

- *Adjustment disorder*: Where the depressive features should follow within three months of a negative life event.
- *Attention deficit hyperkinetic disorder*: It is usually a comorbid condition where inattention, hyperactivity and impulsivity coexist
- *Specific learning disability*: It is also an accompanying disorder. Inability to excel in academics may be associated with dysphoria which can present as depression
- *Conduct disorder*: Here aggression to people and animals, destruction to property, theft and deceitfulness, serious violation of rules with significant impairment to social, personal and academic life. This also coexists in many adolescents
- *Oppositional defiant disorder*: It is usually confused with the externalizing behaviors of depressed adolescents. Negativistic, hostile and defiant behavior exists in the absence of sadness or guilt
- *Substance use disorder*: It is found that most adolescents with substance use are depressed. In most instances depressed adolescents resort to substance use to fight the low mood and seek ecstasy. As these moments of ecstasy are short lived the habit of using mind altering substances becomes a regular habit.

As all the conditions mentioned need a Psychiatrist to identify and differentiate, it is better that a Primary care provider takes the help of the psychiatrist in managing adolescents with features suggestive of depression.

TREATMENT

Hospitalization

The decision to admit an adolescent with depressive features arises in the event of suicidal ideation and plans. To maintain safety, hospitalization might be needed in helping the adolescent stay away from his impulsive self destructive behavior. If there is an associated substance use, admission would help in deaddiction.

Pharmacotherapy and Psychotherapy

Combination of cognitive behavior therapy (CBT) and selective serotonin reuptake inhibitors (SSRI) is observed to give better results than either of them given alone.

Cognitive behavior therapy aims to challenge the maladaptive beliefs and enhance problem solving abilities and social competence.

Pharmacological agents that are used in the treatment of childhood and adolescent depression are Fluoxetine (10 mg), Sertraline (25 mg), Citalopram (10 mg), Escitalopram (10 mg), and Fluvoxamine (25 to 50 mg) with starting doses in the brackets. Dose might have to be enhanced in adolescents.

Duration of Treatment

If there is good response to initiation of antidepressants, maintenance of treatment for 6 months followed by cessation of treatment when the stress levels are low are the recommendations for treating depressive disorder.

Course and Prognosis

Mean duration of depression in children and adolescents is 9 months, if left untreated but with a range of 3 to 250 weeks. Recurrence of symptoms of depression is common during adulthood in up to 40 percent within two years and in 70 percent in another five years.

Depressive disorders are usually associated with relationship difficulties. Poor academic achievement and persistently poor self esteem.

Dysthymic Disorder

Dysthymic disorder in children and adolescents consists of a depressed or irritable mood for most of the day, for more days than not, over a period of at least 1 year.

According to DSM IV TR diagnostic criteria at least three of the following symptoms must accompany the depressed or irritable mood:

- Poor self-esteem
- Pessimism or hopelessness
- Loss of interest
- Social withdrawal
- Chronic fatigue
- Feelings of guilt

- Brooding about the past
- Irritability or excessive anger
- Decreased activity or productivity
- Poor concentration or memory.

During the year of the disturbance, these symptoms do not resolve for more than 2 months at a time. Dysthymic disorder may be followed or may evolve into a major depressive disorder.

When minor depressive episodes follow a significant stressful life event by less than 3 months, it is often part of an adjustment disorder.

Anxiety Disorders

Like pain anxiety has protective functions for human survival. If a person develops anxiety in the presence of danger in the environment, anxiety serves a protective function. If anxiety is disproportionately high or if there is anxiety in the absence of danger it is considered pathological.

Anxiety in an appropriate amount helps in functioning. But an excessive anxiety that disturbs the social, physical and academic functioning of an adolescent is abnormal. Being anxious on the day of the examination or on the Valentine's day before proposing to their loved one is acceptable. But a devastating level of anxiety that prevents an adolescent from interacting with any one or makes the adolescent dread about school to avoid examination is pathological and need intervention.

There are many anxiety disorders and each of them has specific features but all of them are bound together by a common theme of excessive, irrational fear and dread.

Generalized Anxiety Disorder

Children and adolescents who exhibit excessive worries pertaining to their performance in school and social settings and experience at least one physiologic symptom such as restlessness, poor concentration, muscle tension or irritability related to their fears, may be diagnosed to have generalized anxiety disorder. Adolescents with generalised anxiety disorder feel fearful in multiple settings and expect and visualize negative outcomes when faced with social or academic challenges.

Social Phobia

Those adolescents who experience high levels of anxiety while in social situations that makes them avoid participation in social events meet the criteria for social phobia. They experience distress and discomfort in the presence of peers as well as adults. They have concerns about being humiliated, embarrassed or negatively judged.

In the above conditions the experience of adolescent can approach panic or terror. Adolescents may not directly express their worries but their behaviors often reflect their fears. They may refuse to go to school on the day of

examination or presentation, or to a friend's house. They may retreat from group activities and express feelings of loneliness because of their self-imposed isolation.

Sleep difficulties, night mares and morbid fears accompany anxiety disorders. They may have somatic symptoms including gastrointestinal symptoms, nausea, vomiting, stomach aches, and unexplained pains in various parts of the body. Older adolescents complain about palpitations, breathlessness, dizziness, faintness, and feelings of strangulation.

Investigation

No lab investigation can help in the diagnosis of anxiety disorder. But investigation may be necessary to rule out organic reasons for the somatic symptoms.

Adolescents who are able to continue normal functioning with respect to peer group interaction, school attendance and social situations have a better prognosis than those who confine themselves within the four walls of their room.

Treatment

Family education, family psychosocial intervention, CBT and pharmacologic interventions have to be considered while treating adolescents with anxiety disorders.

Obsessive Compulsive Disorder

Obsessive compulsive disorder is characterized by the presence of obsessions and compulsions. Obsessions are recurrent intrusive thoughts associated with anxiety or tension. Compulsions are repetitive purposeful mental or physical actions aimed at reducing fears and tensions caused by obsessions. Many candidates with OCD have their onset during childhood and adolescence. The presenting features are almost similar to that in adults but with one exception. The children and/or adolescents may not perceive their thoughts or behaviors as unreasonable.

The common obsessions in children and adolescents are dirt, germs, disease, followed by worries about harm befalling the family members or themselves. The typical compulsive behaviors are checking, cleaning, counting or arranging items in an order. Associated features are avoidance and delayed task completion.

The compulsive behaviors are carried out to keep the harmful effects from affecting self.

Treatment is a combination of SSRI and cognitive behavior therapy. Fluoxetine (20 to 60 mg), Fluvoxamine (up to 200 mg) and Sertraline (50 to 200 mg) have been approved for treating adolescents with OCD.

OCD is a waxing and waning disorder with a great variation in course and outcome. Almost 50 percent remit completely and another 25 percent have partial remission in a year's time.

Psychosomatic Disorders

All of us have certain expectations when we deal with patients who present with physical symptoms. We expect a reasonable degree of discomfort, we seek for certain pathological manifestations, we acknowledge a realistic amount of emotional and psychological distress to be associated with the physical symptom and we also expect a corresponding setback in day to day functioning of the person with the symptoms.

When the subjective symptoms do not correspond to the objective findings a mental health evaluation is usually considered. These are the disorders which can be referred to as psychosomatic disorders when symptoms such as choking, inability to breathe, hyperventilation, inability to write, paralysis, etc. present in the absence of clinical findings.

CONCLUSION

Early identification of mental health issues in adolescents would help the pediatricians in referring them to mental health professionals at an appropriate time. The pharmacological treatment is recommended for almost for 6 to 9 months duration. Family education and family support by primary care pediatrician to encourage continuous treatment offered by the psychiatrist would help the family in adhering to the treatment advised.

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Parenting of Adolescents

Atul M Kanikar

INTRODUCTION

Parenting is perhaps the most important and possibly one of the most challenging developmental tasks of middle age. The influence of parental behaviors has produced lasting impact on the course of history of India. Right since the golden era of Indian history, legends and philosophers have been giving guidelines on effective ways of dealing with children for better individual and community outcome. Classical examples of family conflicts, parental neglect, extreme obedience as well as fatal adolescent rebelliousness are cited even in the great epics of *Ramayana* and *Mahabharata*. The best citations, however, come from “*Chanakya Niti*” by Kautilya, where situations of healthy milieu and disaster within the family along with the ideal changes in attitude of a parent when the child blooms into a teenager are described. Chanakya says, “A true son must be obedient to his father, a true father should look after his son, similarly true friend is one who is trustworthy and true wife is one who makes her husband happy.” Although not all the mythological and historical theories remain applicable today, the basic impact of various internal and external factors on the entire family dynamics must be considered when one deals with the issues of parenting.

WHAT IS PARENTING?

“There isn’t any formula or method. You learn to love by loving.”

Aldous Huxley

Parenting, by definition means an art of bringing up children. It is a bilateral process where both parents and children learn from each other mostly by their mistakes. This art is more learnt than inherited. The ways in which parental behaviors influence this process are called as parenting styles. Our own parents teach most of these methods to us. The hereditary pattern is commonly exhibited in methods employed in disciplining children. Thus, we see some families where spanking and yelling is very common. Others use words and nonverbal methods with possibly better outcome. External factors like educational background of the parents, sociocultural backgrounds, economic well-being, type of guests visiting the house, size of the family, mother’s profession (whether earning or a housewife) and her status in the family, methods of family enjoyment, grandparental interference, etc. also have a beneficial or harmful role to play.

Without going further into the nature against nurture issue, let us say that, the natural instincts, desires, and methods of parenting need to be upgraded with the current scientific technique, so as to produce a perfect blend both for parents and children. Parenting comprises of various tasks, emotions, responsibilities, difficulties and rewards involved in the process of bringing up children. It is an ongoing process and will remain so. However, the situation worsens in a parent’s middle age when the children enter the stressful adolescence and the grandparents face the aging disasters. The middle generation is thus sandwiched between these two highly sensitive generations.

The principal components of parenting are depicted in the Table 1.

Table 1: Components of parenting

<i>S. No.</i>	<i>Important parental task</i>	<i>Methods</i>
1.	Responding to the needs	Caring for children, spending time and energy for them.
2.	Establishing closeness	Hugging, giving a pat on the back, holding hands, etc.
3.	Helping to be independent	Giving household responsibilities with increasing grade, avoiding unnecessary interference for the tasks, which they can do independently.
4.	Accepting the individuality	Giving obvious respect to what a teenager has to say, consider teenager's point of view, involving them in family discussions, etc.
5.	Nurturing self-esteem	Avoid empty praise, criticizing too much, and have realistic expectations for what a teenager can do.
6.	Accepting our own limitations	Spending quality time together because everybody is busy, having realistic expectations from other family members, understanding the ever changing outside world and our own physical and economic constraints.

There is a significant difference in parenting a younger child and an adolescent. Even during adolescence the early phase, i.e. between 10 to 14 years, is described as the most difficult to handle phase by many parents mainly due to the rebellion shown by a teenager, which is most of the times unexpected. The parental anxiety as shown by strict disciplinary methods, extreme restrictions on the teenager, especially girls, is also at its peak owing to the fact that most parents are not prepared for the changes of menarche that occurs usually in early adolescence. A teenager is also very clumsy (due to disproportionate growth) in this period giving rise to many clashes with the family. A teenager is treated simultaneously as a child and an adult, which adds to further confusion.

As a parent (and a pediatrician too), it is mandatory to know the range of normal behavior and psychosocial development of both—an adolescent and a parent entering his/her middle age. Unless we learn about this universal process, the issue of parenting remains baseless. The developmental tasks of a teenager and the parents may individually or in combination contribute to the family environment, which has to be caring, nurturing and stable for the desired outcome. The art of understanding one another and one of the important life skills called “empathy” can be easily learnt if both parents and teenagers understand these universal changes depicted in the following charts.

The developmental tasks of teenage are given in the Table 2:

Table 2: Developmental tasks in teenage

<i>S. No.</i>	<i>Developmental task</i>	<i>Description in brief</i>	<i>Possible hazards</i>
1.	Hormonal effects leading to sexual maturation.	Adjustment to body and mind, establishing a sexual identity within the norms and values of family, friends and society.	Inferiority complex for late bloomers and awkwardness and risk of abuse/aggressive behavior for early bloomers.
2.	Abstract thinking skills.	Ability to think about ‘thinking’, constructing philosophies, creative thinking, and the intelligence is at its peak.	Moodiness, day dreaming, disturbed sleep and dietary habits, parents feel that something is wrong.
3.	Developing more complex level of perspective taking.	Understanding human relationships and a teenager can empathize with others.	If ignored, the teenager feels neglected leading to self-blame and depression.
4.	New coping skills in decision-making, problem solving, and conflict resolution.	A teenager can think about and plan for the future, can moderate their risk taking to serve goals rather than jeopardize them.	Disputes over issues like career, marriage, etc.
5.	Identify moral standards, values, and belief systems.	Self-analysis of personal values and beliefs rather than those emphasized from childhood by elders.	The concept of ‘generation gap’, and rebellious behaviors.
6.	Understand and express a set of complex emotional experiences.	Ability to identify and communicate more complex emotions, to understand other's emotions better, abstract thinking about emotions.	A teenager may attempt to behave and act like an adult, may become choosy about pet friends and family members.

Contd....

Contd....

7.	To cultivate friendships those are mutually close and supportive.	Shift from friendships based largely on the sharing of interests and activities to those based on sharing of ideas and feelings with more emphasis on nonverbal communication.	A teenager usually does not find an ideal friend/friends who can share mutual trust and understanding.
8.	To establish key aspects of identity.	It is an ability to identify self and its connection to valued people and group. Adolescents also need to develop a positive identity around gender, physical attributes, sexuality, culture and ethnicity.	Failure in these areas can have lifelong effects. Many disorders of adulthood have their roots in adolescence.
9.	To meet the demands of increasingly mature roles and responsibilities.	The list of expectations from the teenager by the family, peers and the society, is frustrating and unending.	Considerable stress.
10.	Renegotiate relationships with adults in parenting roles.	Inclination to separate from the family, along with a desire to be an important part of it simultaneously.	Conflicts over priorities, career, supercompetitions and comparisons.

It is quite obvious from the above chart that adolescence is a stressful and stormy period needing help, guidance and vigilance too by parents and caretakers. The need for parent education is thus very much obvious. However, the task is not all that easy. The common feedback obtained from various parenting workshops conducted over last three years in urban and semiurban middle class families, the principal issues of concern were a sense of unease while talking to children, gross ignorance for developmental tasks and parenting skills, severe time constraints for everybody in the family, uncertainty about teenagers willingness to listen, adolescent's rebel and

undisciplined behavior, external influences and career choices. Many parents tend to hide these concerns at least initially.

In spite of all these and many other hindrances, parents need to take active interest in adolescent's daily activities and keep a noninterfering vigil, failing which a teenager becomes vulnerable to peer pressure and other hazards like low actualization of potentials, underachievement, inadequate coping skills, feeling of inferiority, poor self concept and self-esteem, deviant/risk taking behavior and increased risk of psychosocial problems. The usual causes of family conflicts are depicted in Table 4.

The developmental tasks and main concerns of the middle age Table 3:

Table 3: Developmental tasks and main concerns in middle age

<i>S. No.</i>	<i>Developmental task and important issues</i>	<i>Brief description</i>	<i>Possible hazards</i>
1.	Advancing health restrictions	Decreased physical capacities and mental threshold. Emergence of various disease processes. Premenopausal changes.	Physical and financial stress. Fear of disability and untimely death.
2.	Significant change in various interests	Assuming civic and social responsibilities. Interests are more solitary in nature, e.g. reading, TV watching, etc.	Other family members may feel 'left-out'. Increased sexual desire in females and lessened interest in males.
3.	Tasks related to family life	Relating oneself to one's spouse as a person. Adjusting to aging parents. To provide guidance and economic support to growing children. Increased worries for career of children.	Series of conflicts and family frictions. "Empty nest syndrome" after the adolescents have left for vocational training.
4.	Vocational adjustments	Life after retirement, boredom, financial constraints, feeling of uselessness, self-blame for other family member's failures.	Depression and increased irritability.

Table 4: Causes of family conflict

<i>Adolescent causes</i>	<i>Parental causes</i>
Parents seem old fashioned and bad critics.	Authoritative style.
Unfair/childish disciplinary methods.	Middle age crisis.
Unhealthy sibling relationships.	Grandparents—interference/liability.
Comparisons with parents of peers.	Family triangle and favoritism.
Family gatherings are “boring”.	Expectation of a “dream child”.
Increased social activities.	“Empty nest” syndrome.
Tendency to experiment.	Self-blame and feeling of hopelessness.

Psychologists have described various styles of parental behaviors. The main categories are—authoritarian (“I am the boss, and everybody has to obey me”), permissive (full freedom and no restrictions), negligent (“leave them alone”), avoidant (“leave me alone”) and authoritative (sits across the table, negotiating type). Most parents use all these methods in combination, depending on the situation under consideration. However, the most frequently applied methods decide the type of parental personality. The teenagers also view their parents with these typical labels. As mentioned earlier, most of these styles are repeated through generations. The conflict arises when a parent has to change his/her style because of the changing world that is not within one’s control. Thus, we tend to blame the media, internet and peers for our own shortcomings.

The five principal parenting responsibilities are given in the Table 5:

Table 5: Parenting responsibilities

1. Unconditional love	Being on their side, no matter what. Separating the teenager and the misdeed. Not giving incentives, not bribing them for better results.
2. Keep a close vigil	Monitoring daily routine, knowing the whereabouts and peer group, encouraging group activities but with supervision, interaction with parents of peers, regular visits to the PTA.
3. Discipline	Maximum use of nonverbal communication, explaining family rules clearly, using time appropriate rewards and punishment in proper dose, maintaining consistency and uniformity.
4. Introspection	Parents need to be a good role model themselves; they should also accept a teenager’s as well as their own limitations.
5. Crossing the boundaries	Thinking beyond our own family, forming parent’s self-help groups, taking professional help if necessary.

SPECIFIC ISSUES IN PARENTING A TEENAGER

Discipline

The process of discipline involves a series of well-intended efforts by parents and caregivers to inculcate “the art of controlling oneself”. If properly learnt and consistently practiced, discipline becomes a very important foundation for the growth of children. It brings self-confidence, feeling of mastery over life and positive social experience for children even after growing as adults. The positive feelings themselves add up to bring out a well-behaved and confident parent of the future, who would in turn express positive discipline techniques successfully. The discipline process should act as “vaccination” against untoward effects of peers, media and other difficult to handle situations in life.

Discipline, by definition means, “to teach”. However, by tradition, we equate this with punishment. Discipline also is, encouraging children, guiding them and helping them feel good about themselves. The root word of discipline is disciple—a person who leads others in the way they should go. Discipline is not what you do to the child, but what you do with and for the child, may it be a toddler or a teenager. The short-term goal of discipline is to guide everyday behavior and to protect children from hurting themselves and others, however, the long-term goal should be to bring out a confident, self-disciplined individual, responsible for his/her own behavior, is relying upon self and is comfortable and happy about it.

There are only one/two children per family now, and all parents wish to give the best to their children, there is no another chance. Nobody wants to accept that quite naturally, according to normal distribution probability curve, every child cannot be at the top. What we are giving to our children is a “filtered” parenting (I keep the troubles with me; my children should never face problems). In addition, we have working parents who unnecessarily feel guilty for not giving time to their children, but at the same time want their children to win the ever-increasing competitions, may it be studies, sports or debating.

Sibling Rivalry

Constant fighting, putting downs, arguing and comparisons among children are the causes of sheer frustrations and concern for most parents. Brothers and sisters often use their fights to gain parental attention and to show power. Some bickering is considered as normal but creating dangerous situations and physical fighting are definitely not. It is the most common complaint from the grandparents.

The ignorance as to how to handle the rivalry adds to the anger and helplessness of parents who adopt the age old method of spanking and yelling which worsens the situation. The interference by other family members, e.g. grandparents and favoritism makes it more difficult for

the parents to chalk out resolving strategies. When parents react to hostility with hostility, they are unwittingly promoting sibling rivalry. Research has proved beyond doubt that siblings set up their own private verbal and nonverbal language between themselves that marks their unique relationships. Amongst siblings, the negative behaviors and approaches are also mutually agreed to some extent, ruling out the need for frequent interference by caretakers. Another interesting research finding is that often the younger sibling provokes a negative reaction from the older one and probably knew no other way to grab attention of the older sibling. Provocation is thought to be the best way of initiating contact.

It is the primary duty of the parents to inculcate healthy sibling relationships without punishment and humiliation. Following guidelines may help right from the arrival of the second child.

- Allow children to express their feelings towards each other. Parents should acknowledge the child's feelings first, e.g. anger or frustration, understand their emotions and feelings and let them know that, e.g. "you sound furious! you wish he could have asked you before using your things" or "would you like to draw a picture of how mad you feel". Surprisingly, the anger melts away quickly, when children know that parents know and understand their anger.
- Avoid comparisons as far as possible. The grandparents, relatives and even visitors have this constant habit of comparing children, that too in front of them. No two children are similar, and why should they be? Comparing does not ensure better behaviors. In fact, it increases the jealousy and envy. Praising one child in the presence of another also should be avoided for the same reason.
- Parents should treat their children individually, not equally. One strategy effective for one child may not be so for the other one.
- Never take sides. Parents cannot resist the urge to figure out who started the fight. It is wrong to punish the older or stronger each time. Instead of taking sides, express your comment on the overall behavior.
- Let the children work it out for themselves. Stay out of minor fights. Step in only when children cannot work out the solutions.
- Teach children some better ways of getting attention. This is especially important for the younger sibling. The older child should be asked to use respectful words and praise to strengthen the new method of initiation. Giving children shared responsibilities and taking turns may also work.
- Family gatherings and family meals offer a great opportunity to understand another person's feelings.
- If possible, separate space (corners in the room) should be provided to each child. Putting time limits on the use of common devices like telephone, television, etc.

and dividing age appropriate chores equally also helps in avoiding conflicts. Rules and consequences should be made extremely clear to everybody in the house.

- Counseling and physical examination to rule out neurological disorder remain the last methods for managing intractable and serious physical fights among siblings.

All sibling relationships are not frictional at least not all the times. Consequently, sibling relationships are important aids to the young child's personal and social development. Older sibs serve as role models to imitate and young children discover what is expected from them. From these quarrels, children learn what other children will and will not tolerate, learn how to be good losers as well as gracious winners.

During adolescence, older siblings often criticize the appearance and behavior of the younger child, who in turn likes to tease and bully even younger siblings. If parents try to interfere, they are accused of playing favorites. The children may gang up against the parents and the 'pet' sibling. Moreover, rivalries in adolescence have a more lasting effect in future relationships than those in early childhood.

Grandparents Role

There are more advantages than disadvantages of having grandparents in the family. It all depends on everybody's personalities, expectations, contributions, and communication styles. Often parents and grandparents get into a situation where they are competing at 'parenting'. The smaller issues like disciplining, menu for lunch, TV watching, birthday gifts, dressing styles, doing chores, etc. soon become the topics of disputes. The previous confrontations are remembered and bounced back and conflicts set in. Whatever may be the causes of disputes in between the elders, care should be taken that, the solutions are sought early, the memories do not last long, and the children do not take advantage of the situations. Conflicts within the families are known for ages, it is the unfavorable influences of the outside world that create the constant need for healthy family relationships. Because what the family cannot provide, teenagers will try to recover it from outside world, which will never give the warmth and comfort of a home. Grandparents can and should provide their comfortable lap; one can climb onto to listen to the best stories and useful advices, may it be grandchildren or the parents themselves.

Schools and Colleges

The academic performance of a child and teenager is directly proportional to the parental interests and interactions with school activities irrespective of the financial and educational status of the parents. Both parents should regularly attend the parent teacher association programs

and take part in all the school activities meant for parents. These visits help the parents to know about new activities and opportunities at school, the sustained interests of the teenager, and other issues like peer influence and school violence, etc. The teaching staff also feels more concerned and responsible for the betterment of the pupil. Parents should follow these guidelines as far as possible:

- Reserving at least 15 to 20 minute discussion time for school activities shows that the parents are taking active interest in academics and that education is important to them.
- Helping children and young adolescents in homework and reading with them.
- Setting limits for TV watching and computer games. A well made timetable that is well followed, by everyone in the family is most of the times sufficient.
- Monitoring out of school activities of the teenager helps to prevent future serious consequences.
- In recent times, the coaching classes have dominated the educational world of teenagers. This system breaks the parents financially and students mentally and physically asking for special nutritional needs during entrance examinations. Parents should see that the teenager is not dragged in this distressing routine just because of peer pressure and as far as possible ensure that the school authorities themselves take steps to finish the curriculum well before the examination dates with ample revision sessions. Moreover, in case of failures or poor performance, the teenager should not be blamed in proportion to the money spent.

Boosting Self-Confidence

Teenagers whose parents say, “You can do it” are more likely to respond saying, “Yes, I can and I should”. This can be accomplished by encouraging new experiences since adolescents themselves love to develop new skills, teaching them a wide variety of basic skills including household work (even cooking), dividing a complicated task into portions within reach, giving proper reinforcement and appreciation (remember nonverbal communication) and telling them that mistakes are bound to be there and we learn to walk by stumbling.

Parents need to identify and nurture the natural abilities of the teenager that may be unique. Giving a supportive environment and positive remarks helps these skills to flourish. It also gives a feeling of respect and responsibilities. The final step is to honestly praise the teenager for actual accomplishments in a specific and unexaggerated manner. Association of what a teenager’s desire, with the after effects teaches them to be responsible. For example, if a teenager invites friends, he/she must do most of the cleaning after the party is over. Thus, a parent has done a great job if the teenager starts thinking about what might happen before he/she embarks on a course of action.

Alternatively, parents who treat a teenager like a young child may really end up with one.

Talking Together

With very busy schedules for the entire family, nowadays the parents and a teenager hardly get time to interact. Phone calls, scribbled messages and even e-mails have replaced or (?) eased the communication within families. The moodiness of adolescents and various burdens of parents further cause hindrances. Having at least one family meal together, planning a mutually suitable time, or just turning off the television may help provided there are no conflicting discussions. Family matters, emotional issues, the future, the past memories of parents, current events, personal interests, friends, etc. are the preferred topics for teenagers. The conversation has to be open with equal opportunities for both and at no moment parents should jump to preaching and pleading. Adolescents are capable of making informed choices provided they are allowed to choose. Many teenagers find difficulties in expressing anger, guilt, anxiety and grief. Parents must help and encourage teenagers to ventilate these disturbing feelings. It is all during these casual but useful conversations that parents can imbibe the ways to healthy lifestyles, honesty, courage, self-discipline and one’s commitment to the family. All these sessions go a long way in preventing serious problems in future.

The above technique needs lot of practice and patience at least initially. Parents should remember that in a given situation the teenagers should not be treated like criminals in the court and focusing on the past and putting labels has to be strictly avoided. Everyone in the family including grandparents should participate in the discussion but the ‘moderator’ must be the parents. In most of the routine matters these strategies really work. Everybody feels respected and responsible.

Occasionally there are far more serious situations. For example, a teenager gives way to peer pressure and lands up with drug addiction or an adolescent girl gets morning sickness. Following are some helpful tips for parents for facing these unfortunate but not so uncommon family calamities. Parents must offer unconditional love, whatever is the situation at hand.

Problem solving

State the problem as seen.

Open the discussion showing empathy.

List the possible solutions together.

Veto the unacceptable options.

Evaluate the remaining solutions.

Do the most acceptable to all.

- Parents may show that they understand the situation by saying, “I know, there are plenty of opportunities these days”
- In a firm voice one can mention that as a parent you will never allow anything to hurt the teenager.
- Help should be offered in the best possible way and the problem should be viewed together. Professional help may be taken if necessary.
- Accusation, putting labels and self-blame has to be avoided.
- Further follow-up and encouragement for improved behavior is a must.

Every responsible parent must be aware of certain warning signs in the teenager which may point out high risk behavior. Most of these behaviors are reversible, if picked up early. The mother can be the best clinician at home. Some of these signs include scholastic deterioration, disturbed sleep and appetite, disproportionate irritability, loss of interest in sports and recreational activities, a new set of (senior) friends, stealing money or valuables, avoiding hug and eye contact by parents and antisocial behavior.

Thus, wise parenting is the one that slowly shifts responsibilities, family values and social customs from parents to adolescents with a scope for further improvisations

that are for the betterment of the individual, family and society. There is nothing like an ideal child and a perfect parent. It is never too late to start taking interests and initiatives in adolescent care. The more one learns about it, the more one feels comfortable with a teenager and self. Moreover, the adolescent feels comfortable and confides best in parents for personal issues, thus fulfilling the important criteria of a successful parent. The untoward effects of the media and peers can thus be avoided, if parents can provide themselves as good role models. Teenage problems and parental worries are inevitable today. Running away from the battle will surely not help. Understanding the mechanisms and basics and preparing for the difficulties surely will.

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Red Eye in Children

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INTRODUCTION

Red eye is the most common and nonspecific ocular sign presenting in emergency and outpatient departments. It is the most common ocular problem seen by primary care physicians.¹ Data from Middle East show that red eye accounts for approximately 15 percent of consultations with ophthalmologists and almost 6 percent with general medical practitioners.² Red eye from the patient perspective signifies visible appearance of abnormal redness of the globe, lids or adnexal structures.³ The clinical term 'red eye' is applied to a variety of infectious and inflammatory conditions involving one or more of ocular tissues including conjunctiva, cornea, lids and internal ocular structures. Conjunctivitis is the most common cause of red eye.¹

Signs and symptoms of red eye include redness, discharge, itching, pain, photophobia and changes in vision. Although most cases can be effectively managed in a primary care setting, a thorough understanding of the disease process is essential in recognizing danger signs that require ophthalmologic referral.

DANGER SIGNS

Danger signs point towards a more serious ocular condition including uveitis, keratitis, corneal abrasion, ulcer, glaucoma and thus necessitate a thorough evaluation and treatment by a trained ophthalmologist. The danger signs are:

- Severe pain
- Decreased visual acuity
- Photophobia (intolerance to light)
- Ciliary flush (redness in the immediate area around the circumference of the conjunctival corneal border—the limbus)
- Corneal opacification
- Pupil sluggishly reacting or not reacting to light

- Proptosis (outward bulging of the eyeball)
- Reduced ocular movements
- Raised intraocular pressure
- Immunocompromised host
- Worsening signs or no improvement despite therapy for 3 days.

CAUSES OF A RED EYE

Disorders Primarily of the Globe

Extraocular

- Conjunctiva
 - Conjunctivitis (and keratitis when mechanism is same)
 - Infectious—viral, bacterial, fungal
 - Allergic and hypersensitivity reactions
 - a. Acute
 - Seasonal allergic conjunctivitis
 - Perennial allergic conjunctivitis
 - b. Chronic
 - Vernal keratoconjunctivitis (VKC)
 - Atopic keratoconjunctivitis (AKC)
 - Giant papillary conjunctivitis
 - Phlyctenular conjunctivitis
 - Contact dermatitis/conjunctivitis
 - Toxic reactions
 - a. Chemical exposure
 - b. Topical medications and preservatives
 - Mechanical/irritant
 - a. Contact lens related
 - b. Foreign body
 - c. Trauma—child abuse, injury
 - d. Exposed sutures, glaucoma drainage device
 - Noninflammatory conjunctival redness
 - Subconjunctival hemorrhage

- Abnormal vascular engorgement—polycythemia vera
- Cornea
 - Corneal abrasion
 - Keratitis and corneal ulcer
 - Dry eye syndrome
 - Exposure keratoconjunctivitis
 - Paralytic (Bells palsy)
 - Nocturnal
 - Abnormal lid anatomy with inadequate closure
 - a. Congenital
 - b. Postsurgical
 - Neurotrophic keratoconjunctivitis
- Episclera/Sclera
 - Episcleritis
 - Scleritis

Intraocular

- Infectious or inflammatory
 - Congenital glaucoma
 - Uveitis
 - Anterior
 - Intermediate
 - Endophthalmitis
- Neoplastic
 - Any primary or metastatic malignant tumor (example retinoblastoma)
 - Masquerade syndrome

Disorders of the Eyelids and/or adnexal Structures

Eyelids

- Blepharitis
- Hordeolum
- Chalazion.

Orbital/Periorbital Structures

- Preseptal and orbital cellulitis
- Ruptured dermoid cyst
- Sinus mucocele
- Neoplastic
 - Malignant—primary, metastatic
 - Abnormal vascular engorgement
 - Arteriovenous malformations
 - Carotid cavernous fistula
 - Orbital varix

Nasolacrimal System

- Canaliculitis
- Dacrocystitis
- Nasolacrimal duct obstruction (NLDO) with secondary conjunctivitis
- Lacrimal gland
 - Dacryoadenitis

- Malignancy

Systemic Disorders Associated with Red Eye

- Stevens Johnson syndrome (SJS)
- Kawasaki disease
- Juvenile rheumatoid arthritis (JRA)
- Inflammatory bowel disease (IBD)
- Vitamin A deficiency
- Varicella, mumps, and measles
- Psoriasis
- Behcet disease
- Syphilis
- Tuberculosis.

APPROACH TO A CASE OF RED EYE

An accurate history with a thorough ocular and systemic examination provides the key to correct diagnosis in a case of red eye.

History Taking

In a child, a careful history taken from a reliable informant provides important background information for clinical examination. Questions to ask in the patient history include symptoms of the patient with onset and duration. Patient is specifically asked about pain, itching, discharge, decreased vision, intolerance to light and other danger signs which necessitate prompt referral to an ophthalmologist. The patient is enquired about:

- Any recurrent or seasonal occurrence of the symptoms
- Previous treatment received especially any over the counter medicines
- Any history of contact lens use
- Any preceding history of trauma or upper respiratory tract infection (indicating towards viral etiology of red eye)
- Any family history of hay fever, allergic rhinitis, asthma, atopic dermatitis that may point towards an allergic etiology of red eye
- History of any associated systemic illness like joint pain in JRA, abdominal pain, diarrhea in IBD.

Specific Clues to Etiology of Red Eye from History

Many associated symptoms of red eye are nonspecific. However, certain associations strongly suggest a particular diagnosis Flow chart 1.

- *Itching*: The pathognomonic symptom of ocular allergy is itching.⁴ Mild itching may also be associated with blepharitis, dry eye and occasionally infective conjunctivitis.¹
- *Discharge*: The type and amount of ocular discharge should be enquired. A serous discharge is most commonly associated with viral or allergic ocular conditions. A mucoid (stringy or ropy) discharge is

characteristic of allergy or dry eyes. A mucopurulent or purulent discharge with associated morning crusting and difficulty in opening the eye lids is suggestive of bacterial infection. Chlamydial disease tends to have mucopurulent discharge. Copious purulent discharge in first 3 to 5 days of life should raise suspicion of gonococcal conjunctivitis.⁵

Characteristics of discharge associated with red eye:

Etiology	Serous	Mucoid	Mucopurulent	Purulent
Viral	+	-	-	-
Allergic	+	+	-	-
Bacterial	-	-	+	+
Chlamydia	-	+	+	-
Neisseria	-	-	-	+
Dry eye	+	+	-	-

- *Unilateral or bilateral presentation:* Allergic conjunctivitis usually presents bilaterally. Infections caused by viruses and bacteria (including *Chlamydia*) initially present in one eye due to direct contact of eye with microbe, but the other eye gets involved soon after. Iritis, herpes, corneal abrasions, keratitis are usually unilateral.

General Survey

A detailed systemic examination indicates towards the etiology and systemic association of the red eye. Face examination may reveal herpes labialis in a case of herpetic conjunctivitis. Lymph node examination may reveal palpable preauricular and submandibular lymph node in viral or chlamydial conjunctivitis, toxic conjunctivitis secondary to topical medication. Palpable lymph nodes are rare in bacterial conjunctivitis except in hyperacute conjunctivitis caused by *Neisseria* species.¹

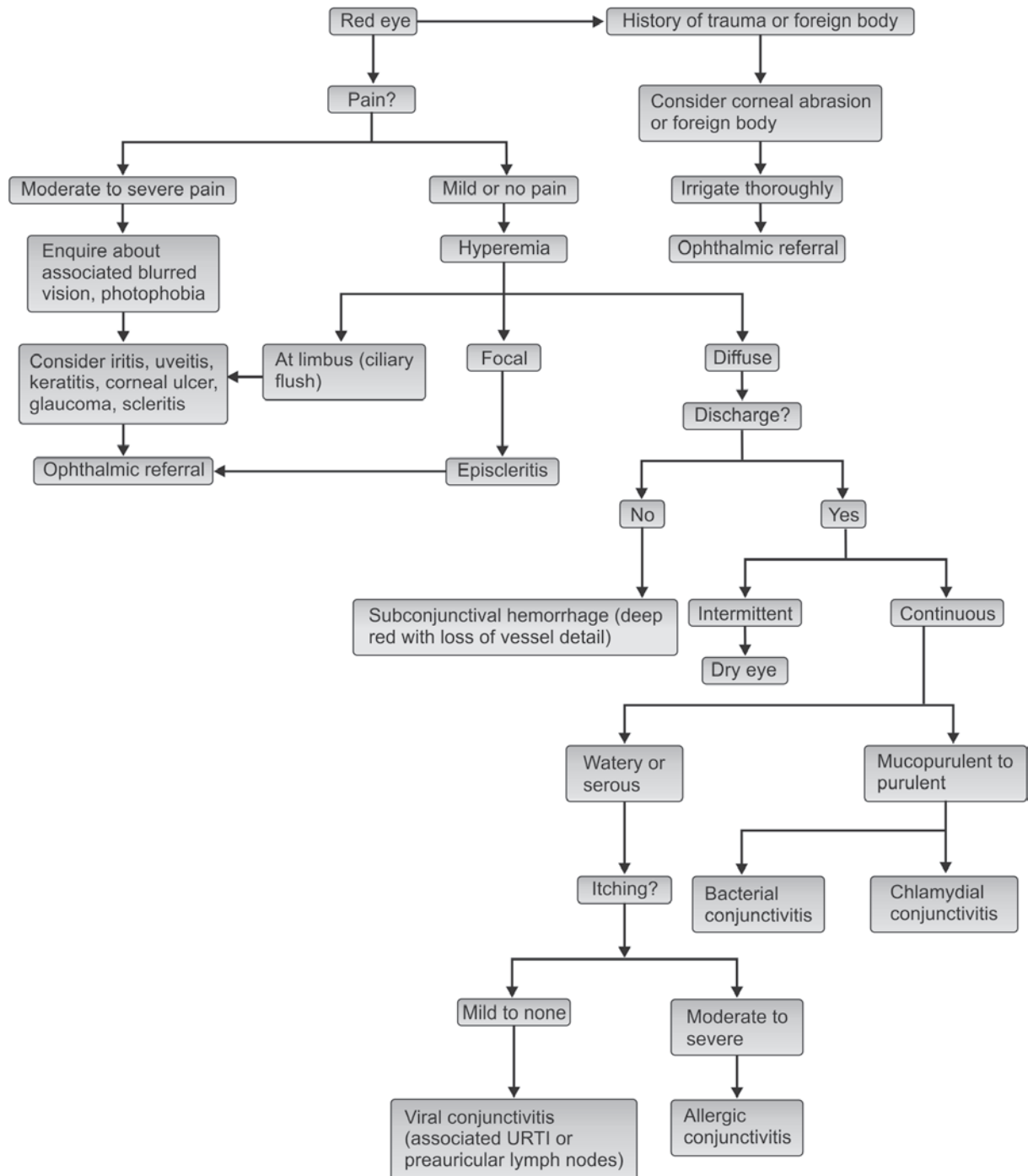
Ocular Examination

Examination of the red eye should be performed after contact lens or glasses (if child is wearing any) are removed. Examination is best done by using a slit lamp biomicroscope and a direct ophthalmoscope. In their absence, a magnifying instrument along with a pen light is very useful. A close look at the different external tissues of the eye individually provides essential information for etiological diagnosis of the red eye. Ocular examination includes:

- *Visual acuity:* Visual acuity of each eye is checked individually on the snellen chart with and without spectacles. Visual acuity usually remains unaffected in conjunctivitis unless there is an associated keratitis as in AKC, keratitis, uveitis, congenital glaucoma, episcleritis, scleritis all pose a serious threat to vision and require referral.⁶

- *Eyelid and adnexal structures:* Eyelids and eye lashes are examined for erythema and thickening of eyelid margins and crusting at the base of the eye lashes (blepharitis, dermatitis), periorbital discoloration (allergic shiners),⁷ blepharospasm (inability to keep eyes open) and ptosis. Eyelids may become swollen after exposure to an allergen or after insect bites.
- *Lid eversion:* Both the upper and the lower lids are everted to look for papillae or follicles. Presence of these reflects the chronicity of the conjunctival inflammatory response.⁷ Follicles are greyish, clear or yellow bumps that vary in size from pinpoint to 2 mm in diameter. They are usually associated with viral and chlamydial infections and have conjunctival vessels on surface. Papillae are cone shaped elevations on the conjunctiva, each containing a small tuft of blood vessels.⁸ Papillae are usually seen in chronic allergic disease.
- *Conjunctiva:* The conjunctiva is examined for chemosis (swelling), hyperemia, palpebral and bulbar papillae or follicles and any debris or obvious mucus in the tear film. The nature and amount of discharge is noted.
- *Location of redness:* In order to differentiate conjunctivitis from more serious forms of ocular inflammation the location of the redness is important. Diffuse conjunctival redness is most likely conjunctivitis. Circumciliary congestion (around the circumference of conjunctival-corneal border) indicates intraocular inflammation due to uveitis, endophthalmitis or raised intraocular pressure.⁵ Intraocular inflammation will more likely be associated with pain and globe tenderness but no discharge except tearing whereas in conjunctivitis there is discharge but no pain. Localized area of redness on conjunctiva may be related to a foreign body, trauma, episcleritis or scleritis. Deep red areas over conjunctiva with loss of vessel detail represent subconjunctival hemorrhage from trauma or a vascular maneuver.
- *Cornea:* The cornea should be perfectly smooth and transparent. Any greyish or milky white areas may indicate corneal ulcer. Mucus plaques adhering to cornea or conjunctiva are pathologic (dry eye, conjunctivitis). Discrete swellings with small white dots at the limbus (Horner Trantas dots) are commonly associated with chronic forms of conjunctivitis like AKC, VKC.
- *Anterior segment:* Iris appearance, anterior chamber reaction (cells or flare), are checked (anterior uveitis). Pupillary reactions are noted.
- *Ocular motility:* Limited ocular motility in eyes with painful red swollen eyelids point towards orbital cellulitis.
- *Intraocular pressure measurement (IOP):* Perkin's hand held tonometer can be used to measure IOP in children. In cooperative children Goldmann applanation tonometry can be done on a slit lamp. Raised IOP is seen in congenital glaucoma, secondary glaucoma due to uveitis or trauma.

Flow chart 1: Diagnostic algorithm for red eye



- *Posterior segment:* Posterior segment examination reveals vitreous exudates in intermediate uveitis and endophthalmitis. Optic disk evaluation is to be done for congenital glaucoma.

CONJUNCTIVITIS

The conjunctiva is a thin, translucent membrane that has a bulbar and a palpebral part. The bulbar part covers the white part of the eye ball (the sclera), and the palpebral part covers the inner surface of the eyelid. The term conjunctivitis refers to a broad group of conditions presenting as inflammation of the conjunctiva. Conjunctivitis is the most common cause of red eye.

Etiology: Conjunctival inflammation may be the result of infection or allergy or toxic reaction.

Common etiology of conjunctivitis by age:⁵

Age groups	Common etiology
Neonates <24 hours	Chemical conjunctivitis (silver nitrate)
<1 week	<i>Neisseria gonorrhoeae</i>
<1–2 weeks	<i>Chlamydia trachomatis</i>
Infants and toddlers—without otitis media	<i>Haemophilus influenzae</i> <i>Streptococcus pneumoniae</i> <i>Branhamella catarrhalis</i>
with otitis media	<i>Haemophilus influenzae</i>
School age children 1–5 years	HSV, varicella zoster
School age children and adolescents	Viral conjunctivitis Allergic conjunctivitis

Signs and symptoms: Signs and symptoms are similar with each of these etiologies. The redness of conjunctivitis spares the limbus. Ocular pain, photophobia, and decreased vision are not usually seen in conjunctivitis (with the exception of adenoviral keratoconjunctivitis). Itching and foreign body sensations are more likely due to allergic causes. Allergic or viral etiologies are associated with clear or mucoid discharge whereas purulent discharge suggests bacterial etiology. Preauricular lymphadenopathy and pharyngitis is suggestive of a viral etiology. There is no consensus as to whether bacterial or viral conjunctivitis is more common in pediatric age group. Weiss et al⁹ in 1993, Teoh et al⁵ in 2003 and Granet⁶ in 2008 have pointed bacterial conjunctivitis as the most likely cause of acute conjunctivitis in children. Whereas Sethuraman et al¹⁰ in 2009 and Seth et al¹¹ in 2011 have reported the incidence of viral conjunctivitis to be higher than that of bacterial conjunctivitis.

Bacterial Conjunctivitis

Patients with bacterial conjunctivitis present with red eye with mucopurulent discharge (Fig. 1) which causes eyelash matting and eye lid closure on waking up in the morning. This typical history and the presence of mucoid or purulent

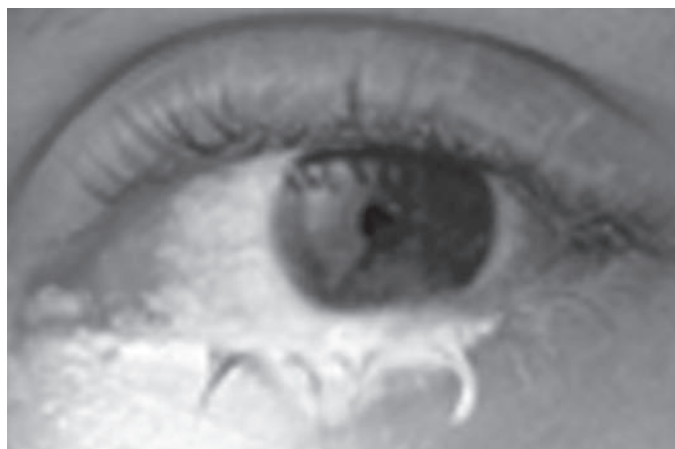


Fig. 1: Bacterial conjunctivitis (For color version see plate 20)

discharge on examination are highly predictive of bacterial conjunctivitis.¹² It is most commonly spread through direct contact with contaminated fingers. Bacterial conjunctivitis is classified as hyperacute, acute or chronic based on duration and severity of clinical manifestations.^{13,14}

- Acute bacterial conjunctivitis is the most common form of bacterial conjunctivitis in primary care setting.¹³ It typically has an abrupt onset with tearing and ocular irritation developing in one eye initially but spreads to the opposite eye within 48 hours. Mucopurulent or purulent discharge develops within one or two days. Symptoms persist usually for less than four weeks. Examination reveals diffuse hyperemia of the bulbar and palpebral conjunctiva. *Haemophilus influenzae* is the most commonly isolated organism followed by *Streptococcus pneumoniae* and *Staphylococcus aureus*.¹² *Treatment:* In most cases diagnosis is based on clinical findings. Laboratory studies are performed only in severe cases and those unresponsive to initial treatment¹ to identify the organism and determine its sensitivity to antibiotic agents. Treatment consists of a broad spectrum topical antibiotic like fluoroquinolones (Ciprofloxacin 0.3%, Gatifloxacin 0.3%, moxifloxacin 0.5%) used three to four times per day. This empirical approach is highly effective and adverse consequences are rare.^{15,16}
- Chronic bacterial conjunctivitis is the most commonly caused by *Staphylococcus* species.¹ It usually develops in association with blepharitis and meibomian gland inflammation. Examination reveals flaky debris, erythema and warmth along the lid margin, eyelash loss and bulbar conjunctival hyperemia. Some patients also have recurrent styes and chalazion. Treatment includes establishment of good eyelid hygiene using warm compress and eyelid margin massage and application of appropriate topical antimicrobials.
- Hyperacute bacterial conjunctivitis is often associated with *Neisseria gonorrhoeae* in neonates, sexually active

adolescent. The infection has an abrupt onset, with rapid progression leading to corneal perforation. It is characterized by copious purulent discharge, pain, decreased vision. In neonates it typically presents in first three to five days of life.^{17,18}

Treatment includes hospitalization and adequate eye irrigation and administration of ceftriaxone 25 to 50 mg/kg intravenously or intramuscularly in a single dose. Conjunctival scrapings should be sent for culture and gram stain.⁵

Chlamydial Conjunctivitis

The most common organism causing ophthalmia neonatorum is *Chlamydia trachomatis*.¹⁷ Infants get exposed to *Chlamydia trachomatis* from mothers infected cervix during vaginal delivery. The incubation of *Chlamydia* is typically 1 week.⁶ Presentation is with mild to moderate hyperemia and discharge which can be scant, mucoid or copious purulent.

Treatment is with oral erythromycin 50 mg/kg/day divided into four daily doses for 10 to 14 days.

Viral Conjunctivitis

- *Adenoviral conjunctivitis*

Most viral conjunctivitis is caused by Adenovirus.⁵ It is usually a self-limiting disease and produces a follicular reaction. All forms of adenoviral conjunctivitis are extremely contagious. Transmission of infection occurs through direct contact with infected persons, contaminated instruments, swimming pool water or personal items.¹³

- *Pharyngoconjunctival fever*

Adenovirus types 3, 4 and 7 cause pharyngoconjunctival fever. Typically associated features are fever, pharyngitis, preauricular adenopathy. It is self-limiting and symptoms resolve between four days to two weeks.⁵⁻¹⁰

- *Epidemic keratoconjunctivitis*

Adenovirus serotypes 8, 19 and 37 are most commonly responsible for epidemic keratoconjunctivitis. It mostly affects older children. Symptoms include severe discomfort, photophobia, early follicular or late papillary reactions and small petechial hemorrhages. Many patients develop keratitis with subepithelial stromal infiltrates 7 to 10 days after onset of conjunctivitis.¹⁰

- *Acute hemorrhagic conjunctivitis*

Acute hemorrhagic conjunctivitis is most commonly caused by picorna viruses such as enterovirus and coxsackie virus and can also be caused by adenovirus type 11. It is also highly contagious and occurs in epidemics.¹⁹

- *Herpes virus conjunctivitis*

Herpes simplex virus conjunctivitis may occur with primary infection or with recurrence. Primary infection usually occurs between 1 and 5 years.²⁰ Recurrent

infections occur in adults. Ocular infections are mostly due to HSV-1 except in neonates in whom HSV-2 is more prevalent. Transmission of virus occurs through direct contact. Associated findings helping in diagnosis are lid vesicle, upper respiratory tract infection, gingivostomatitis, preauricular lymphadenopathy. Eighty percent cases of HIV conjunctivitis are unilateral.⁵ Corneal involvement with classic dendrites occurs in 50 percent of patients.

Conjunctiva can be affected by varicella zoster virus by primary or secondary infection. Conjunctivitis usually occurs in primary varicella (chicken pox) but corneal involvement is rare. Secondary infection occurs in distribution of ophthalmic division of the trigeminal nerve and is known as herpes zoster ophthalmicus. Corneal involvement and iritis are common.

Molluscum contagiosum can cause chronic follicular conjunctivitis and corneal changes (fine epithelial keratitis) in children causing red eye.²¹

Treatment: Primary treatment is patient education. Children should be kept away from the school until there is no discharge and to be advised not to share clothes, utensils. Treatment for viral conjunctivitis is supportive. Cold compress, artificial tears and topical vasoconstrictors may provide some relief. Topical steroids should be avoided as they have side effects and may aggravate the condition. Topical antibiotics are usually unnecessary as secondary bacterial infections are rare.⁵ For herpetic keratoconjunctivitis the topical medications that are used are trifluridine, idoxuridine or vidarabine.²² Oral acyclovir can be used in severe or recurrent lesions. Acyclovir resistant varicella zoster virus is treated with foscarnet.

Allergic Conjunctivitis

Allergic conjunctivitis is a group of diseases affecting the ocular surface associated with type 1 hypersensitivity reactions. It can be classified into acute diseases including seasonal and perennial allergic conjunctivitis and chronic diseases include vernal keratoconjunctivitis, atopic keratoconjunctivitis, and giant papillary conjunctivitis. Thus, the spectrum of conjunctivitis ranges from acute IgE mast cell mediated disorders (seasonal and perennial allergic conjunctivitis) to mixture of lymphocyte-mast cell-eosinophil mediated disorders (vernal keratoconjunctivitis, atopic keratoconjunctivitis) to predominantly lymphocyte mediated disorders (giant papillary conjunctivitis).⁷

Seasonal and Perennial Allergic Conjunctivitis

Seasonal and perennial allergic conjunctivitis accounts for 98 percent of patients with ocular allergy whereas AKC and VKC accounts for only 2 percent of all ocular allergies.⁴ Direct exposure of the ocular mucosal surfaces to environmental allergens most commonly grass and tree

pollen in seasonal allergic conjunctivitis and dust mites and animal dander in perennial allergic conjunctivitis⁶ causes cross linkage of membrane bound IgE which triggers mast cell degranulation releasing histamine, the primary contributor for the development of seasonal allergic conjunctivitis. Associated history of seasonal rhinitis is often present in these patients. Family history of atopy is present in around 70 percent of patients with seasonal allergic conjunctivitis.²³ Hay fever, asthma, atopic dermatitis are considered major atopies and idiopathic urticaria, nonhereditary angioedema, food allergies are considered minor atopies.

Patient complains of typical symptoms of ocular itch, watering, sneezing. On clinical examination conjunctival chemosis may be present although subtle and thus only visible on slit lamp biomicroscopy. Diagnosis is mainly clinical. Laboratory testing may be done to quantitatively estimate serum IgE level and for skin testing for hypersensitivity to allergens.

Treatment includes environmental control, cold compress, artificial tears and topical vasoconstriction. These cases are ideally treated with combination of antihistamine-mast cell stabilizers that are the newer antiallergic agents.⁴ (like olopatadine 0.1 percent, ketotifen 0.025%, azelastine 0.05% and epinastine 0.05%). Desensitization immunotherapy also has role in the treatment.

Vernal Keratoconjunctivitis

Vernal keratoconjunctivitis is a chronic bilateral disease of childhood with greater prevalence in males living in warm climates. It is an allergic conjunctival inflammatory disorder with an associated secondary keratopathy. It tends to burn out by the age of 30.²⁴

Symptoms are profound itching, redness, ropy discharge, tearing and severe photophobia. Tarsal VKC is characterized by classic hallmark of giant papillae in the upper tarsal conjunctiva leading to Cobblestone appearance (Fig.

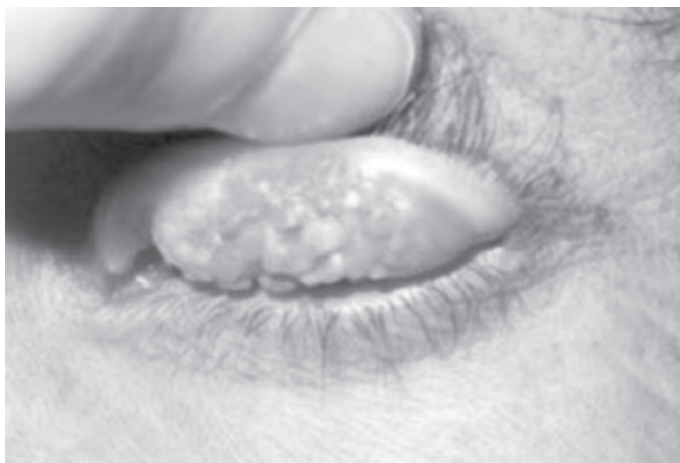


Fig. 2: Giant papillary conjunctivitis with cobblestone appearance (For color version see plate 20)

2). In *Limbal VKC* large papillae are seen in conjunctiva at the corneoscleral limbus with collections of inflammatory cells rich in eosinophils at the apices of the limbal papillae called Horner-Trantas dots (Fig. 3).²³ The other signs include ropy lardaceous mucus thread in inferior fornix, an extra lower eyelid crease (Dennie Line),⁷ localized lipid deposition in anterior stroma of cornea resembling a small segment of arcus (Pseudogerontoxon)²⁵ pseudomembrane formation of the upper lid when everted and exposed to heat (Maxwell-Lyon sign), keratopathy which typically begins as diffuse superficial keratitis and afterwards form a frank trophic epithelial defect known as Shield Ulcer (Fig. 4).

Treatment: It includes cold compress, artificial tears, antihistaminic agents and mast cell stabilisers. Topical corticosteroid is required for break through attacks of highly

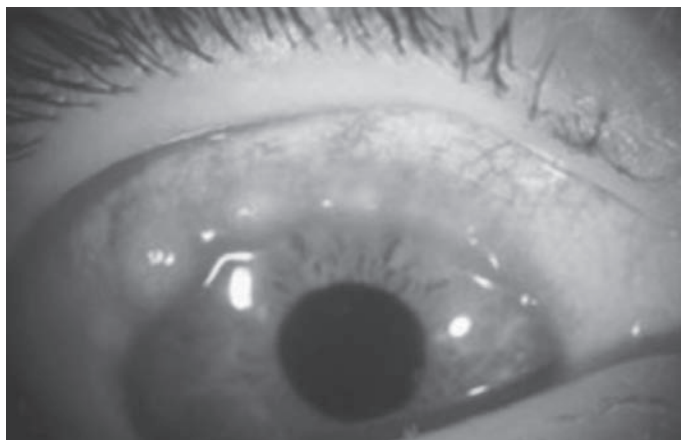


Fig. 3: Limbal VKC with Horner-Trantas dots (For color version see plate 20)

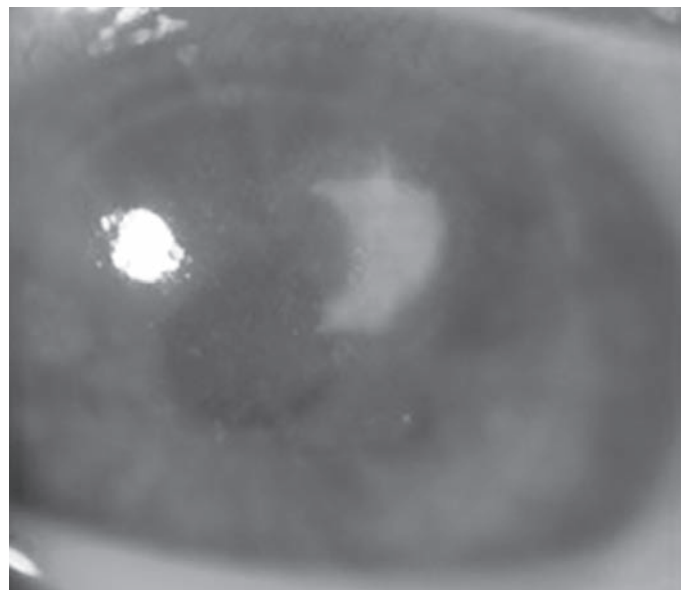


Fig. 4: Shield ulcer (For color version see plate 20)

active VKC. The pulse therapy strategy²³ involves instillation of one percent prednisolone acetate or phosphate four times daily for two days, with subsequent tapering to three times daily for succeeding two days, twice daily for two days after that, once daily for an added three days and subsequent discontinuation thereafter. For extreme mucus production 10 to 20 percent N-acetylcysteine drops four times daily used and for persistent epithelial defect bandage soft contact lens may be used.

Atopic Keratoconjunctivitis

Atopic keratoconjunctivitis is a severe chronic inflammatory disorder involving eyelid skin, cornea, conjunctiva and lens that is commonly seen in association with atopic dermatitis.¹¹ It usually appears in late teens and progress into fifth decade of life.

Symptoms

It includes bilateral ocular itch, burning and foreign body sensation, excessive tearing and profuse mucoid discharge, lid eczema.²³ Symptoms are more severe in winter. Family history of atopy is present. Clinical signs are conjunctival hyperemia, episcleral vessels, papillae on upper tarsal conjunctiva and presence of chronic blepharitis. In severe cases conjunctival scarring, fornix shortening, symblepharon, corneal ulceration and neovascularization, cataract formation may occur.²⁶

Treatment

It includes antihistaminic and mast cell stabilizing drops, topical steroids. In case of acute exacerbations frequent topical corticosteroids should be initiated with topical mast cell stabilizers. The corticosteroids are then tapered off over two to three weeks. Topical cyclosporine (0.5% to 2%) can be used if symptoms persist after removal of steroid.

Giant Papillary Conjunctivitis

Giant papillary conjunctivitis is an immune response to long-term exposure to foreign bodies in the eye like

deposits on ocular prostheses,²⁷ exposed sutures,²⁸ contact lenses.²⁹ It develops as a result of tarsal conjunctival sensitization to allergic material present on surface of contact lens together with trauma to the upper tarsal conjunctiva due to excursion of eye lid over contact lens at each blink.²³

Symptoms

Common symptoms are itching, mucus production, decreasing contact lens tolerance. Examination of upper tarsal conjunctiva reveals conjunctival hyperemia and giant papillae greater than 1 mm in diameter.²³ The cobblestoning is more easily seen with cobalt blue light source after instilling fluorescein dye.

Treatment

Treatment involves reducing contact with source of irritation. In patients who want to continue contact lens wear- proper lens hygiene, modification of contact lens material (low cost disposable lens), limitation of contact lens wearing time are to be advised. A mast cell stabilizer along with low potency topical steroid for short period can help in resolution of conjunctival changes.⁶

Contact Dermatitis

Contact dermatitis is an inflammation of the eyelid skin or conjunctiva or both resulting from exposure to allergens or irritants.³⁰ Allergic contact dermatitis is due to a type IV hypersensitivity reaction whereas the irritant contact dermatitis is due to direct toxic effect of the irritant.

It is usually caused by topical drugs or cosmetics. Topical drugs implicated in contact dermatitis are:³⁰⁻³²

- Preservatives—Benzalkonium chloride, Thiomersal
- Antiglaucoma drugs:
 - Prostaglandin analogs—Latanoprost
 - Beta blockers—Timolol
 - Carbonic anhydrase inhibitors—Dorzolamide, Brinzolamide
 - Parasympathomimetics—Pilocarpine
 - Sympathomimetics—Brimonidine

Points	Bacterial conjunctivitis	Viral conjunctivitis	Allergic conjunctivitis
Common etiologic agent	<i>Haemophilus influenzae</i> <i>Streptococcus pneumoniae</i> <i>Neisseria gonorrhea</i> <i>Chlamydia trachomatis</i>	Adenovirus Herpes simplex virus Herpes zoster virus Enterovirus	Pollens Animal danders Allergen
Prevalent age	Neonate to toddlers	School age to adults	Late childhood to early adulthood
Type of discharge	Purulent	Watery	Mucoid
Smear of exudates	Neutrophils, Bacteria	Lymphocytes	Eosinophils
Lymphadenopathy	Occasional	Common	None
Slit lamp findings	Papillary response	Follicular response	Chemosis, mild congestion
Associated symptoms	Otitis media	Pharyngitis	Rhinitis, asthma, eczema
Treatment	Antibiotics	Cold compress Artificial tears Topical vasoconstrictors Antivirals	Antihistaminics Mast cell stabilizers Decongestants NSAIDs

- Anti inflammatory drugs—Ketorolac, Corticosteroids
- Antimicrobials—Aminoglycosides, Sulfonamides, Cefazolin, Vancomycin, Chloramphenicol
- Antivirals—Acyclovir
- Antiallergic drugs—Chlorpheniramine maleate, Sodium cromoglycate
- Anesthetics—Proparacaine
- Mydriatics and cyclopegics

Clinical Features

Features of contact dermatitis are pruritus, erythema, edema, vesiculation in acute dermatitis and may be associated with scaling and desquamation in chronic cases.

Treatment

Avoidance of the causative agent and topical corticosteroids for about 5 to 10 days.

Subconjunctival Hemorrhage

Subconjunctival hemorrhage is diagnosed clinically. Patient usually presents with a bright red eye preceded by a trauma. Vessel details are not visible.

Treatment: Patient is reassured that it is a harmless condition with blood reabsorption occurring over a few weeks and no treatment is needed. Ocular lubricants may be given.

DISORDERS OF SCLERA

Scleritis is uncommon in children but can occur in association with juvenile rheumatoid arthritis or infections with herpes simplex virus, tuberculosis, mumps, syphilis and varicella. Episcleritis occurs in association with systemic diseases like erythema multiforme, syphilis and severe drug allergies (e.g. penicillin).¹⁰

Clinical features: It usually presents with localized area of redness (Fig. 5). Pain is usually associated with scleritis

and not with episcleritis. Topical phenylephrine constricts the vessels of the conjunctiva but not of the episclera or sclera and thus helps in differentiating conjunctivitis from scleritis or episcleritis.

Treatment: It involves managing the underlying condition. Supportive care includes use of artificial tears, non-steroidal anti-inflammatory agents. Topical steroids may be useful for severe cases.

CHILDHOOD GLAUCOMA

Childhood glaucoma can be simply classified as primary or secondary. Primary glaucomas, often genetic in origin comprise those in which a developmental abnormality of the anterior chamber angle leads to aqueous outflow obstruction. It can further be divided into primary congenital glaucoma, developmental glaucoma and juvenile open angle glaucoma. In developmental glaucoma associated ocular and systemic anomalies are typically present. In secondary childhood glaucomas, aqueous outflow obstruction is acquired from usually an inflammation or neoplasia.³³

Clinical Features

The classic triad of features of primary congenital glaucoma are epiphora (excessive tearing), photophobia, blepharospasm. The parents also complain of redness, large cornea. On examination there is increased corneal diameter, corneal edema, refractive error, raised intraocular pressure (IOP). Gonioscopy to view the angle structures can be done in an infant using koepple gonioslens along with a portable slit lamp for illumination and magnification. Fundoscopic evaluation of the optic nerve is essential. Cupping of optic nerve head proceeds more rapidly in infants and is more likely to be reversible if pressure is lowered early. In older children visual fields should be tested.

Treatment

An early reduction in IOP should be targeted to reduce corneal edema and chances of optic nerve damage. Definitive treatment of primary congenital glaucoma is surgical usually a combination of trabeculectomy with trabeculotomy is done. Medical therapy plays an adjunctive role. Preoperative medications may help to clear the cornea and facilitate angle surgery and postoperatively they may help control IOP until adequacy of surgical procedure has been established.

UVEITIS

Uveitis is defined as inflammation of any part of the uveal tract (iris, ciliary body, choroid). Children accounts for only 2.2 to 13.8 percent of patients in many uveitis clinics.³⁴ But it is significant for causing numerous complications, many of which are vision threatening.³⁵ These complications increase with duration of disease. So an early diagnosis and prompt referral to an ophthalmologist is essential in these cases. Anterior uveitis is most common

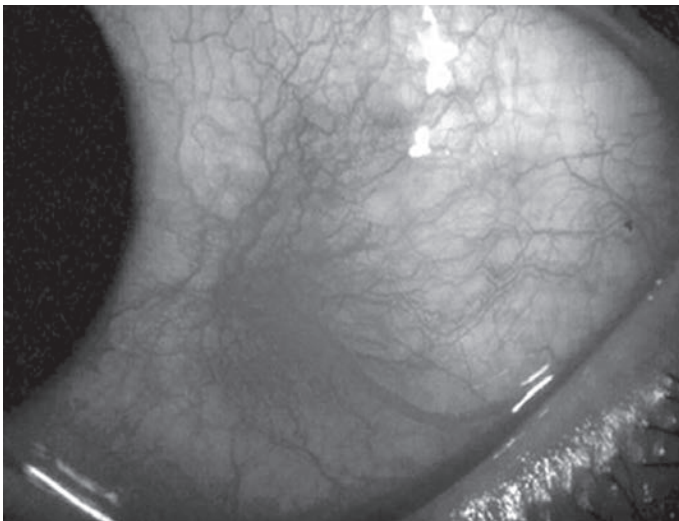


Fig. 5: Localized congestion in scleritis
(For color version see plate 20)

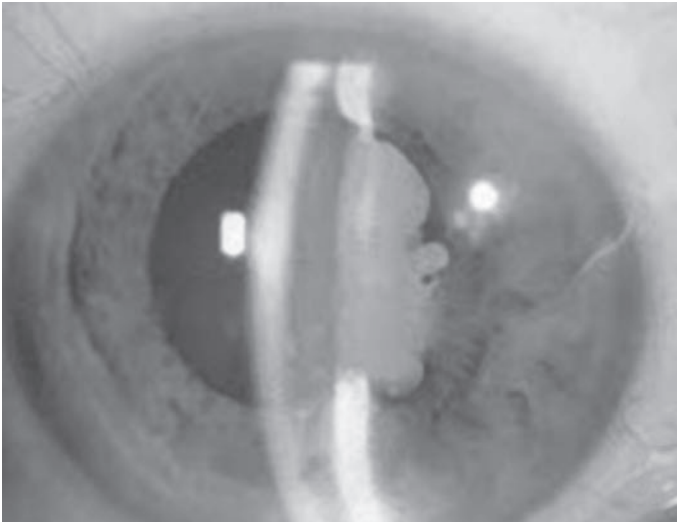


Fig. 6: Anterior uveitis with posterior synechiae
(For color version see plate 20)

followed by intermediate uveitis, posterior uveitis, and panuveitis. The most common cause of anterior uveitis is juvenile idiopathic arthritis whereas for intermediate uveitis it is idiopathic. The most frequent type of posterior uveitis is toxoplasmic retinochoroiditis.³⁶

Clinical Features

Presenting features are red eye, pain, reduced vision, floaters and photophobia. On examination on the slit lamp biomicroscope anterior chamber cells and flare (Fig. 6), retrolental cells are usually seen. Indirect ophthalmoscopy reveals vitreous exudates in intermediate uveitis and toxoplasma scar in posterior uveitis.

Complications

The most common causes of vision loss in children with uveitis are cataract, band keratopathy, glaucoma, cystoid macular edema.³⁶

Treatment

Treatment needs to be individualized depending on the suspected etiology of the disease. The medications include cycloplegics, corticosteroids (topical, local injection, intravenous, oral or combination) non steroidal anti inflammatory drugs or drugs like sulfasalazine, methotrexate, azathioprine, mycophenolate mofetil, leflunomide, cyclosporine, tacrolimus, etanercept, infliximab, intravenous immunoglobulin, alpha interferon, adalimumab and daclizumab.

DISORDERS OF THE EYELIDS

Blepharitis

Blepharitis is an inflammation of the eyelid that is often associated with conjunctivitis and keratitis. It can be



Fig. 7: Blepharitis with crusting around base of cilia
(For color version see plate 21)

anatomically subdivided into anterior and posterior. Anterior blepharitis is the inflammation of the eyelids and follicles while posterior blepharitis involves meibomian glands. Anterior blepharitis is usually infectious- bacterial (*Staphylococcus*), viral (Molluscum contagiosum) and parasitic (Phthiriasis) or seborrheic.³⁷ Posterior blepharitis may be either be seborrheic, obstructive or a combination of both or may be associated with acne rosacea which is rare in children.

Clinical Features

Common symptoms of blepharitis are irritation, burning sensation, tearing, photophobia, blurred vision, red eyes. These are usually worse in the morning because during sleep inflamed lids are in close contact with ocular surface and there is also a decrease in tear production which is associated with constant release of inflammatory mediators.³⁷

Examination reveals telangiectatic vessels of eyelid margin, inspissated meibomian gland, conjunctival hyperemia, punctate keratopathy, corneal ulceration. Hard crusts around base of cilia are typically found in staphylococcal blepharitis (Fig. 7). Seborrheic blepharitis is characterized by soft crusts, lipid secretion and hyperemia at the lid margin. Long standing chronic blepharitis presents with hypertrophy of lid margins, scars, trichiasis, madarosis, poliosis, chalazion ulceration of lid margins. In posterior blepharitis symptoms are more pronounced than signs. Pressure on tarsus releases a thick lipid secretion.

Treatment

The mainstay of treatment is maintaining eyelid hygiene for a prolonged period. Warm compresses followed by light scrubbing of the eyelid with a cotton swab dipped in a mixture of baby shampoo and water is to be done. For patients with staphylococcal blepharitis a topical antibiotic is to be applied. In severe cases oral antibiotics may be prescribed. Erythromycin is usually used for young



Fig. 8: Stye (For color version see plate 21)

children and doxycycline for older children. Topical corticosteroids may be helpful in patients with marked inflammation.³⁸ As many patients with blepharitis have aqueous tear deficiency artificial tears may improve the symptoms. Any associated skin condition should be treated.

HORDEOLUM

It is an acute focal inflammation of the eyelid with abscess formation. It can be of two types:

- *Internal Hordeolum:* Infection of the meibomian gland.
- *External Hordeolum (stye):* Infection of the gland of zeiss (Fig. 8).

Most common bacteria causing hordeolum is *Staphylococcus aureus*.³⁹

Symptoms: Presenting symptoms are pain, redness, swelling of eyelids.

Treatment: It is usually self limited and resolves within five to seven days with spontaneous drainage of abscess. Conservative management includes warm compress and topical antibiotics. Systemic antibiotics can be used if there is associated cellulitis.

Chalazion

Chalazion is a chronic lipogranulomatous inflammation of the meibomian glands (internal hordeolum) due to obstruction of the gland orifices on the eyelid margin. Sebum of the gland is released into the tarsus and surrounding soft tissues resulting in an inflammatory response. *Staphylococcus aureus* has been implicated in these lesions. Seborrhea, acne, blepharitis all predispose to chalazion.

Clinical Features

It presents as a painless slowly enlarging lump in either lid, usually away from the lid margin. A large centrally located chalazion may result in visual disturbances

and astigmatism. It can rarely lead to conjunctivitis or cellulitis.

Treatment

Conservative treatment is the first line of management. Warm compress for three to five minutes two to four times daily should be given. This should be followed by massage of the eyelids to release the chalazion contents. Topical antibiotics may be used. Intralesional injection of steroid (triamcinolone acetonide) helps in healing but carries risk of hypopigmentation of overlying skin.⁴⁰⁻⁴²

Large persistent chalazion requires surgical drainage and curettage. A study conducted by Mustafa et al⁴³ in children found that the three procedures of intralesional corticosteroid injection, incision and curettage and a combination of these two techniques were safe, effective and convenient. He also found that intralesional corticosteroid injection is good for patients with allergy to local anesthesia and chalazion close to the lacrimal drainage system. He recommended incision and curettage for patients with infected chalazia and the combined treatment for large, recurrent and multiple chalazia.

PRESEPTAL AND ORBITAL CELLULITIS

The orbital septum is a membranous sheet that extends from the orbital rim to the eyelids and acts as the anterior boundary of orbit. Infection and inflammation of tissues anterior to orbital septum constitutes preseptal cellulitis, whereas extension into the postseptal orbital tissues constitutes orbital cellulitis. In children *Staphylococcus aureus* or nonhemolytic streptococci, Group A beta hemolytic streptococci, *Staphylococcus aureus* and *Haemophilus influenzae* are the most commonly associated.⁴⁴

Spread

Infection reaches orbit by three methods—Implantation, local extension or hematogenous spread. Ethmoidal sinusitis is the most common predisposing cause for orbital cellulitis.⁴⁵

Clinical Features

It is twice more common in males than females. Preseptal cellulitis tends to occur in children younger than five years whereas postseptal involvement occurs predominantly in children older than five years child usually presents with pain, redness, swelling of periorbital region. There may be associated fever, malaise. A thorough history of upper respiratory tract infection, lacrimal outflow obstruction, sinusitis and trauma has to be taken. On examination presence of proptosis, restriction of extraocular movements or loss of vision along with periorbital edema, are features of postseptal spread of infection.²³ Signs of meningitis must also be sought for.

Diagnosis

A complete blood count should be obtained as white cell count is often elevated. Pus and blood cultures should be sent. Computed tomography with contrast is needed for identifying sinusitis, presence of subperiosteal or orbital abscess. Magnetic resonance imaging is especially useful for diagnosis of cavernous sinus thrombosis and intracranial extension. Ultrasound is of limited use.

Treatment

Mild preseptal disease with no constitutional symptoms and willing for frequent follow-ups are managed with oral antibiotics from the outpatient department. However, if child looks toxic, diagnosis is unclear or orbital cellulitis or abscess is suspected then patient is hospitalized, imaging ordered and parenteral antibiotics initiated. Currently the initial choice for parenteral therapy is ampicillin-sulbactam. Vancomycin or clindamycin can be added in sick children in view of increasing methicillin resistant *Staphylococcus aureus*. Indications for surgical intervention that is drainage of abscess are large abscess, ophthalmoplegia, decreasing vision, lack of improvement despite 48 hours of aggressive medical management.

CONCLUSION

Children presenting with red eyes to the pediatrician are very common. It is essential that a thorough history is taken and a systematic physical examination is performed. Once a diagnosis is made and a vision threatening etiology is ruled out, immediate treatment followed by a close follow-up ensures good prognosis. Although most cases can be followed up by the primary care physician, prompt referral to a trained ophthalmologist must be considered in cases with danger signs to prevent severe complications.

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Binocular Vision, Ocular Motility, Squint and Amblyopia

AK Grover, Shaloo Bageja

ANATOMY AND PHYSIOLOGY OF THE OCULAR MOTILITY

Three factors are important for coordination between the two eyes. These are the six extraocular muscles, three cranial nerves and the higher brain functions.

- *Extraocular muscles:* There are six extraocular muscles controlling eye movement: the four rectus muscles (medial, lateral, superior, inferior), and two oblique muscles (superior and inferior) (Fig. 1)

While the medial and lateral rectus muscles are responsible for (in turning) and abduction (out turning) of the eye. The superior and inferior rectus, and the superior and inferior oblique muscles each have primary and secondary actions, depending of the position of the eye (Table 1).

Unocular movements are called 'ductions' and binocular movements are called 'versions'. When the eyes are looking straight ahead, they are said to be in the primary position. There are six cardinal position of gaze

Table 1: Showing actions of extraocular muscles

Muscle	Primary action	Secondary action	Tertiary action
Medial rectus	Adduction		
Lateral rectus	Abduction		
Superior rectus	Elevation	In torsion	Adduction
Inferior rectus	Depression	Ex torsion	Adduction
Superior oblique	In torsion	Depression	Abduction
Inferior oblique	Ex torsion	Elevation	Abduction

(i.e. directed to one side or the other; either looking out and up, straight out or out and down) or into one of the two midline vertical positions (looking directly up or directly down) (Fig. 2). Deviations from these positions of gaze provide the basis for diagnosis of a squint.

- *Cranial nerves:* The extraocular muscles are supplied by the third, fourth and sixth cranial nerves. All the ocular

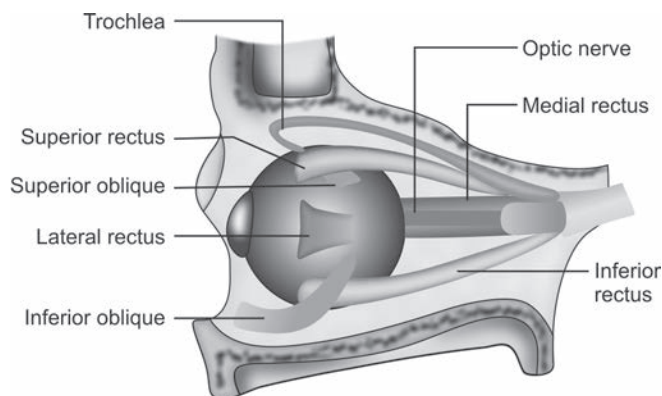


Fig. 1: Extraocular muscles (Courtesy: Khurana AK. Strabismus and Nystagmus. In: Comprehensive Ophthalmology, 4th edn 2007.pp. 313-37)

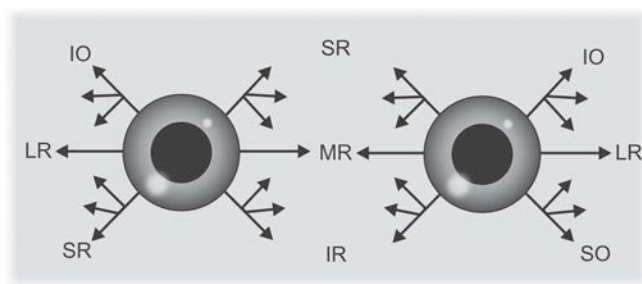


Fig. 2: Action of extraocular muscles. SR- superior rectus, MR- medial rectus, IR- inferior rectus, SO- superior oblique, LR- lateral rectus, IO-inferior oblique (Courtesy: Khurana AK. Strabismus and Nystagmus. In Comprehensive Ophthalmology, 4th edn. 2007.pp. 313-37)

movements occur due to third cranial nerve other than lateral abduction (lateral rectus) which is generated by the sixth (abducent) cranial nerve and a downward, inward gaze (such as looking where to put your feet when going down a flight of steps—superior oblique) which is generated by the fourth (trochlear) cranial nerve.

- *The higher brain centers:* The third, fourth and sixth brainstem nuclei ensure the correct functioning of their relevant cranial nerves. There exists a highly accurate supranuclear control of eye movements which keeps the two eyes yoked together so that the image of the object of interest is simultaneously held on both foveas despite movement of the perceived object or the observer's head and/or body. The higher cortical centers control the speed of eye movements either when following a moving target (pursuit) or jumping from one target to another (saccades).

BINOCULAR SINGLE VISION

When a normal individual fixes his visual attention on an object of regard, the image is formed on the fovea of both the eyes separately; but the individual perceives it as a single image. This state is called binocular single vision. It is a conditioned reflex and is not present at birth (Table 2).¹

ANOMALIES OF BINOCULAR VISION

Anomalies of binocular vision include:

- *Suppression:* It is a temporary active cortical inhibition of the image of an object formed on the retina of the squinting eye when both eyes are open.
- *Amblyopia:* Amblyopia is derived from two Greek words (amblys-dull, ops-eye), literally meaning dull vision. It is a partial loss of vision in one or both eyes, in the absence of any organic disease of ocular media, retina and visual pathway. The most sensitive period for development of amblyopia is first six months of life and it usually does not develop after the age of 6 years.

It can be broadly classified as functional (reversible) or organic (irreversible). The other classification based on the etiology includes five major types:

- Amblyopia ex anopsia (stimulus deprivation, e.g. due to a cataract or corneal opacity)
- Congenital amblyopia (organic)
- Anisometropic amblyopia (associated with difference in refractive error between two eyes)
- Ametropic amblyopia (associated with uncorrected refractive error, correctable by using glasses)
- Strabismic amblyopia (associated with squint).

- *Abnormal retinal correspondence (ARC):* In a state of normal binocular single vision, there exists a precise physiological relationship between the corresponding points of the two retinae. Thus, the foveae of two eyes act as corresponding points and have the same visual direction. This adjustment is called normal retinal correspondence (NRC). When squint develops, patient may experience either diplopia or confusion. To avoid these, sometimes (especially in children with small degree of esotropia), there occurs an active cortical adjustment in the directional values of the two retinae. In this state fovea of the normal eye and an extrafoveal point on the retina of the squinting eye acquire a common visual direction (become corresponding points). This condition is called abnormal retinal correspondence (ARC) and the child gets a crude type of binocular single vision

- *Confusion and diplopia:* Binocular diplopia is due to formation of image on dissimilar points of the two retinae. This is due to paralysis of extraocular muscle or post-traumatic orbital floor fracture due to entrapment of the muscle.

SQUINT

Squint refers to a misalignment of the eyes. The image is therefore, not in corresponding areas of both eyes, which may result in eventual amblyopia in childhood or diplopia in adulthood.

CLASSIFICATION OF STRABISMUS

There are a number of ways of classifying squints. It can be congenital (onset before six months of age) or acquired. It can be intermittent or constant.

Broadly, strabismus can be classified as below:

- Apparent squint or pseudostrabismus.
- Latent squint (Heterophoria)
- Manifest squint (Heterotropia)
 - Concomitant squint
 - Incomitant squint.

Pseudostrabismus

It is a condition in which in spite of parallel visual axis, the eye seems to be squinting. This may occur in children before adequate depth of medial canthus develops.

Table 2: Showing important milestones in visual development

Age	Milestones
At birth	No central fixation, eyes move randomly
By first month of life	Fixation reflex starts developing, establishes by sixth month
By six month	Macular stereopsis and accommodation reflex develops
By 6 years	Full visual acuity (6/6) is attained and binocular single vision is developed

Pseudoesotropia (i.e. eye appears to turn inward) is usually seen in a patient with prominent epicanthal fold and Pseudoexotropia (i.e. eye appears to turn outward) in hyper-teleroism.

Latent Squint (Heterophoria)

It is a condition in which the eye tends to deviate whenever the fusion breaks. Therefore, when the influence of fusion is removed the visual axis of one eye deviates away. It is called orthophoria when the two eyes are perfectly aligned. The tendency to converge is esophoria. The tendency to diverge is exophoria.

Finally, the prefixes 'hypo' and 'hyper' refer to a downward or upward deviation respectively. This form of squint is less common.²

Concomitant Squint

It is a type of manifest squint in which the amount of deviation in the squinting eye remains constant in all the directions of gaze and there is no associated limitation of ocular movements. It can be due to sensory and motor obstacles such as refractive errors, anisometropia, corneal opacities, cataract, diseases of macula (e.g., central chorioretinitis), optic atrophy, ptosis, congenital abnormalities of orbit and extraocular muscles.

Epidemiology

- *Ocular misalignments are common in newborns*: one study found the prevalence of these to be about 73 percent in one month-old babies, reducing to 50 percent in two month-old babies and virtually disappearing in normal four month-olds.³
- Pathological misalignment is prevalent among older children, affecting about 5 percent of 5 year-olds⁴ (of these, 60 percent have eso-deviations and 20 percent have exo-deviations). This drops to ~3 percent in the 13 to 24 years old age group.

TYPES OF CONCOMITANT SQUINT

Three common types of concomitant squint are:

- Convergent squint (esotropia)
- Divergent squint (exotropia)
- Vertical squint (hypertropia).

Convergent Squint (Esotropia)

It is the inward deviation of one eye. It can be unilateral (i.e. one eye only deviates always while the second normal eye takes fixation) or alternating (either of the eyes deviates inwards when the other eye takes up fixation).

It can be:

- Accommodative esotropia
- Nonaccommodative esotropia
- Secondary esotropia.

- *Accommodative esotropia*: It occurs due to overaction of convergence associated with accommodation reflex. It is of three types: refractive, nonrefractive and mixed (Figs 3A and 3B).

- *Nonaccommodative esotropias*: It includes all those primary esodeviations in which amount of deviation is not affected by the state of accommodation.

It includes:

- Essential infantile esotropia. It may present anytime after birth or within the first 6 months of life. It is characterized by fairly large angle of squint ($>30^\circ$), alternate fixation in primary gaze and crossed fixation in lateral gaze.
- Essential acquired or late onset esotropia. It typically occurs during first few years of life.

- *Secondary esotropia*

It includes:

- Sensory deprivation esotropia. It results from monocular lesions (in childhood) which either prevent the development of normal binocular vision or interfere with its maintenance such as cataract, severe congenital ptosis, aphakia, anisometropia, optic atrophy, central chorioretinitis, etc.
- *Consecutive esotropia*: It is due to overcorrection following surgery for exotropia.

Divergent Squint (Exotropia)

It is the outward deviation of the eye. It can be unilateral or alternating.

It has been classified into following types:

- *Congenital exotropia*: It is quite rare and is usually present at birth.



Figs 3A and B: Fully accommodative squint (Courtesy: vision-centreindore.com/eyedisease_children.html) (For color version see plate 21)

- *Primary exotropia:* It usually starts as intermittent squint in early childhood and is associated with normal fusion and no amblyopia. Precipitating factors include bright light, fatigue, ill health and day-dreaming. If not treated in time it decompensates to become constant exotropia. Steropsis is usually absent
- *Sensory exotropia:* It is a constant unilateral deviation which results from long standing lesions (in adults) (Fig. 4), associated with poor vision in the affected eye e.g. traumatic cataract, corneal opacity, optic atrophy, retinal detachment and macular lesions
- *Consecutive exotropia:* It is a constant unilateral exotropia which results due to surgical overcorrection of esotropia.

EXAMINATION

History

A meticulous history is very important. It should include: age of onset, duration, mode of onset (sudden or gradual), any illness preceding squint (fever, trauma, infections, etc.), intermittent or constant, unilateral or alternating, history of diplopia, family history of squint, any history of use of glasses or previous surgery and so on.

Inspection

- Type of squint—convergent or divergent squint.
- A young baby should be examined for the presence of epicanthal folds (crescentic folds of skin on each side of the nose) which could give rise to pseudoesotropia: the impression that the eyes are turned inwards when in fact they are not.
- Look for facial asymmetry (either craniofacial abnormalities or head tilt) and obvious eye abnormalities, e.g. ptosis or proptosis.



Fig. 4: Twenty-four-year-old male showing divergent squint in the left eye (For color version see plate 21)

Hirschberg's Test

This gives a rough estimate of the degree of strabismus. Hold a pen torch about an arm's length (~33 cm) away from the patient and shine it in front of their eyes. Ask the patient to look at the light, if possible. Observe where the reflection of the pen torch lies with respect to the cornea. It should be central bilaterally. If it lies at the inner margin of the pupil, there is an outward deviation (exotropia) of the eye. If it lies at the outer margin, an esotropia is present. Roughly, the angle of squint is 15° and 45° when the corneal light reflex falls on the border of pupil and limbus, respectively (Fig. 5).

Cover/Uncover Test

An object to focus on is held in front of the patient who is instructed to focus on it. One eye is completely occluded for few seconds and the uncovered eye is observed for movement as it focuses on the object. This eye is then covered and the other eye is observed for movement. Movement of the eye outwards confirms that there is an esotropia (i.e. the eye was turned inwards initially) and vice versa for exotropia. The test is repeated for objects at 6 meters and far distance.

Alternate Cover Test

This is done in a similar fashion to the previous test but the occluder is rapidly switched from one eye to the other. There is now no longer bifoveal stimulation (so each eye is seeing a separate image). Observing the eye movement as the occluder is removed, note whether it moves inwards (i.e. there is a latent exophoria and the eye has to move in to see again) or outwards (revealing a latent esophoria).

Ocular Movements

Both uniocular as well as binocular movements should be tested in all the cardinal positions of gaze.

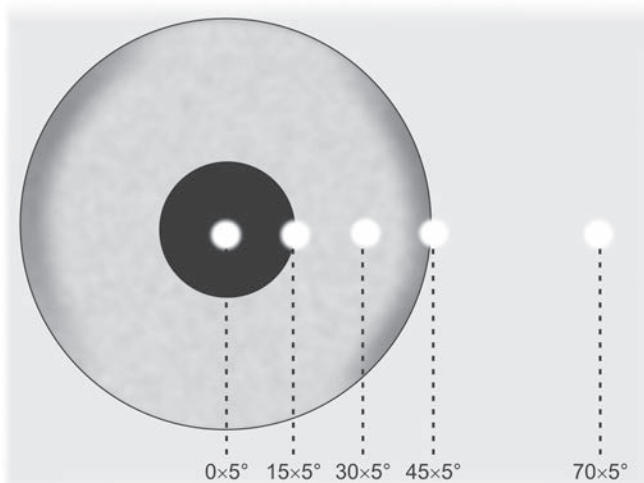


Fig. 5: Hirschberg corneal reflex test. Courtesy: (Khurana AK. Strabismus and Nystagmus. In: Comprehensive Ophthalmology, 4th edn.2007.pp.313-37)

Pupillary Reactions

These may be abnormal in patients with secondary deviations due to diseases of retina and optic nerve.

Media and Fundus Examination

It may reveal associated disease of ocular media, retina or optic nerve.

Visual Acuity Assessment and Refraction

It is most important, because a refractive error may be responsible for the symptoms of the patient or for the deviation itself. Preferably, refraction should be performed under full cycloplegia, especially in children.

MEASUREMENT OF ANGLE OF DEVIATION

It is performed by:

- Prism bar cover test
- Krinsky corneal reflex test
- Synoptophore.

Tests for grade of binocular vision and sensory functions

- Worth's four-dot test
- After image test
- Test for fixation
- Sensory function test with synoptophore
- Neutral density filter test.

MANAGEMENT

- Needs referral
 - A neonate with a constant squint or with a squint that is worsening from two months of age should be referred to an ophthalmologist.³
 - Any older child with a suspected squint should be seen in the eye clinic.
 - Any acute onset squint should be referred.
 - The earlier the referral, the better chance the child has of avoiding the possibility of amblyopia.
- Treatment is guided by the exact nature of the squint and by the patient's age
- *Refractive error correction:* Correction of refractive errors will be the important first step in the management of these individuals
- *Amblyopia management:* If amblyopia is present, will need management before any surgical intervention.⁵ A number of forms of treatment have been devised, however, whatever the method employed the need for early diagnosis and treatment cannot be overstressed. Correction of the basic pathology either a refractive error, or a cataract or strabismus is the first step in management. The main stay of treatment includes occlusion therapy which involves covering the better eye so as to stimulate development of vision in the amblyopic eye. If the treatment is begun early

and carried out meticulously it gives very satisfactory results. A definitive protocol for occlusion has to be chalked out for all the individual cases depending on the age and density of amblyopia. The other forms of treatments include the red filter treatment and drug penalisation. Drug penalisation involves use of medicines to paralyse ciliary body of the better eye so that the weaker eye may be used to overcome amblyopia. Pleo-optics, visual exercises and Cambridge vision stimulator (CAM) are the other systems available which have been used in the past but are largely out of use today

- *Surgery:* Patients may go on to have surgical alignment after refractive correction and amblyopia therapy if required. A combination of muscle recession (it is moved backwards on the globe and so its action is weakened) and antagonistic muscle resection (a segment of muscle is removed, so strengthening its action) is used with the aim to restore binocular function. Sometimes, adjustable sutures are used to enable minor corrections to be made without having to go through a further full surgical procedure.⁶

INCOMITANT SQUINT

- Paralytic squint
- A-V pattern heterophorias
- Restrictive squint.

Paralytic Squint

This refers to the deviation of eye due to paralysis of one or more extraocular muscles. It can be due to neurogenic (encephalitis, meningitis or brain tumors involving nuclei or nerve, diabetes, hypertension) or myogenic lesions (myositis, trauma, thyroid myopathy) or due to lesions at the level of neuromuscular junction (myasthenia gravis).⁷

Clinical Features

- Confusion and diplopia
- Restriction of eye movement
- Compensatory head posture
- False projection
- Past pointing.

Pathological Sequel of an Extraocular Muscle Palsy

In all cases of extraocular muscle palsy, certain sequel take place after some time. These occur more in paralysis due to lesions of the nerves than the lesions of muscles. These include:

- Overaction of the contralateral synergistic muscle.
- Contracture of the direct antagonist muscle.
- Secondary inhibitional palsy of the contralateral antagonist muscle.

Isolated Nerve Palsies

Third cranial nerve:

- *Presentation:* There may be external ophthalmoplegia where there are partial or complete motility problems resulting in varying degrees of squint.
 - Eyeball is turned down, out and slightly intorted due to action of lateral rectus and superior oblique.
 - There may be internal ophthalmoplegia (partial or complete impairment of pupillary reactions).
 - There may also be a ptosis.
- *Etiology:* Pupil-sparing causes tend to relate to ischemic microvascular disease (and rarely, cavernous sinus syndrome). Pupil-involving disease usually arises as a result of an aneurysm but can also occur as a result of a tumor, trauma, pituitary apoplexy, herpes zoster and leukemia. Children may exhibit this as part of an ophthalmoplegic migraine.

Fourth Cranial Nerve

- *Presentation:* Binocular vertical diplopia, difficulty in reading and the head tilt.
- *Etiology:* This may also be congenital or idiopathic. It may be due to trauma, vasculopathy (often related to diabetes and hypertension) and demyelinating disease.

Sixth Cranial Nerve

- *Presentation:* Horizontal diplopia which is most pronounced on lateral gaze on the affected side.
- *Etiology:* Vasculopathy (usually diabetic, hypertensive or atherosclerotic) and trauma are the most common causes but it is also often idiopathic. Less common causes include an increase in intracranial pressure, cavernous sinus mass, multiple sclerosis, giant cell arthritis, inflammation and infection. Children may also get this as a benign, postviral (or postvaccination) condition as well as due to increased intracranial pressure and Gradenigo's syndrome (multiple cranial nerve palsies associated with complicated otitis media).

Double Elevator Palsy

Presentation: It is characterized by paresis of the superior rectus and the inferior oblique muscle of the involved eye.

Etiology: It is a congenital condition caused by third nerve nuclear lesion.

Multiple Nerve Palsies

- *Presentation:* there may be a combination of unilateral III, IV and VI cranial nerves resulting in limitation of eye movement (and therefore diplopia), facial pain corresponding to one or more branches of the V cranial nerve, a ptosis and small pupil (Horner's syndrome) or a dilated pupil if the III cranial nerve is affected.

- *Etiology:* there are a number of conditions and syndromes which can give rise to this clinical picture:
 - Arteriovenous fistula (carotid-cavernous or dural-cavernous).
 - Tumors within the cavernous sinus (primary or metastatic).
 - Intracavernous aneurysm.
 - Mucormycosis (particularly in uncontrolled diabetic and immunocompromised patients).
 - Pituitary apoplexy.
 - Herpes zoster.
 - Cavernous sinus thrombosis.
 - Tolosa-Hunt syndrome.
 - Rarely sarcoidosis, Wegener's granulomatosis, tuberculosis.

Investigations of a Case of Paralytic Squint

In addition to basic squint examination, a paralytic squint requires additional tests:

- Diplopia charting
- Hess screen test
- Forced duction test.

Management

- *Treatment of the cause:* If squint is due to any cause, it should be managed accordingly.
- *Conservative measures:* One should wait and watch for self-improvement to occur for a period of 6 months. One can prescribe vitamin B-complex as neurotonic and systemic steroids for nonspecific inflammations.
- *Treatment of annoying diplopia:* It includes use of occluder on the affected eye to prevent confusion and diplopia.
- *Surgical treatment:* It should be carried out in case the recovery does not occur in 6 to 12 months.
- *Aim of treatment:* Is to provide a comfortable field of binocular fixation, i.e. in primary gaze and lower quadrants.
- *The principles of surgical treatment:* Involve strengthening of the paralysed muscle by resection; and weakening of the overacting muscle by recession.

'A' and 'V' Pattern Heterotropia

When the amount of deviation varies more than 10° and 15° upward and downward gaze, they are called 'A' or 'V' pattern squint respectively.

A' and 'V' esotropia: In 'A' esotropia the amount of deviation increases in upward gaze and decreases in downward gaze. The reverse occurs in 'V' esotropia.

Restrictive Squint

In restrictive squint, restriction of the extraocular muscle is not due to nerve palsy but it is mechanically restricted. Forced duction test is positive (i.e. a restriction is encountered on passive rotation).

Common causes of restrictive squint are:

- Duane's retraction syndrome
- Brown's superior oblique tendon sheath syndrome,
- Strabismus fixus
- Dysthyroid ophthalmopathy
- Incarceration of extraocular muscle in blow-out fracture of the orbit.

DUANE'S SYNDROME

In this condition, there is unilateral or bilateral lateral rectus activity during adduction and reduced activity in abduction. This results in a limited ability to abduct the eye and a narrowing of the palpebral aperture on adduction (as, effectively, both medial and lateral recti are acting simultaneously). Most cases are managed conservatively, as there is no amblyopia due to the eyes being straight in the primary position. If this is not the case, surgery will be performed to correct it.

BROWN'S SYNDROME

This condition may be congenital or acquired (iatrogenic or inflammatory—Rheumatoid arthritis, pansinusitis or scleritis) and is characterised by malfunction of the trochlear nerve or the superior oblique. Congenital cases are occasionally treated with surgery and acquired cases may respond to a course of steroids along with treatment of the underlying cause.

DYSTHYROID EYE DISEASE

Graves' disease is due to an autoimmune disorder. Ocular changes includes painful red eye, a reduced visual acuity,

proptosis, lid retraction and lid lag. These patients may also have restricted eye movements (particularly elevation and abduction) giving rise to a squint with diplopia.

STRABISMUS FIXUS

It is a rare condition characterized by bilateral fixation of eyes in convergent position due to fibrous tightening of the medial recti.

ORBITAL BLOW OUT FRACTURES

These are isolated comminuted fractures which occur when the orbital walls are pressed indirectly, 'Blowout fractures' mainly involve orbital floor and medial wall. Orbital soft tissue with extraocular muscle may incarcerate in the fracture resulting in restriction of the ocular motility.

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Visual Assessment and Screening in Children

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INTRODUCTION

An accurate visual assessment is critical to diagnosis and follow-up of most pediatric ophthalmic disorders. The term visual assessment encompasses a large number of visual function parameters prominent among which are visual acuity, color vision, contrast sensitivity, visual fields, binocularity/stereopsis and vision related electrophysiology. Perhaps the single most important of this list would be visual acuity since that is representative of the extent of the disease and the consequent disability it generates. In this chapter, we discuss the various methods that may be used for visual assessment in various age groups and interpretation of the results. We also discuss the need and protocol of screening for common ophthalmic disease in children.

VISUAL DEVELOPMENT

The pediatrician must be aware of the normal milestones that mark the development of the visual system to correctly ascertain whether a particular finding is abnormal. Any delay in these milestones is a red herring and should pave way for further examination and investigations of the ocular and nervous system. Table 1 defines broadly, the most common milestones of the developing visual system and the expected visual acuity at various ages. These milestones have been used in various clinical and special tests for visual assessment.

VISION ASSESSMENT

Visual Acuity

“Visual acuity” refers to the ability of the eye to resolve an image and depends upon the optimal functioning of the retina and visual pathway. While this is easy to document in adults, visual acuity assessment in children is a different ball game altogether. Commonly, visual acuity is

represented in the form of a fraction where the numerator refers to the distance at which it is tested and denominator represents the actual line read by the patient. The normal visual acuity is 20/20 on the Snellen chart.

Clinical Assessment of Visual Acuity

While an accurate assessment of visual acuity may not be possible without the use of any special charts or equipment, a reasonable estimate may be made at the bedside by careful history taking and observation of the child.¹⁻³ During the period of observation, the child should be in the mothers lap or a comfortable position, cooperative and interested in the examiner.

Historical Clues

A well elicited history can give important clues to the visual status of the child. Some of the important questions to be asked are:

- Do the parents think that the child sees well
- Does the child hold objects close to his/her face to see them
- Do the eyes appear straight or deviated and are there any abnormal movements of the eyes
- Does the child close one eye or is there any drooping of the eyelids
- Was there any injury to the eyes, however minor it may be
- Is there any family history of ocular problems such as color blindness or glaucoma or early onset refractive errors, etc.
- Has there been any feedback from school regarding difficulty for the child in seeing the board or playing sports.

Observational Clues

For infants younger than six months, note the response the child has to a light source such as a torch. The child

Table 1: Development of vision and visual acuity

<i>Age</i>	<i>Visual Milestone</i>	<i>Visual acuity</i>
29 weeks gestation	Pupillary reactions to light	6/480-6/120 (by OKN)
30 weeks gestation	Dislikes and responds to bright light	
Birth	Blinks to light; prefers soft diffuse light	6/360 – 6/120 (by OKN)
1 week	Vetibulo-ocular reflex, Optokinetic nystagmus seen	
2 weeks	Small saccades develop; follows horizontal moving objects	
1 month	Fixation developing, can watch mothers face for prolonged time	6/480–6/120 (by PL tests)
2 months	Fixation well developed; bifoveal fixation; larger saccades; pursuits and convergence movements; follows vertically moving objects	6/120–6/60
3 months	Watches movements of own hands and reaches out towards interesting objects; prefers photographs to patterns	
4 months	Foveal differentiation complete; sensory fusion and accommodation begins to develops	6/120–6/30
5 months	Blink response to visible threat (menace response); grasps and explores objects; stereopsis begins to develop	6/90–6/24 6/12–6/6 (by VER)
6 months	Accommodation well developed; fusional vergence well developed	
9 months	Visual differentiation of objects' picks up small objects	6/48–6/12 6/6 (by VER)
18 months	Visual acuity at adult levels on pediatric acuity cards	6/18–6/7.5
3 years	Visual acuity at adult levels on snellen chart; contrast sensitivity well developed	6/15–6/7.5 (24 months) 6/12–6/6 (36 months)
5 years	Stereopsis fully developed	6/5
9 years	Critical period of monocular deprivation ends	

should show an interest in the light and attempt to follow it as the examiner moves it around. The examiner should then occlude one eye with his hand such that the hand is close to but not touching the eye. Now the response to a moving light source should be rechecked (for each eye separately). If the child resists occlusion of one eye, then it may mean a poorer visual acuity in the fellow eye. Also after the appropriate age, visual recognition of the mothers face can reliably point at some visual potential. Another bedside assessment that may be done is by using a direct ophthalmoscope to look at both the eyes from a distance of two to three feet. An asymmetrical red reflex may suggest a squint or a difference in refractive error between the two eyes. Also, examining the pupil responses can rule out any major visual deficit in the eyes.

For older infants, additionally, small objects such as candy pieces or brightly colored beads can be used to assess visual acuity. Also, children at this age group should be able to fix and maintain steady fixation for both stationary objects and moving objects in the near range of the child.

Toddlers and preschool children may be clinically assessed by whether the child can walk around without banging into obstacles and play with his/her peers and follow and catch objects such as a small ball or car, etc. Better

assessment may be made by their ability to recognize small shapes and objects and also by their ability to draw and color pictures. A rough estimate of visual acuity may be made by documenting the smallest object that the child can see and the approximate distance at which it was seen. The visual acuity (snellen equivalent in decimal units) in such a case is $0.3 \times \text{object distance (in mm)} / \text{object size (in mm)}$.

For school going children, their ability to read from books or appropriately draw and color detailed pictures as well as play sports is a sign of good visual functions. Formal visual acuity testing in such children is usually quite reliable and should always be attempted with the aid of special charts.

Formal Assessment of Visual Acuity²⁻³

Despite an excellent clinical bedside evaluation, the only way to accurately quantify visual acuity is by using equipment and charts designed for this purpose. These tests may determine either detection acuity (the smallest object that the eye can just detect) or resolution acuity (the minimum separation of pattern stimulus or highest frequency on a grating that the eye can resolve) or recognition acuity (the ability of the eye to detect and recognize objects or

letters). Of these the tests for recognition acuity are preferred to give a true picture of the visual ability of the eye though they may not be performed in very young children. While there have been numerous visual acuity tests developed and used over time, Table 2 mentions the most commonly used tests and the age group for which they are most appropriate.

Visual Evoked Response

This electrophysiological test records the change in the cortical electrical pattern detected by surface electrodes monitoring the occipital cortex following light stimulation of the retina. The stimuli could either be a flash of light or a checkerboard patterned. For purposes of visual acuity assessment, a pattern stimulus using varying sizes of the checkerboard squares reflecting 60, 30 and 15 seconds of arc is used. The smallest size to generate a reliable response is a good estimate of visual acuity. Along with Optokinetic nystagmus, this test tends to better estimate the true acuity than some of the other tests described below.

Optokinetic Nystagmus

Various tests directly or indirectly utilize the normal optokinetic nystagmus evoked by a revolving drum to estimate the visual acuity. In each of these, there is a varying size of grating or images on the drum and the smallest of which evokes an OKN response reflects the visual acuity. Prominent examples include the Catford drum which contains dots of varying size from 15 to 0.5 mm diameter and

oscillates at a distance of 60 cm from the child. These dots represent vision from 20/600 to 20/20. Similarly, there is the Harcourt's OKN drum which uses gratings of different resolution to detect acuity. This technique of testing tends to overestimate visual acuity.

Boeck Candy Bead Test

Multiple edible candy beads of variable sizes are shown to the child on the palm of the examiners hand. The smallest size that the child can see and reach out to eat is documented. This gives an approximate idea of the child's visual acuity.

Teller Acuity

This belongs to a group of tests based on the behavioral pattern of an infant to prefer to fixate a pattern stimulus rather than a blank, both being of the same brightness called as the preferential looking tests. Teller acuity cards are designed for a simpler and rapid testing particularly for children up to 18 months of age. These contain patches of square-wave gratings (vertical black and white stripes) which range in spatial frequency, from 38.0 cycles/cm to 0.32 cycles/cm changing in half octaves. This is equivalent to doubling of the denominator in snellen terms. When the child is unable to resolve a pattern, the whole pattern and card appears to be grey as the background of the card. A fixed testing distance of 38 cm for infants less than 6 months and 55 cm for children up to three years is used. The child is shown these patterned cards while a hidden

Table 2: Methods for visual acuity assessment in various age groups

<i>Age group</i>	<i>Methods used (Fig. 1)</i>	<i>Type of test/acuity</i>
Under 6 months	Response to occlusion Visual evoked response Optokinetic nystagmus	Resolution acuity Resolution acuity
6-18 months	Boeck candy beads Stycar graded balls test Teller/Keeler acuity cards Cardiff acuity cards	Detection acuity Detection acuity Resolution acuity Recognition acuity
18 months – 3 years	Cardiff acuity cards Kay picture test Sheridan-Gardiner test	Recognition acuity Recognition acuity Recognition acuity
3-5 years	Kay picture test & Allen/LEA symbols Sheridan-Gardiner test Cambridge crowding cards Glasgow acuity cards Stycar test Snellen letters Snellen numbers Tumbling E HOTV	Recognition acuity Recognition acuity Recognition acuity Recognition acuity Detection and recognition acuity Recognition acuity Recognition acuity Recognition acuity Recognition acuity
More than 5 years	Sheridan-Gardiner test Snellen letters or numbers LogMAR	Recognition acuity Recognition acuity Recognition acuity

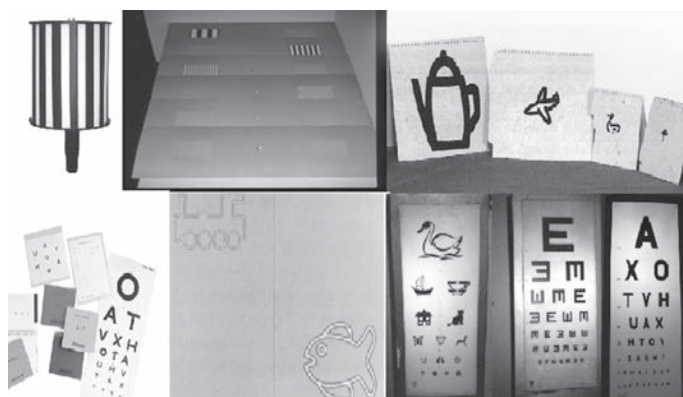


Fig. 1: Top Row (Left to right): Optokinetic nystagmus drum; Teller cards; Kay picture test (For color version see plate 21)

observer is seeing the child's preference towards looking at these stimuli vis-à-vis a plain grey card. Till the child can see a pattern, he shows interest in seeing the card but when the size of the gratings gets too small to resolve, the child does not show any preference towards the card. This lack of fixation is noted by the observer and forms the basis of a reliable visual acuity. However, there are few drawbacks of this technique of testing which include the fact that it tests for near vision, and may miss small refractive errors. Also being resolution acuity, it may overestimate the vision and may miss out on amblyopia.

Cardiff Acuity

This test is based on vanishing optotype. The targets are pictures drawn with a white band bordered by two black bands, all on a neutral grey background. The average brightness of the picture is equal to that of the grey background. If the child's vision is good enough to resolve the white and black bands, the picture will be visible but if the bands are too narrow for the child to resolve them, the picture merges with the grey background, and simply becomes invisible. The visual acuity is reported on the basis of the smallest resolvable picture by the child.

Kay Picture Tests/Allen Test/LEA Symbols

Charts with only those pictures proven to be both recognizable and accurate are used. Research comparing the pictures with Snellen optotypes has shown a high correlation and thus an accurate acuity. A matching card helps shy or under-confident children. Other picture identification tests include the Allen test and LEA symbol tests for slightly older children which consist of various pictures of progressively decreasing size on a snellen like chart projected at a distance.

Sheridan Gardiner

Traditionally, it consists of single letter optotypes. The test is a matching test designed for use with children but is

also suitable for use with those with learning difficulties or with patients who do not share a common language with the examiner. The drawback of this test was an overestimation of acuity in amblyopic children and therefore now a modified test with linearly arranged alphabets is available.

Glasgow Acuity and Cambridge Crowding Cards

A significant 'crowding effect' has been found in children between the ages of three and six years and in amblyopes. Test based on single optotypes are not sensitive to amblyopia as linear optotypes, owing to the absence of contour interaction. In the glasgow acuity cards, a surround box is placed half a letter width away from the single test optotypes to improve the test sensitivity while in the Cambridge crowding cards, there is a central letter in a five letter array (with varying spaces) which needs to be identified.

HOTV test

The HOTV test is a letter matching test used in children who have difficulty in naming letters. In this, they have to match the letters shown to them at a distance with the matching cards in their hands. The test initially included only four letters H, O, T, V but has been expanded in the Sheridan test to include X, A, U, L and C also.

Bottom Row (Left to right): Sheridan Gardiner; Cardiff cards; Allen picture test; Snellen 'E' and alphabet chart

STYCAR

The STYCAR group of tests are sight tests for young children and retards. They consist of stycar balls test where small balls are attached to sticks of varying lengths to see up to where a child can see. Also the graded balls test and miniature toys tests work on similar principle. The STYCAR letters test consist of single or multiple letters from the Sheridan test which are to be matched by the child. These letter tests have similar value as the direction identification tests.

Snellen Charts and the LogMAR Chart

These are the most common performed visual acuity test in adults and most visual acuity is compared to Snellen equivalents. The charts are easy to read and quick assessment of visual acuity can be made. There are various types of charts such as the tumbling E or C charts for children who don't yet know the alphabets and the alphabet chart for those who are school going. Normally, the Snellen chart is read at a six metres distance and the normal visual acuity is 6/6. However, the Snellen chart does have few drawbacks such as a nongeometric pattern of letter size reduction or the absence of crowding phenomenon in the larger optotypes. These drawbacks are overcome in the LogMAR chart which has the same number of letters in each row and the letter sizes decrease in a strict

geometric progression leading to an accurate measurement of change.

Near Vision Charts

Near vision in children is very important since a child's visually stimulating world is very close to him/her. Though most of the above mentioned methods actually measure near or intermediate distance acuity, various specialized near vision charts are available. These include snellen near vision chart, jaegers chart among many others.

COLOR VISION

While neonates and young infants possess some ability to distinguish colors, it is inferior to that in adults. The eye starts to recognize colors around two to six weeks of age and this ability matures by around the age of four to six months. Assessing color vision perception in infants is difficult and possibly inaccurate and often they are attracted by the brightness and contrast of the object rather than by its color; therefore simply assuming that because a child is preferentially looking at colored objects is an improper way of assuming normal color vision. The most common chart used to assess color vision is the Ishihara chart which consists of numbers or lines made of colored dots which are surrounded by more such dots of a different color. On the basis of the child's ability to correctly read the number or trace the lines, color vision is reported to be normal or abnormal. Special charts similar to the classic Ishihara chart are available for children where shapes replace the numbers and lines, thus making it possible to test even smaller children. Other tests such as the Farnsworth Munsell or 100-Hue test are more cumbersome and possible only in the older children. Besides these, there are many online child friendly tests now available. If there is a family history of color blindness or parents suspect the same then the child should undergo a screening at least once prior to entering nursery since his learning may get significantly affected if the teachers and parents remain unaware and do not modulate their teaching methods.

CONTRAST SENSITIVITY

Contrast sensitivity has been described to be the single most complete measurement of spatial vision with a higher predictably of visual dysfunction than visual acuity alone. However, it requires special testing charts and equipment and limited normative data is available for younger children. It is generally been seen that the contrast sensitivity function rapidly develops between 6 and 12 weeks of age and then develops slowly to reach adult levels around 9 to 12 years of age.⁴ Ophthalmologists would usually perform contrast sensitivity testing using either a Pelli-Robson chart or a FACT chart in cases where retinal or optic nerve

dysfunction is suspected. There is no indication of doing regular screening of contrast sensitivity function.

VISUAL FIELDS

Visual field refers to the area in space the eye can see. It is determined and limited by the placement of the eye in the confines of the bony orbit. The visual field is often affected in many ocular conditions which impact the retina or optic nerve as well as in cortical dysfunctions. While a clinical assessment of visual fields can be done by finger-play or a confrontation test, objective/quantitative evaluation requires either a kinetic perimeter (Goldmann perimeter) or a static perimeter (Humphrey perimeter). Children frequently have difficulty in performing a fields test since it requires them to maintain a central fixation for an extended period of time. Therefore, visual field reports are often fallacious and need careful interpretation. The interactive protocols in automated perimetry enable faster testing as well as newer game based visual field testing are likely to be more reliable.

STEREOPSIS

Stereopsis refers to the ability to perceive depth and is a higher cortical function which depends on the presence of symmetrical good visual acuity of both eyes and normal binocularity. It is subnormal or absent in cases of amblyopia and strabismus and requires to be screened in only those cases. The normal value is 60 seconds of arc or better. It may be tested for near using various tests including Titmus fly test, Randot test, TNO test, etc. or for distance using distant Randot or Frisby-Davis (FD2) tests.

ELECTROPHYSIOLOGY

Electrophysiology of the eye includes visual evoked response (VER), electroretinogram (ERG) and electro-oculogram (EOG) which can determine the integrity of the visual system, retina and retinal pigment epithelium respectively. These tests require highly specialized equipment and are reproducible even in somewhat uncooperative children. Visual evoked response (VER) as a tool to assess visual acuity has been discussed above but besides that, its main utility is to determine whether the visual pathway extending from the retina and optic nerve to the occipital cortex is intact and functioning optimally. Pediatricians may often come across VER reports in terms of amplitude and latency which they should be able to grossly interpret. Though each laboratory has their own range of normal values, generally speaking amplitudes less than 8 to 10 microvolts and latency longer than 110 ms should be considered as subnormal. The interpretation of ERG and EOG are best left to the ophthalmologists and require clinical correlation.

OCULAR SCREENING IN CHILDREN

Pediatric ocular conditions are often silent and since children are often unable to express themselves regarding a poor quality of vision or low visual acuity, it is pertinent to screen them. While a large number of ocular afflictions are known in children, well defined screening protocols are established for only a handful of the sight threatening ones.^{6,7} The pediatrician is the first contact of the children and is therefore the ideal channel for an opportunistic screening of ocular diseases (Table 3).

Screening of the Neonate

The attending neonatologist should screen the newborns' eyes for any evidence of discharge or matting suggestive of ophthalmia neonatorum and also for any obvious ocular malformations such as cryptophthalmos, anophthalmos, etc. The neonatologist should also be alert to the fact that large appearing or hazy appearing corneas can be an indication of congenital glaucoma and need immediate evaluation by the ophthalmologist.

Screening for Retinopathy of Prematurity (ROP)

The American Academy of Ophthalmology and Pediatrics suggest a screening fundus examination for all infants born weighing 1500 g or less or with gestational age of 28 weeks or less and also for any premature infant weighing up to 2000 g, believed to be at risk by the attending pediatrician (has received supplemental oxygen or has an unstable neonatal course). The examination should be done 4 to 6 weeks from birth, or by 31 to 33 weeks postconceptional

age, whichever is earlier. Screening criteria formulated according to Indian scenario include screening all infants with birth weight less than or equal to 2000 g or those born at gestational age of less than or equal to 35 weeks.

Preschool Vision Screening

There are varying reports from literature about the need, correct age and screening test to screen for refractive error, amblyopia and strabismus in preschool children. Amid all the controversies, the American Academy of ophthalmology has defined the need to perform preschool vision screening at 3 to 3.5 years age. This includes screening for amblyopia using the crowded LogMAR chart. Screening for strabismus using the cover uncover test and screening for any refractive errors. While photostereopsis and use of autorefractors is commoner in the west, such a practice is nearly non-existent in India. An important question regarding who should screen also exists and various countries have differently recommended orthoptists or optometrists or trained lay people to perform the screening. In India, though not formally introduced, such screening is most likely going to be performed by the ophthalmic assistants and optometrists under the vision 2020 initiative.

School Screening

School screenings are being carried out under the national program for control of blindness and Vision 2020. School teachers are trained to assess and document visual acuity and all children with visual acuity worse than 6/9 are given

Table 3: Simple screening methods at various age groups and indications to refer to an ophthalmologist

Age group	Method/test	Ophthalmology referral if:
New born to 3 months	Inspection	Structural abnormality
	Red reflex	Abnormal or asymmetric
3-6 months	Red reflex	Abnormal or asymmetric
	Fix and follow light	Unable to fix or follow, abnormal movements
6-12 months	Red reflex	Abnormal or asymmetric
	Fix and follow	Unable to fix and follow, abnormal movements
	Alternate occlusion	Resists occlusion of 1 eye
	Corneal light reflex	Reflex not central in either eye
1-3 years	Corneal light reflex or cover-uncover test	Reflex not central in either eye; squint of eye
	Visual acuity (observation)	Unable to see small objects
	Head posture	If persistent and reproducible
	Activity (walking, coloring, etc.)	If holding objects to close or mixing colors
3-4 years	Cover uncover	squint of eye
	Visual acuity	If worse than 20/30 or two line difference between eyes
5 years	Visual acuity	If worse than 20/30 or two line difference between eyes
	School performance	Sits close to board or holds books too close to eyes.

glasses after refraction or referred if not improving after refraction. This is a successful model and is being increasingly implemented in various public schools.

Screening for Other Ocular Conditions

There is no defined screening protocol to look for conditions such as retinoblastoma, cataract, retinal dystrophies or glaucoma, etc. and it is probably not feasible to separately screen for each of these diseases. On the other hand, opportunistic screening such as when the child visits the doctor or during preschool and school screening may be the only way when such conditions can be looked for.

Special Conditions Requiring Screening

Children with juvenile rheumatoid arthritis need to be screened for anterior uveitis as this is usually silent and sight threatening. Since, the eye disease can precede the joint involvement, the first examination should be done after one month of diagnosis of JIA. The maximum likelihood for ocular involvement is four years after the onset of arthritis.

Children with Type I diabetes mellitus should be screened five years after the onset of diabetes and annually thereafter for retinopathy. If the child is older than nine years, the first ophthalmic examination should be done three to five years after diagnosis.

Color vision screening should be done in the preschool age for children who have a positive family history of color blindness.

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SUMMARY

This chapter focuses on five common diseases in the field of pediatric dermatology, namely, atopic dermatitis, acne vulgaris, vitiligo, molluscum contagiosum and warts. We present an overview of these entities highlighting the recent advances in literature both in pathogenesis and management. An attempt is made to identify and emphasize novel treatment modalities that are especially suitable for the pediatric population. We believe the information contained herein will be of value to pediatricians who frequently manage these dermatologic conditions.

UPDATE ON PREADOLESCENT AND ADOLESCENT ACNE

Acne vulgaris is a common dermatologic disorder affecting 28 to 61 percent of the population in the age group 10 to 12 years and 79 to 95 percent between 16 to 18 years of age. The pathogenesis of acne is multifactorial and includes four key factors, namely:

1. Excess sebum production
2. Ductal hypercornification in sebaceous follicles
3. Colonization of sebaceous follicles with *Propionibacterium acnes*
4. Inflammation.

Acne in preadolescents and adolescents differs from that in adults in several ways. In the former groups the sites of predilection are forehead, nose and paranasal areas, and cheeks (upper face). With advancing age there is a cephalocaudal progression and in postadolescents and mature adults acne tends to involve more of lower face (Table 1). Further, whilst adolescent acne shows a mix of comedones and inflammatory lesions (acne vulgaris meaning common acne), in preadolescents it tends to be mostly comedonal and in adults it is inflammatory. Acne is more difficult to treat in preadolescents partly because

of compliance issues and partly because of a tendency on the part of the treating physician to employ suboptimal therapies. Also, onset of acne in preadolescents portends a more severe disease in ensuing years.

The success of acne management depends on careful evaluation of each patient for each of the pathogenetic factors, the anatomic distribution, and the number and type of lesions. The morphology of acne lesions is perhaps the most important parameter for choosing treatments (Table 2). The acne treatment is a program that is highly individualized and also takes into account the logistics and the motivations.

Role of *Pityrosporum* in Adolescent Acne

Pityrosporum orbiculare, (also known as *Malassezia furfur*) is a lipophilic yeast that colonizes the follicles in preadolescent years (along with *P. acnes* and *Staphylococcus epidermidis*). Although it is a commensal, it sometimes overgrows and turns pathogenic and causes seborrheic dermatitis. In teenagers, *P. orbiculare* occasionally produces papules and pustules in seborrheic distribution (central face, forehead, nasolabial folds, perioral area, sternal area, upper back and shoulders) mimicking acne. Termed *Pityrosporum folliculitis*, this entity tends to occur most commonly at the onset of puberty due to the activation of the sebaceous glands. *Pityrosporum folliculitis* may coexist with acne vulgaris. If unrecognized it can get aggravated by the use of antibiotics. What is even less recognized is that *P. orbiculare* may directly contribute to acne pathogenesis? This appears to be a tropical phenomenon more at play in the preadolescent population. Its pathogenetic role in acne is suggested by concomitant seborrhea capitis (dandruff), distribution of lesions along the frontal and temporal hairline, on the glabella and paranasal areas, predominance of papules and pinhead sized pustules, and a lack of response to antibiotics. If suspected, the acne

Table 1: Acne patterns in different age groups of patients

<i>Acne type</i>	<i>Pattern</i>	<i>Type of lesions</i>
Preadolescent	Forehead and paranasal areas	Comedones
Adolescent acne	Forehead, temples, malar area, cheeks, chin	Comedones, papules, pustules
Adult	Jawline, perioral	Mostly papules

Table 2: Spectrum of efficacy of topical agents in acne treatment

<i>Decrease in comedones</i>	<i>Sebosuppressive</i>	<i>Antimicrobial</i>	<i>Anti-inflammatory</i>
Tretinoin	++	-	-
Isotretinoin	++	-	+/-
Adapalene	++	-	+
Tazarotene	++	-	+/-
Azelaic acid	+	-	+/-
Erythromycin	+/-	-	++
Clindamycin	+/-	-	++
Benzoyl peroxide	+	-	+++
Salicylic acid	+/-	-	-

treatment program must include antifungal agents such as miconazole (topical gel), ketoconazole (shampoo), and itraconazole (orally).

Diet and Acne

The role of diet in the causation of acne (hitherto denied) has been resurrected. A large retrospective, cohort study reported that excessive intake of milk during adolescence was associated with more acne. Interestingly, this association with acne was more marked for skim milk than other forms of milk suggesting that the fat content of milk was not the reason. It was hypothesized that the hormone content of milk (estrogens, progesterone and androgen precursors) and the presence of bioactive molecules such as insulin-like growth factor-I (IGF-1) were the likely reasons.

Adolescents in westernized societies may be repeatedly hyperinsulinemic due to their high glycemic diet. Hyperinsulinemia in turn may initiate an endocrine cascade that affects the sebaceous gland and follicular keratinization through the involvement of IGF-1, IGFBP-3 (insulin growth factor binding protein-3), androgens, and retinoid signaling pathways, thereby causing hyperandrogenism and acne. This has been substantiated through studies demonstrating that diets rich in low-glycemic load foods reduced serum concentration of testosterone and increased levels of SHBG (Serum hormone binding globulin). Hyperinsulinemic diets, therefore, may represent a previously under-recognized environmental factor in the development of acne indirectly through androgen

Table 3: Mechanism of action of available treatment modalities

Benzoyl peroxide	Antimicrobial weakly comedolytic
Topical retinoids	Comedolytic Anti-inflammatory
Topical antibiotics	Antimicrobial
Systemic antibiotics	Anti-inflammatory (primarily) Antimicrobial
Oral contraceptives	Sebosuppressive
Systemic retinoids	Comedolytic Anti-inflammatory Sebosuppressive Antimicrobial (Indirectly)

mediated sebum production and alteration of follicular keratinization.

Enough evidence now exists in the literature highlighting the association of acne and high glycemic loads, certain dairy products and ingestion of refined sugars.

Management

Acne can persist for years and its long-term ramifications can be significant. Early and effective treatment is essential to avoid the physical and psychological scarring it may cause. The following considerations are important for successful management of acne:

- Customized skin care
- Individualized treatment program

- Adequate treatment duration
- Post-treatment maintenance.

The spectrum of efficacy of the topical agents used in the treatment of acne is illustrated in Table 2.

Of these, topical retinoids are the mainstay in the treatment of preadolescent and adolescent acne. They inhibit the formation of and reduce the numbers of comedones (primary lesion of acne), promote normal desquamation of the follicular epithelium and enhance the penetration of other drugs. A newly recognized function of topical retinoids has been their anti-inflammatory action through modulation of the immune response (Table 3).

The consensus recommendations for the use of topical retinoids are as follows:

- They should be the primary treatment for most forms of acne
- Use early for best results
- Apply to the entire affected area and not just the lesions
- Combine with antimicrobials in inflammatory cases.

A concern with the use of antibiotics in the treatment of acne has been the emerging resistance of *P. acnes* to the various antibiotics being used. A report from the 'Global alliance to improve outcomes in acne' emphasizes certain precautions while prescribing antibiotics in order to prevent antibiotic resistance. These are:

- Use oral antibiotics when topicals are not enough
- Withdraw antibiotics as soon as possible
- When repeating choose the same antibiotic
- Use benzoyl peroxide in combination to eliminate resistant strains
- Avoid concomitant dissimilar topical and oral antibiotics.

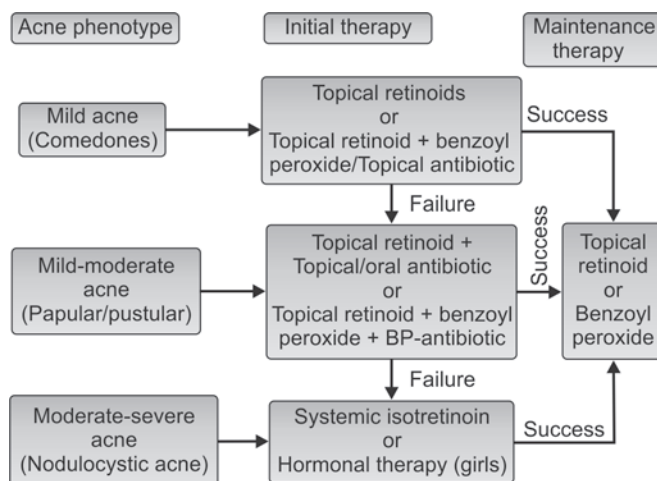
Because of the multifactorial nature of the pathogenesis of acne, a combination of different classes of drugs that affect different areas of pathophysiology should be used. No single therapy is able to counter all the four factors involved in the pathogenesis of acne.

A simple algorithm for the effective management of preadolescent and adolescent acne is illustrated in Flow chart 1.

ATOPIC DERMATITIS—A DERMATOLOGIST'S PERSPECTIVE

Atopic dermatitis (AD) is a chronic inflammatory skin condition with impaired cell-mediated immune function and compromised skin barrier. It is characterized by erythema, edema, vesicles and oozing in the acute stage and thickening and hyperpigmentation (lichenification) in the chronic stage. Approximately 70 percent of cases of atopic dermatitis start in children under 5 years of age. Asthma develops in 70 percent of the cases and allergic rhinitis in 35 percent. About 40 percent of children with AD are

Flow chart 1: Treatment of acne



free of symptoms by early adolescence although up to 50 percent may have recurrences in adulthood.

The severity scales used in clinical trials are generally not suited for rapid assessment in the clinic. Parameters such as presence or absence of sleep disturbances, number and location of involved sites, and the clinical course are suitable indicators of severity and provide the best basis for making decisions about treatment. Skin biopsy is of little value in the diagnosis of AD. It is important to keep in mind that early-onset disease, severe early disease, concomitant asthma and allergic rhinitis, and a family history of atopic dermatitis may predict a more persistent course.

Etiology

Atopic dermatitis (AD) is a complex disease relying on an inter-play of several factors. Many genes have been identified over the years; however, genetics alone cannot explain the rising prevalence of AD in some countries. Current epidemiological research has suggested a key role of the environment in mediating disease expression. Allergens such as house-dust mite and certain foods may also be important in addition to *Staphylococcus aureus* infections, exposure to heat and to irritants that disrupt the skin barrier.

Atopic Dermatitis and the "Hygiene Hypothesis"

Atopic dermatitis (AD) is more common in urban than in rural communities and more prevalent in western industrialized countries than in developing countries. It is also shown that AD is more in children growing up in smaller families and families of higher socioeconomic status therefore it has been suggested that the disease is more likely to occur when the developing immune system is deprived of the obligatory stimulation through certain nonpathogenic microbial antigens. This hypothesis has prompted the use of probiotics such as *Lactobacillus* GG supplementation as a new

therapeutic approach towards treatment of AD although sufficient data is unavailable to substantiate their efficacy.

Management

The treatment of atopic dermatitis involves a combination of preventive measures aimed at suppressing the symptoms of disease and individualized treatment for controlling and preventing recurrences. The successful management requires a multipronged approach.

Breastfeeding and Diet in Atopic Dermatitis

It has been shown that exclusive breastfeeding during the first-three months of life is associated with lower incidence rates of atopic dermatitis in children with a family history of atopy. This effect is lessened in the general population and negligible in children without first-order relatives. Therefore, breastfeeding should be strongly recommended to mothers of infants with atopy in the nearest family as a possible means of alleviating or even preventing AD. Since this is not the case in children without such history for whom breastfeeding is recommended for its other multiple benefits. Avoiding foods suspected to cause flares may be helpful in young children with severe disease. However, there is little evidence to support dietary exclusion of milk and eggs in unselected cases except for infants with AD who produce IgE antibodies to egg proteins in whom egg-free diets before the age of 2 years may be of benefit.

Topical Corticosteroids

Topical steroids have been the mainstay of treatment of AD for many years. They are chosen on the basis of their potency which is determined by their potential for vasoconstriction—a surrogate for clinical efficacy and skin thinning. In general, topical steroids of mild and moderate potency are used on the face and genitals (where the skin is thin), whereas, those of moderate to potent strength are used over other areas of the body. However, in the pediatric age group low potency steroids may be sufficient for use in all areas of the body and only in chronic AD (lichenified lesions) should higher potency steroids be used.

Reduced efficacy of topical steroids has been an area of concern in AD but it is important to remember that this may be related more to inappropriate use of the steroid in relation to disease severity rather than steroid resistance or tachyphylaxis. With the advent of newer preparations of topical steroids (like mometasone) once daily application have proven to be as effective as twice daily or more frequent applications thereby minimizing the risk of local side-effects. It is also essential while treating AD that the topical steroids be used for an adequate duration (up to few days after clinical clearance as assessed by the parents of children being treated) rather than intermittent use of

steroids for the fear of side-effects that results in partial clearance of lesions with more frequent recurrences.

Topical Calcineurin Inhibitors

Tacrolimus, the prototype of this category of drugs, is a nonsteroidal topical immunomodulator now used for the treatment of AD with the advantage of having efficacy similar to topical corticosteroids (gold standard for the treatment of AD) in addition to an excellent safety profile. Tacrolimus inhibits T-cell maturation and activation by the inflammatory cytokines through the blockage of calcineurin action, an important mediator of cytokine release. Topical tacrolimus is available in an ointment base of two strengths -0.03 and 0.1 percent. The lower potency of 0.03 percent is preferred for application on the face and genitals and the 0.1 percent over other areas of the body. Topical tacrolimus 0.1 percent ointment has shown to be similar in efficacy to midpotency topical steroids and it may be used alone or in combination with steroids. Tacrolimus offers the advantage of not causing skin atrophy or telangiectasia despite prolonged use as compared to its steroid counterpart. Five-year studies have shown a good safety profile with the only side-effect being mild burning sensation at the time of first application that clears with subsequent use. There has been some concern about the increased risk of infection with the use of topical tacrolimus in AD due to local suppression of the immune system, however, studies have shown that the risk of infection (bacterial or viral) either remains the same or reduces with continued use of tacrolimus. It has been indicated that the lower incidence of cutaneous infections in long-term studies could be related to sustained improvement in AD (with associated improvement in the skin barrier function) with extended use of tacrolimus. In addition, it has been reported that topical tacrolimus significantly reduces *Staph. aureus* colonization in AD lesions (responsible for exacerbation in majority of AD cases) and specifically blocks the release of *S. aureus* superantigen induced T-cell proliferation in AD.

Pimecrolimus is the more recent member of the calcineurin inhibitors available in USA in a cream formulation as Elidel® but not available in India as of now. It targets T-cells and mast cells by inhibiting the production of cytokines and other inflammatory mediators essential for the activation of these inflammatory cells. In contrast to corticosteroids, it does not affect Langerhans cells or fibroblasts and therefore does not have any inhibitory effect on collagen synthesis eliminating the most infamous adverse effect of skin atrophy seen with the use of topical steroids. Pimecrolimus differs from its contemporary tacrolimus in the following ways:

- It is available in a cream formulation as opposed to the ointment form of tacrolimus

- More suited for application around the eyes
- Permeates through the skin less than tacrolimus resulting in less transcutaneous absorption after topical application thereby having less potential for systemic effects when used over a large surface area
- High anti-inflammatory activity and theoretically more favorable balance of anti-inflammatory versus immunosuppressive activity than tacrolimus.

In March 2005, the US FDA issued an alert to all health-care professional concerning a potential link between topical pimecrolimus and tacrolimus and cancer (mainly lymphoma and skin cancers) on the basis of studies in animals, and case reports, and the current knowledge of how these drugs work. The alert emphasizes the importance of using these preparations in children above 2 years of age, when first-line treatments have failed or cannot be tolerated, and advises intermittent and short courses. Although, recently there has been data in the literature that does not support these concerns and propagates the use of the topical calcineurin inhibitors in patients with atopic dermatitis in whom topical corticosteroids cannot be employed for the fear of causing irreversible side-effects. These calcineurin inhibitors have provided a fresh approach to the chronic management of this frequently relapsing disease and although their long-term safety (greater than 5 years) is not yet established their judicious use and surveillance can avoid problems.

Role of Antihistamines

Because both atopic dermatitis and asthma are treatable but not curable conditions, the development of strategies for prevention of the diseases has a high priority. AD is a common precursor to the development of asthma and it was suggested that the use of an H1-antagonist might reduce the development of asthma at least in subgroups with evidence of high IgE levels. Thus, the early treatment of atopic child (ETAC) study was conducted to establish whether the intervention merely suppressed symptoms or truly prevented disease. The ETAC study was a double-blinded, parallel-group, randomized trial of 0.25mg/kg body weight cetirizine administered twice daily compared to placebo in children between the age group of 1 to 2 years with AD for a study period of 18 months and a follow-up period of another 18 months. The study concluded that cetirizine compared to placebo truly delayed or in some cases prevented the development of asthma in a subgroup of infants with AD sensitized to grass pollen or house-dust mite.

Subsequently, a multicountry double-blinded, randomized, placebo-controlled trial called the ETAC trial was done for a study period of 18 months to analyze the effect of long-term use of cetirizine on the severity, natural history and treatment of AD. The study showed that the severity of AD decreased significantly over the study

period of 18 months in both groups (placebo and cetirizine 0.25 mg/kg twice daily) but the use of other supportive treatment for AD like topical corticosteroids and oral antihistamines was significantly reduced in the cetirizine group. The study also showed that the duration of use of topical steroids was reduced in the cetirizine group and this steroid-sparing effect was statistically significant.

In view of the proven safety of cetirizine, it was suggested that the use of this drug might help to reduce the duration and amount of topical steroids used in the treatment of AD in infants although further studies are needed to confirm if the use of oral antihistamines can alter the natural history of the disease. In the experience of the senior author (RK) once daily use of an oral antihistamine like cetirizine over an extended period of time (6 months to 1 year) is rewarded with fewer relapses and acute exacerbations and this is likely linked to a drop in total IgE. Also, such an extended treatment is devoid of toxicity or tachyphylaxis.

CHILDHOOD VITILIGO

Vitiligo is an idiopathic disorder characterized by depigmented macules that result from the destruction of melanocytes. The disease is cosmetically disfiguring and may produce a profound psychological impact due to the associated social pressures. Vitiligo affects between 1 to 2 percent of the world population; however, the prevalence in India is about 2.5 percent. The onset of the disease in about 50 percent of the affected people is before the age of 20 years with a peak between 4 to 8 years, thus making vitiligo an important pediatric problem.

The clinical presentations may vary and include generalized (most common), segmental and acrofacial types. Segmental vitiligo of childhood tends to be less progressive than other types but reportedly is more recalcitrant to therapy.

Etiology

The current opinion on the causation of vitiligo favors the composite theory. There is a genetically determined defect either inherent to the melanocyte or in the melanocyte-keratinocyte signaling pathway that causes the defective melanocytes to accumulate excess of intermediate products in the melanin biosynthesis pathway. This leads to melanocyte apoptosis causing the release of cell-surface antigens from these dead melanocytes that in turn sensitize the immune system resulting in the formation of antibodies and cytotoxic T-cells. Eighty percent of vitiligo patients have melanocyte autoantibodies and the level of these antibodies is directly proportional to the disease activity and severity.

Although majority of the cases of vitiligo are idiopathic, there is a subset of individuals who have 'chemical

leukoderma' (morphologically indistinguishable from true vitiligo). Chemical leukoderma has been documented to occur following exposure to certain chemicals, the most common being phenolic compounds with catecholic derivatives. Many have been demonstrated to be preferentially cytotoxic to melanocytes with high dose exposure resulting in apoptosis. There is an unsuspected presence of such potential chemical depigmenting agents in solid rubber as phenolic derivatives are used as rubber additives and for hardening of rubber. Day-to-day exposure to such depigmenting chemicals can come from everyday use items like rubber footwear. Such individuals with a genetic disposition may then develop depigmentation at the site of contact (soles with sparing of the insteps) and the depigmentation spreads beyond the area of contact, probably via an immune-mediated mechanism. It is at this stage that the disease is recognized and often mistaken for true idiopathic vitiligo. However, if the causative agent is not avoided (rubber footwear) the disease becomes resistant to treatment or the response to the treatment is slow (personal observation of the authors).

In some cases, especially in the early part of the disease, when the lesions appear hypopigmented as opposed to depigmented the diagnosis may be questioned. In such cases, the use of Wood's lamp (ultraviolet of 365 nm) is extremely helpful. If a given lesion accentuates under Wood's light it indicates the complete loss of pigment and the diagnosis of vitiligo can be made with considerable certainty. In few cases, however, a histopathological assessment through a skin biopsy may be needed to confirm the diagnosis.

Management

There are certain considerations to be kept in mind while planning the treatment of vitiligo. It is important to keep in mind the duration of disease, disease activity and extent of depigmentation. The following are the aims of treatment:

- Arresting disease activity by preventing further damage to the melanocytes
- Repigmenting the depigmented lesions by stimulating melanogenesis in the residual melanocytes
- Attempting to modify the natural course of disease by adequate control at the appropriate time.

For the past two decades, monotherapy with topical steroids has been the most common treatment for vitiligo in children. Topical steroids are most effective in small newly depigmented areas. They work by limiting the amount of antimelanocyte autoantibodies produced locally. However, the risk of cutaneous atrophy and telangiectases, especially on the face and intertriginous areas in addition to the ocular side-effects secondary to periorbital application precludes their use over extended periods of time. It is for this reason that tacrolimus, a macrolide immunosuppressant is now being used as a novel treatment for vitiligo.

The effectiveness of topical tacrolimus in treating vitiligo may stem from its suppression of autoantibody recognition of cell-surface melanocyte antigens and inhibition of subsequent cytotoxic T-lymphocyte reactions.

Tacrolimus is used topically in the concentration of 0.03 percent on the head and neck and 0.1 percent over the trunk and extremities as once or twice daily applications in children over 2 years of age. Repigmentation over the head and neck is greater and quicker than over the trunk and extremities with the eyelids responding most rapidly and quickly. As seen with topical steroids, tacrolimus does not have any side-effects of atrophy, telangiectases and striae even after extended use. The adverse effects are minimal and limited to mild initial burning at the site of application that resolves with subsequent applications. Tacrolimus is a particularly welcome agent for the recalcitrant group of patients with segmental vitiligo, especially on the head and neck. There has been some suggestion in the recent literature that UV light and tacrolimus ointment in combination may be superior to tacrolimus alone, however UV light is not necessary for the beneficial effect of the drug.

Tacrolimus ointment has limited absorption from the vitiliginous skin and so no significant blood levels have been detected even when the drug is applied over large areas of the body. Tacrolimus has not been found to be phototoxic, photoallergenic or photosensitizing that further establishes its safety for use over depigmented skin. Given its immunomodulatory properties and safety profile, tacrolimus provides a new therapeutic alternative to steroids for the treatment of localized childhood vitiligo.

Management of Active Childhood Vitiligo

Role of Levamisole

Levamisole is an antihelminthic drug with immunomodulatory properties that has been used for the treatment of vitiligo for many years. It is used in children in the dose of 50 mg to 100 mg/day on two consecutive days in a week for 6 months to a year in slowly or equivocally progressive disease. There has been limited data to substantiate the efficacy of levamisole in controlling disease activity and the few studies done show varied results in marginally active vitiligo. Levamisole has limited side-effects like altered taste sensation and nausea. Agranulocytosis, though documented is extremely rare. In view of its potential efficacy and excellent safety profile, levamisole offers to be an additional tool in the armamentarium of the treating physician.

Oral Corticosteroids

Use of oral steroids as oral minipulse therapy (prednisolone 0.5 mg/kg dose on two consecutive days a week) is effective in arresting disease activity in patients with active/progressive vitiligo. This form of therapy is virtually

devoid of adverse-effects and there is sufficient data in the literature to support its safety even in children. Oral steroids in this form may be used for 6 months or more to arrest the disease and induce remission. In rare case where oral minipulse is unsuccessful, daily oral steroids (prednisolone 0.5 mg/kg for a period of 1 to 2 months is both effective and justifiable.

Immunosuppressants

When the parental concerns about the spread of disease are extreme and the social pressures abound then immunosuppressants have been used by the authors. This is reserved for special cases where oral steroids have not been able to adequately arrest disease activity but only after discussing the pros and cons with the parents of the children under treatment. Azathioprine, is the preferred choice of the authors with experience of over 10 years. The drug is used in a dose of 50 mg/day in children for a period of 6 months to a year. Due to the availability of the drug as 50 or 100 mg tablets, it is difficult to use the drug in the mg/kg dosage. Azathioprine works as a steroid sparing agent such that steroids can be discontinued sooner (within 6 months of starting treatment) and azathioprine continued for an extended period of time (senior author's experience) till the disease is rendered inactive. Azathioprine is a well-tolerated drug with rare side-effects. Before the initiation of therapy blood tests, urine analysis and a chest X-ray are done to rule out any latent infections. Also, immunizations are administered before the start of therapy and live vaccinations are avoided during the course of treatment. In the experience of the authors, no serious adverse effects or systemic toxicity has been observed in both new and follow-up cases and after many years of discontinuing therapy.

Summary

The face and neck respond best to all therapeutic approaches, while the acral areas the least. For generalized vitiligo, phototherapy with narrow-band UVB is the most effective with the fewest side-effects. PUVA is the second best choice. Topical steroids are the preferred drugs for localized vitiligo. They may be replaced by topical immunomodulators which display comparable effectiveness and fewer side-effects. The efficacy of vitamin D analogues is controversial with limited data. Surgical therapy can be very successful, but requires an experienced surgeon, limiting its widespread use. No single therapy for vitiligo can be regarded as the most effective as the success of each treatment modality depends on the type and location of vitiligo.

NOVEL TREATMENTS FOR MOLLUSCUM CONTAGIOSUM

Molluscum contagiosum (MC), a common cutaneous viral infection in children is caused by a double-stranded DNA

pox virus. Published data estimate the incidence of MC to be 1.2 percent to 22 percent worldwide. The peak age of MC is between 2 to 12 years and the condition is highly transmissible in this population. The infection spreads via skin to skin contact, through fomites, and autoinoculation. It tends to be more common in children with atopic dermatitis, and in immunodeficiency states such as leukemias, posttransplantation, and HIV-infection. These associations suggest that a defective T-cell immunity may play a role in MC infection.

MC lesions are clinically distinctive and appear as pearly, translucent papules, a few millimeters in diameter, and usually show a depression or a dell on the summit. The lesions multiply rapidly, especially in areas of increased moisture and skin to skin contact such as axillae, groins, antecubital and popliteal fossae. Erythema, if noted, around the lesions signifies an inflammatory host response against the viral pathogen portends spontaneous clearing. MC frequently shows spontaneous clearing, however, this sometimes takes months to years.

Autoinoculation, superinfection, transmission of the virus to susceptible contacts, and cosmetic stigmata are some of the concerns for which parents request treatment. Available therapeutic options are destructive modalities such as manual curettage, cryotherapy with liquid nitrogen, and electrofulguration. Even though cryotherapy and manual curettage are very effective options their use in the pediatric population is limited by the pain associated with such treatments, and the possibility of scarring. Topical agents such as tretinoin cream are moderately effective but prolonged treatment time, inconsistent response, and the erythema, burning and pruritus associated with its use make it a less favorable option.

A relatively unrecognized effective topical agent that may be used for the treatment of MC is cantharidin. It is an extract of the blister beetle, *Cantharis vesicatoris*, a member of the *Mecoidae* family of arthropods. It is a protein phosphatase inhibitor that penetrates the epidermis and induces vesiculation. Since the poxvirus resides in the superficial layers of the epidermis the vesiculation disrupts the virus which is subsequently shed off together with the crust of the lesion after a few days. The use of cantharidin for the treatment of MC was first described in 1961 by Funt, but limited data and concerns for safety have tempered with widespread acceptance of this form of therapy.

Cantharidin is available in two forms:

- *Canthacur* 0.7 percent Cantharidin
- *Canthacur PS* 1 percent Cantharidin
5 percent Podophyllin
30 percent Salicylic acid

Canthacur is manufactured by *Pharmascience inc. for paladin labs inc.* Montreal, CANADA H4P2T4 (ordering information 1-888-376-7830/ 514-340-1112).

Cantharidin application is a clinic procedure and is not recommended for home use. It is extremely easy to apply and when done so in a consistent and controlled manner, it is devoid of any complications.

The main advantage of this form of therapy over others is that it is painless in addition to being effective and therefore, aptly suited for use in children.

Attention to the following practical details ensures success when using cantharidin.

- The blunt end of a toothpick is used for precise application of a tiny amount of cantharidin over each lesion avoiding contact with the surrounding normal skin.
- The site is allowed to dry for 2 to 3 minutes. If the fluid spreads it can blister the normal skin around the lesion as well.
- A maximum of 20 lesions may be treated per visit
- Parents are instructed to rinse off the treated areas with soap and water after 4 to 6 hours (or occasionally sooner if the child feels discomfort)
- Repeat treatment is done at 2 to 4 week intervals.

A small percentage of patients treated may experience transient burning or pruritus and rarely, pain on the day of the treatment which responds to a single dose of paracetamol. Vesiculation occurs on the second or third day followed by crusting after a week and then the scab falls off. The lesion resolves without scarring. No superimposed infection has been reported in the literature or observed by the authors. Cantharidin, therefore, is a very safe and effective monotherapy for Molluscum Contagiosum in children.

Another painless modality that may be used for the treatment of MC in children above 4 years of age, is imiquimod. Imiquimod, an imidazoquinolone derivative, and the prototype of a family of topical immune response modifiers, causes specific stimulation of a local antiviral response through the activation of both innate and cell-mediated acquired immune responses via induction, synthesis and release of specific cytokines from monocytes and macrophages. Imiquimod is available as 5 percent cream in small sachets (3-12 sachets per box). It is used as local application three times a week which may be increased to

daily application after 2 to 4 weeks. Since the product is light sensitive, it is advised to open each sachet with a pin-prick and store the rest in the refrigerator for subsequent use. This not only preserves the product but also makes it more cost-effective. Studies have shown resolution of majority of the lesions within 16 weeks of therapy with minimal to no recurrences. The most common adverse effect is erythema localized to some of the treated lesions. The outcome is clearance of the lesions with excellent cosmetic outcome compared to other painful and potentially scarring alternative therapies. No systemic toxicity has been reported making topical imiquimod application an antiviral and nondestructive treatment option for treatment of molluscum contagiosum presenting as a major therapeutic advance.

Since 1999, studies have been published that satisfactorily tested the use of potassium hydroxide (KOH) in different concentrations for the treatment of molluscum contagiosum but none compared these to placebo, a recent randomized control trial compared the efficacy of 10 percent and 15 percent KOH with placebo and demonstrated that KOH may be a good therapeutic alternative for the treatment of molluscum contagiosum as it is effective, easy to apply, self-administered, inexpensive, readily available and with minimal side-effects.

Amongst the numerous treatment modalities available for the treatment of MC, choosing the right treatment is often difficult. The effectiveness of therapy and the ease of administration are two key factors to keep in mind while treating children. We provide a summary of the painless yet effective options that are available for the treatment of MC in children (Table 4).

WHATS NEW IN THE TREATMENT OF EXTRAGENITAL WARTS

The prevalence of human papillomavirus (HPV) infection is continuing to increase globally. Subtypes of HPV associated with nongenital warts (verruca vulgaris, verruca plana, and verruca plantaris) include HPV 1, 2 and 3. Pediatric population is particularly susceptible to these

Table 4: Therapies for molluscum contagiosum in children

<i>Treatment</i>	<i>Advantages</i>	<i>Disadvantages</i>
“Watchful waiting”	Painless; no scarring	Potential for spread
Cryotherapy	Effective	Painful; multiple sittings
Curettage	Effective; immediate results	Painful; risk of scarring
Tretinoin cream	Readily available; inexpensive	Minimal efficacy; poor tolerance
Cantharidin	Very effective; painless	Restricted availability
Imiquimod cream	Effective; painless	Expensive; prolonged duration of treatment
Potassium hydroxide	Self-administered; inexpensive; readily available	Limited data to support efficacy and safety

infections that tend especially to be resistant to treatment in immunocompromised patients.

A variety of therapeutic modalities have been used in treatment of warts. These are mainly directed towards tissue destruction and include electrosurgery, cryotherapy, topical salicylic acid, topical and oral retinoids, and intralesional bleomycin, plus some newly available methods such as pulsed-dye laser. These modalities are either of limited efficacy (salicylic acid, retinoids) or are painful and, therefore, not appropriate for use in children. Warts in immunocompromised patients are notoriously persistent and often refractory to standard treatment. It is in this context that the use of imiquimod becomes valuable and attractive.

Imiquimod is the first member of a new class of drugs, the immune response modifiers, and is a potent stimulator of innate and cell-mediated immune pathways resulting in potent antiviral, antitumor, and immunoregulatory properties. Imiquimod, available as a 5 percent cream formulation, is currently approved by the US FDA as patient applied therapy for external genital and perianal warts and is safe for use in children aged 4 years and above. Multiple treatment regimens have been tried but it is recommended that it be used five times weekly for up to 16 weeks. The largest study to date reported beneficial effects in 56 percent of all patients treated with 30 percent achieving complete clearance and a greater than 50 percent reduction in lesion size in the remaining 26 percent. The response to imiquimod is better for warts located on the trunk, face or dorsa of hands compared to the feet possibly due to decreased penetrability of the drug through the thick keratin layer in acral areas. The adverse effects are few and minor, like – mild erythema and, rarely, erosions confined to the site of application. Imiquimod, therefore, is a new, safe, moderately effective option for the treatment of cutaneous warts with the distinct advantage of being painless (a major consideration when treating children). It is also an effective option for treatment of recalcitrant warts especially in immunocompromised patients.

Another pain-free treatment option (extensively discussed in the treatment of molluscum contagiosum) is cantharidin. This is particularly useful for the treatment of periungual warts in children. The formulation containing cantharidin with podophyllin and salicylic acid (CAN-THACUR PS) is especially suited for use in plantar warts that are either difficult to treat or are resistant to most forms of therapy. This treatment modality has the advantage of being a simple office procedure that offers an effective, safe and nontraumatic option for the treatment of warts.

Salicylic acid has been an option for home treatment of verrucae especially on palmoplantar areas for many years, however, its limited efficacy has made it more of an adjunct therapy usually in combination with other clinic treatments like cryotherapy. A recent trial of patients with

plantar warts showed no evidence of difference in clearance of verruca at 6 months between daily application of salicylic acid (50%) for 8 weeks and cryotherapy (4 treatments 2 to 3 weeks apart; 10 second cycle). Cryotherapy, however, was a more painful and more expensive treatment option between the two. This study has renewed the role of salicylic acid as a stand-alone treatment option for verruca, especially when a painless and inexpensive option is sought.

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Kangaroo Mother Care

MMA Faridi, Veenu Aggarwal

INTRODUCTION

Poor child survival is still a major concern in India and other developing countries. Current neonatal mortality rate of 39 per 1000 live births accounts for approximately 2/3 of all infant deaths.¹ A closer look reveals that neonatal deaths are concentrated among preterm and low birth weight babies. There are five principles for newborn care.

- Maintaining temperature
- Practicing asepsis
- Providing nutrition- breastfeeding or breast milk feeding as the source of nutrition
- Monitoring of danger signs
- Appropriate follow-up.

The *in utero* temperature is 38°C and fetus spends considerable time there. At birth baby is drenched with amniotic fluid, has large surface area compared to body weight, experiences low environmental temperature, generally suited to adults, with large temperature gradient and soon starts losing heat. It has been estimated that a newborn baby loses about 0.1°C rectal temperature per minute losing about 1°C in 10 minutes. This equals to expenditure of 200 Calories. Thus, heat loss is accompanied by increased glucose consumption that may lead to hypoglycemia if heat loss is allowed to occur. Hypothermia has serious pathophysiological repercussions and increases the risk of mortality by 40 percent.

Breast milk is the natural and ideal food for the baby, and breastfeeding is the most preferred method of feeding the newborn that goes beyond providing nutrition, preventing infections, developing bonding with the mother, leaving imprints for better cognitive development and IQ, and ensuring quality survival. Early initiation of breastfeeding within one hour of birth has been shown to reduce neonatal mortality by 22.3 percent and if breastfeed can be started within 24 hours it can still prevent 16 percent neonatal mortality.

Sepsis neonatorum is the single most important cause of neonatal mortality. Health facility acquired infection is an important issue in the neonatal intensive care units world over. In developing countries financial and human resources for neonatal care are limited. Any simple, low cost, reproducible intervention for low birth weight (LBW) infants that can reduce neonatal morbidity and mortality would be an important advancement in the neonatal care. Kangaroo mother care (KMC) is one such effective and evidence based adjunct to conventional neonatal care.

WHAT IS KMC?

The KMC envisages a baby rearing method that has practical similarities to marsupial care giving where the premature infant is kept warm, insulated from external noxious stimuli and fed mother's milk ad libitum, in the pouch situated on the abdomen of the marsupial mother close to breast. The kangaroo mother, most famous member of marsupial species, makes herself an 'incubator' thus maintains temperature of the premature fawn and provides unhindered breastfeeding as the main source of food and stimulation. Kangaroo mother care (KMC) was first suggested by Rey and Martinez in Colombia in 1978. They showed beneficial effects of KMC in maintaining body temperature of the preterm and LBW newborn infants both in the hospital as well as in the community. Subsequent researches have proved that KMC is safe; effective in maintaining normothermia; encourages exclusive and prolong breastfeeding; improves child survival and helps in better cognitive development in both developed and developing countries.

Evidence of the effectiveness and safety of KMC is available only for preterm infants without medical problems, the so-called stabilized newborn. Research and experience show that:²

- Kangaroo mother care (KMC) is at least equivalent to conventional care (incubators), in terms of safety and thermal protection, if measured by mortality.
- Kangaroo mother care (KMC) by facilitating breastfeeding, offers noticeable advantages in cases of severe morbidity.
- Kangaroo mother care (KMC) contributes to the humanization of neonatal care and to better bonding between mother and baby in both low and high-income countries.
- Kangaroo mother care (KMC) is, in this respect is a modern method of care in any setting, even where expensive technology and adequate care are available.
- Kangaroo mother care (KMC) has never been assessed in the home setting.

HOW KMC WORKS ?

Kangaroo mother care (KMC) revolves around mother and baby togetherness. Baby's skin intimately touches mother's or other care giver's skin. Touch and temperature sensations exchange two ways. Following attributes, though more may be in store, can explain KMC.

Skin to Skin Contact

Naked baby with diaper is kept day and night, between the mother's breasts, with his abdomen firmly attached to her chest in upright position by a cloth (binder). Mother's body heat warms the baby and maintains normothermia. There is some evidence that maternal body temperature increases or decreases depending on the baby's body temperature. Thus, mother acts as a servocontrol heater.

Breastfeeding

Mother is able to do frequent and exclusive or predominant breastfeeding. Close proximity and SSC enhance oxytocin reflex that helps flowing breast milk from the lactiferous glands to the areola.

Bonding and Stimulation

Skin to skin contact (SSC) brings baby very close to mother. Movement of the chest and abdomen, and cardiac pulsations of the mother stimulate the baby and help in early maturation and prevention of apnea.

Enteromammary Circulation

Skin to skin contact (SSC) transmits and transfers commensal organisms from the maternal skin to the baby which helps in preventing colonization by harmful pathological bacteria. At the same time neonatal skin flora, that represents NICU/hospital pathological organisms, is transmitted to the mother who in turn makes antibodies against them. These antibodies are passed on to the baby

through breast milk and prevents development of the disease.

Olfactory Stimulation

Maternal pheromones produce individual smell and odour. Skin to skin contact (SSC) gives enough opportunity to the baby to 'sense and feel' her mother. It stimulates the baby and helps in development and better IQ.

Monitoring Danger Signs

Mother is intimately involved in the care. She can easily appreciate changes in the baby which may be pathognomonic like color change, lethargy, poor feeding, abdomen distension, vomiting, etc.

Confidence Building

Mother takes substantial charge of the newborn care. Her confidence boosts. Kangaroo mother care (KMC) gives her a sense of fulfilment that she can look after her pre-term and LBW baby and that she is important to her child as much as health workers. This morale boosting is very important for continuance of the care at home after discharge.

Early Discharge

Kangaroo mother care (KMC) has been credited with early discharge from the hospital. It saves money and risk of nosocomial infections.

BENEFITS OF KMC

The most important ones are promotion of exclusive breastfeeding and providing effective thermal control.

Other advantages are:

- Kangaroo mother care (KMC) prevents apnea by stimulation.
- Prevents nosocomial infection.
- Prevents exposure to nursery noise and bright light.
- Improves maternal and infant bonding
- Provides satisfaction and builds confidence in mother in care of delicate LBW baby.
- Cheap but equally effective, convenient substitute of expensive conventional neonatal care.²
- Early discharge from hospital.
- Diminishes pain during painful procedures in sick LBW babies.³

KMC LOGISTICS

K=Knowledge, skills, setting, communication

M=Money, manpower; machines, management, monitoring

C=Care for feeding, comfort, confidence

K = Knowledge, Skills, Setting, and Communication

The success of the KMC depends upon the counseling skills of the health givers. After initial stabilization of the baby in the NICU/health facility, nurse/physician must talk to the mother and family including father about KMC. Let mother understand advantage of thermal control and of breastfeeding or breast milk feeding in the care of the newborn baby. She then is introduced about the concept of KMC and how it maintains temperature and helps in breastfeeding. Once mother is confident and willing to undertake KMC, then nurse may give some 'practical help' by positioning the baby between breasts of the mother for 30 to 60 minutes and be supportive to her in the beginning. Later on KMC sessions may be prolonged to 6 to 8 hours and even to 24 hours.

Kangaroo mother care (KMC) can be implemented at different levels like small maternity facilities which lack special equipment (incubators, warmers). If possible LBW babies who are sick should be referred otherwise KMC can be implemented if a skilled health worker is available. Kangaroo mother care (KMC) can be provided in the following situations:

- Hemodynamically stable baby
- Birth weight >1.8 Kg—Usually stable, if so initiate soon after birth
- Birth weight 1.2 - 1.79 Kg—If stable, may initiate at home. If needing referral then while transporting baby can be kept in continuous skin to skin contact with the mother. In hospital KMC can be initiated after stabilization.
- Birth weight <1.2 kg—After delivery they usually develop serious prematurity related complications. Kangaroo mother care (KMC) can be initiated only after hemodynamic stabilization along with ongoing O₂, iv fluids or tube feeding.

M = Money, Manpower, Machines, Management, Monitoring

In general no equipment or elaborate arrangement is required to do KMC. All mothers irrespective of parity, age, education, religious affiliations or working status can provide effective KMC. However, it is important that place where KMC is being given should be clean and comfortable and secure to maintain privacy. The room temperature should be 22 to 24°C; low noise level, reclining chairs, bed with adjustable backs or ordinary beds with extra pillows; reading material and free access to father/family members.

Mother can wear any clothing that pleases her but whatever she wears it should accommodate the baby firmly and comfortably in contact with her skin. The garment shouldn't be too tight. The support binder (carrying pouch), is the only special item needed for KMC which helps mother holding baby safely close to her chest. To begin with, use a piece of cotton cloth, about a meter

square, folded diagonally in two and secured with a safe knot or tucked up under the mother's armpits. This leaves mother with both hands free and allows her to move around and do routine work while carrying the baby on to her chest.

Baby is placed naked except diaper, woollen cap and socks. If room temperature drops below 22°C, she should wear a cotton, sleeveless shirt, open at front to allow her face, chest, abdomen, arms and legs to remain in skin contact with mother's chest and abdomen. Then mother covers herself and the baby with her usual dress.

It is very important that mother maintains hygiene. It should be explained to her that she should take bath and change clothes daily. She should wash hands with soap and water each time she uses toilet. Diaper should be changed at least 4 hourly if wet and soiled. Baby's bottom may be cleaned with warm water. There is no need of using dettol or any other antiseptic-mixed water for bottom cleaning.

Mother should manually monitor body temperature of the baby by touching his abdomen and then his feet by back of her hand. Ideally both should be warm.

C = Care for Feeding, Comfort, Confidence

Breastfeeding should be done on demand when she feels that baby is trying to suck on the breast. Else breastfeeding may be offered if three hours have passed especially in LBW baby. If baby is fed by cup or nasogastric tube then measured amount of expressed breast milk may be given while baby remains in contact with maternal skin.

By accepting what mother says, thinks or feels about KMC, empathizing and praising her for doing good job boosts her confidence. It is very important that mother feels comfortable and some help is available to her for her own needs like toilet, eating and sleeping. Reading material and availability of television will keep her busy and less tense.

It is important to have a breastfeeding expert in place who can counsel her and train her for making good positioning and expression of the breast milk. Family support is extremely important. Other family members like grand mother and father can also be surrogate for the mother. However, advantage of KMC by mother outweighs anybody else.

KMC PROCEDURE

- Kangaroo positioning—Skin to skin contact between the mother and her upright baby between mother's breast on her bare chest and under her clothes.
- Head turned to one side in slightly extended position which allows open airways and eye to eye contact between baby and mother.
- Hips should be flexed and abducted in a "frog" like position and arms should be flexed.
- Baby's abdomen should be at the level of mother's epigastrium.

- Support the bottom of the baby with a binder. Binder's top should be just under the baby's ear.

MONITORING

- They should be careful about the position of baby's neck, which should not be too flexed or too extended.
- Baby's breathing
- Baby's skin color
- Baby's temperature (she should feel for baby's hand and feet)
- Number and consistency of stools
- Baby's weight (daily in hospital, otherwise weekly)
- Head circumference (should be checked once weekly)
- Reassure her that there is no danger if the baby has hiccups, sneezes
- Teach the mother (and family members) to recognized danger signs.
 - Breathing to fast or very slow
 - Chest indrawing, grunting
 - Frequent and long apnea
 - Body temperature low/high
 - Difficulty in feeding
 - Convulsions
 - Diarrhea
 - Yellow skin.

LENGTH OF KMC

Kangaroo mother care (KMC) may begin with 30 to 60 minutes. It is more to give support to the mother and making her confident. The duration may be extended to 6 to 8 hours in a stretch. It is desirable to do KMC for 24 hours with interruptions for changing diapers, hygiene, cord care of baby and for her own needs like changing sanitary pads or using toilet if not comfortable with KMC. Sessions shorter than 1 to 2 hours

should be avoided as frequent handling is stressful for the baby.

Daily bathing is not needed and it is not recommended. Bathing should be short with warm water (37°C). Baby should be dried thoroughly immediately afterwards wrapped in warm clothes and put back in KMC position quickly.

CRITERIA FOR DISCHARGE

- Good general health of baby and no concurrent infection.
- Feeding well and is exclusively or predominantly breast fed.
- Gaining weight (at least 15 gm/kg/day) for three consecutive days.
- Temperature is stable in KMC position for three consecutive days.
- Mother is confident in caring for the baby and is able to come for follow-up regularly.
- When baby starts showing signs of intolerance to KMC in the form of wriggling movement, becomes uncomfortable, cries and fusses every time mother tries to put her in pouch (usually at around 40 weeks of post-menstrual age).

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Neonatal Myopathies

Veda V Vedanarayanan

Abstract

Weakness and hypotonia are the cardinal clinical presentation of myopathies in newborn. Arthrogryposis occurs in some of them with weakness and hypotonia. Myopathies result from a variety of causes in neonates and they include myotonic muscular dystrophy, congenital muscular dystrophy, congenital myopathy and metabolic myopathies. Clinical evaluation, electrodiagnostic tests, serum CK and metabolic tests are useful in evaluating these patients. Definitive diagnosis is made with muscle biopsy and genetic studies for mutations.

Muscle diseases are important causes of hypotonia and weakness in neonates. They present either as a floppy neonate or with arthrogryposis. The clinical syndrome of floppy neonate is very easy to recognize. It is characterized by reduced resistance to passive movements of limbs, limbs kept in positions that are unusual and laxity of joints. The causes for floppy neonates are several and include diseases of the brain, spinal cord and the motor unit. (Table 1). It is not uncommon to have a disease involve multiple sites involved in motor function. Clinical examination, imaging of the brain and spinal cord, comprehensive electrodiagnostic studies and muscle biopsies may be required to determine the cause of this syndrome. Arthrogryposis is a clinical syndrome that results from muscle weakness and/or reduced movement of joints in the intrauterine period. It is characterized by stiffness in joints secondary to contracture of soft tissues around the joints. It often involves the distal joints in upper and lower limbs. This often occurs with hypotonia and weakness and hence the syndrome of floppy infant and arthrogryposis may occur together.

The clinical evaluation at the bedside can often lead to localization of the cause for hypotonia and weakness. Diffuse encephalopathies from hypoxic ischemic injury, sepsis, metabolic disorders and from sedating medications often produces impairment of consciousness in the infant. Lack of alertness, spontaneous eye opening, weak and poorly sustained cry to stimulation are clues. Often the appearance of the infant provides more information about the state of alertness in the newborn period. It can be difficult to evaluate mental status in moderate to severe premature neonate. Babies with myelopathies are often alert, although weak and hypotonic in limbs unless the clinical picture is complicated by encephalopathy (often ischemic encephalopathy). In diseases of the motor unit (motor neurons, peripheral nerves, neuromuscular junction and muscle) neonates are often alert. The reduction in muscle tone is often more prominent in muscles of limbs and axial musculature, in contrast axial muscles are weaker than the limb muscles in encephalopathy. Tendon reflexes are absent or normal and may be hyperactive in encephalopathy. Arthrogryposis can occur in upper and lower motor neuron disorders.

LABORATORY EVALUATION OF HYPOTONIC NEONATES

The laboratory evaluation begins with measurement of serum CK. It is normal in encephalopathies and in disorders of motor neuron, neuromuscular junction and polyneuropathies. Even in neonates with myopathy serum CK is often normal. The serum CK is elevated in myopathies with muscle necrosis or leaky muscle membranes, such as in congenital muscular dystrophies, acid maltase deficiency and inflammatory myopathies. The currently used normal values for serum CK are from normal adults and normal values in normal healthy neonate are not available.

Table 1: Differences between central hypotonia and hypotonia from neuromuscular weakness

Item	Central hypotonia	Neuromuscular weakness
Alertness	Reduced often	Often normal
Muscle tone	Axial muscles > appendicular	appendicular > axial
Tendon reflexes	May be hyperactive	normal or absent
Neonatal reflexes	Persistence	loss of reflexes as in normal infants

The nerve conduction studies (NCS) and needle electromyographic (EMG) examination differentiates between disorders of muscle, nerve, neuromuscular junction and motor neuron. The performance of these studies in neonates, especially in those with arthrogryposis, is technically difficult. In neonates with myopathy the sensory nerve conduction studies are normal and the motor nerve conduction studies may show reduction in motor compound muscle action potential (CMAP) with normal conduction velocity, distal and F wave latency. Repetitive nerve stimulation studies (RNS) are normal. The needle EMG examination is the most critical part of the electrodiagnostic study. The spontaneous activity may show fibrillation potentials when muscle fiber necrosis is present, as in congenital muscular dystrophies. It is normal in most congenital myopathies where the muscle fiber necrosis is absent. The voluntary motor unit potentials are abnormal and have increase in polyphasic turns with reduction in amplitude and duration. The recruitment is often abnormal and shows a pattern of early recruitment (more than usual number of motor units are activated to achieve a given amount of force). The assessment of motor unit morphology and recruitment pattern can be difficult in neonates. Definitely abnormal EMG showing myopathic change makes the diagnosis of myopathy more definite; however a normal EMG cannot exclude a myopathy in neonates.

The gold standard for diagnosis of myopathies is comprehensive pathological examination of muscle biopsy. The examination includes a battery of histochemical stains: NADH reaction, SDH reaction, PAS stain, modified trichrome stain, cytochrome oxidase stains and oil red-O reaction. Immunocytochemical reaction for cytoskeletal proteins are integral part of evaluation.

Additional studies and clinical features can provide clues to diagnosis. Congestive cardiomyopathy with myopathy suggests Pompe's disease. Thin ribs, osteopenia of bones and bell shaped chests are seen in congenital myopathies and spinal muscular atrophy. Malformations of brain and eyes can be seen in patients with some forms of congenital muscular dystrophies. Electroencephalograph (EEG) may be required to determine if there is significant encephalopathy in babies.

The examination of parents, especially mother, can lead to diagnosis in the neonate. Congenital myotonic dystrophy in the newborn can be diagnosed with confidence in a floppy infant when the typical phenotype of myotonic dystrophy is seen in mother (weakness of face and distal muscles in limbs with myotonia). Roughly 1 to 10 percent of mothers with myasthenia gravis give birth to babies with transient neonatal myasthenia gravis. Babies born to mothers with congenital myopathies may have a more severe form neonatal onset. Myotubular myopathy, especially the X-linked variety is mild in severity in mothers. Congenital myopathies and congenital muscular

dystrophies are inherited by autosomal and sex linked inheritance, and hence it is not uncommon to find evidence of myopathy in parents or siblings.

CONGENITAL MYOTONIC MUSCULAR DYSTROPHY

This condition refers to the severe clinical neonatal presentation seen in some of the babies born to mothers with relatively mild myotonic dystrophy. This is one of the common causes for muscle diseases in neonates. The diagnosis is easily made by careful clinical examination of their mothers for muscle weakness and myotonia.

The pregnancy is often complicated by hydramnios and premature labor. The babies have severe hypotonia and generalized weakness with inability to suck and swallow and sometimes to breathe. The striking feature is bilateral facial weakness with a peculiar tented appearance to the lips. Contractures of distal joints are seen often. Cardiac arrhythmias are rare, and evidence of smooth muscle dysfunction present as abdominal distention and dysmotility of the gastrointestinal tract. Unlike in adults with myotonic dystrophy, myotonia is absent on clinical and needle EMG exam.

The disorder is from intronic expansion of CTG repeats in myotonin gene located on chromosome 19. The size of the expansion is greater than 1000 repeats in neonates with CMD unlike in the affected adults where the repeat numbers are in 100s. The diagnosis can be confirmed by DNA studies showing the CTG repeat expansion in myotonin gene.

Muscle biopsy is not required for diagnosis, with the availability of genetic studies. The muscle biopsies done in the past have shown type 1 muscle fiber atrophy, increase in fibers with internalized nuclei. These biopsies are indistinguishable from patients with centronuclear myopathy (discussed below).

Management is supportive in the neonatal period. Most infants will improve over time. Breathing and feeding improve over weeks and majority of patients will walk by 2 to 3 years of age. Mental retardation is common and variable.

CONGENITAL MUSCULAR DYSTROPHY (CMD)

This term refers to a group of disorders characterized by weakness, hypotonia and frequently with joint contractures in neonates and dystrophic muscle biopsy (muscle fiber necrosis, regeneration and scarring). The weakness and hypotonia are seen in axial and appendicular muscles and contractures are often seen in distal joints and rarely proximally. Abnormalities of the brain and eye occur with some forms of congenital muscular dystrophies. Based on recent knowledge of the biochemical defect, CMD are classified into four groups:

Group 1: Defects in the laminin alpha-2 (Merosin) in the basement membrane;

Group 2: Abnormal glycosylation of alpha-dystroglycan;

Group 3: Disorder of collagen VI

Group 4: Reduction in integrin alpha 7, laminin alpha 2 receptor with normal levels of laminin alpha-2

CMD FROM DEFICIENCY OF LAMININ ALPHA-2

Reduced fetal movements are frequent and neonates are often severely weak. Difficulty with breathing, suck and swallow are common. Joint contractures, often distal in distribution, are common. Partial external ophthalmoplegia is seen in some of the patients. The serum CK is elevated, usually 10 to 150 times of normal and it decreases with reduction in muscle bulk over years. Seizures are seen in 8 to 30 percent of patients. The intelligence in later life is normal. Magnetic resonance imaging (MRI) of the brain is abnormal and shows bright T2 lesions in periventricular white matter, however the white matter in the cerebellum and brain stem are normal. Heterotopias in cerebral hemispheres, focal cortical dysplasia and irregular cortical laminations occur in some.

Muscle biopsy shows patchy areas of muscle fiber necrosis and regeneration with endomysial fibrosis. Immunohistochemical staining for laminin alpha-2 (merosin) is absent and confirms the diagnosis.

CMD FROM DISORDERS OF GLYCOSYLATION

Four forms of CMD occur from disorders of glycosylation of alpha-dystroglycan. Dystroglycan is the central component of the dystrophin-glycoprotein complex. It is critical for the normal maturation in brain, eye and muscle. All four forms of CMD present with severe, generalized hypotonia and weakness. Brain and eye involvement is seen in all forms and they vary in severity. In Walker Warburg syndrome (the most severe form) the brain shows type 2 lissencephaly. In other forms varying degrees of disturbance in neuronal migration occurs such as: pachygyria, heterotopia or cortical dysplasias with hydrocephaly. The eye involvement ranges from total loss of vision to high myopia. The different types of CMD from glycosylation defect are:

Disorder	Gene
Fukuyama CMD	Fukutin
Muscle eye brain disease	POMTGnT1
Walker Warburg syndrome	POMT1
CMD 1C	FKRP
CMD 1D	LARGE

The strength and function improves over time. The prognosis is often complicated by the presence of brain and eye abnormalities.

CMD FROM COLLAGEN 6 DEFECTS (ULLRICH'S CMD)

Collagen 6 disorders present a phenotypic spectrum, ranging from severe phenotype in the neonatal period to a milder phenotype presenting in adulthood. The neonatal phenotype presents with hypotonia and weakness at birth. Contractures are seen in proximal joints, often with kyphoscoliosis and torticollis. Joint laxity is seen distally. The calcaneus is prominent and protruded. No central nervous system involvement is seen and intelligence is normal. The serum CK is normal or slightly elevated. The muscle biopsy shows dystrophic features as in other CMD. The diagnosis is made by DNA studies on collagen 6 gene.

CONGENITAL MYOPATHIES

This group of muscle disorders is defined by specific histopathological changes, lack of progression or improvement in most instances. Some of the congenital myopathies present in neonatal period and others are detected in infancy, childhood and sometimes later. In patients becoming symptomatic in neonatal period, generalized weakness and hypotonia are the prominent clinical signs. Difficulties with suck and swallow are common and respiratory failure can be seen sometimes. Facial abnormalities can be seen and consist of long myopathic facies with tented lips. High arched palate is present in all. The weakness is generalized in distribution involving trunk, limb, facial and bulbar muscles. Extraocular muscles are involved in some of the congenital myopathies, and present as limitation in eye movements and ptosis. The ribs are often thin on X-rays and pectus excavatum, bell shaped chest are seen due to weakness of the chest wall muscles and diaphragm. Serum CK is usually normal. The EMG is myopathic or normal without fibrillations. Involvement of heart, brain, eyes or other organ system is generally absent unless they are secondarily involved due to the muscle weakness.

Nemaline Myopathy

This condition is characterized by rod or thread-like structures in cytoplasm of muscle fibers. In addition there is atrophy of type 1 fibers (Fig. 1). The severe congenital form presents in neonatal period with profound muscle weakness. Arthrogryposis is rare and cardiomyopathy is seen rarely. Early mortality is common although some may survive long-term. The gene defects are heterogeneous and in the autosomal recessive form, mutations have been described in the genes coding for nebulin and tropomyosin.

X-Linked Myotubular Myopathy

This myopathy is characterized by the presence of central nuclei in numerous muscle fibers and is similar in appearance to the myotubes. Type 1 fibers are small (Fig. 2). The

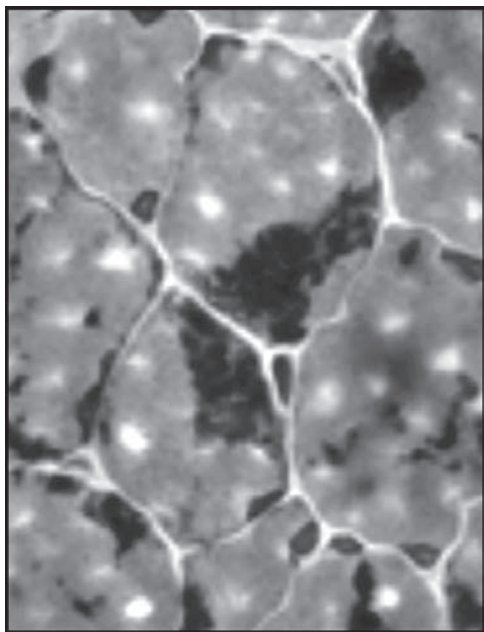


Fig. 1: Muscle biopsy stained with modified trichrome stain showing nemaline rods (*For color version see plate 22*)

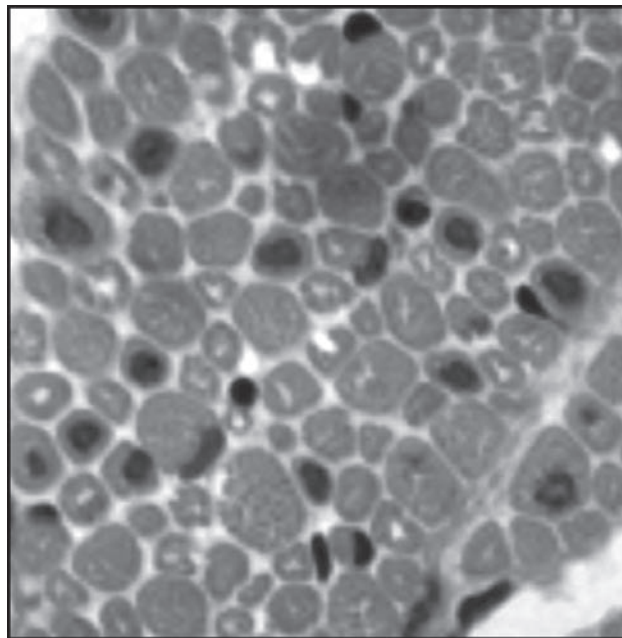


Fig. 2: Myotubular myopathy. H&E stain, showing many muscle fibers with central nucleus (*For color version see plate 22*)

X-linked recessive form presents in neonatal period with profound weakness and frequently with respiratory failure. The babies are usually long, often greater than the 90 percent in length, and have macrocephaly with hydrocephalus in some. Feet and fingers are often long and face is long. Ptosis with limitation of extraocular movements is seen in many. Ambiguous genitalia occurs rarely in these infants. The mortality is high, although there are reports of improved survival in some of these babies.

The mutation is in the myotubularin gene, a highly conserved gene responsible for regulation of genes involved in normal growth and maturation of muscle fibers. The exact mechanism involved in the pathogenesis is not clearly understood.

Congenital Fiber Type Disproportion

This congenital myopathy is characterized by selective atrophy of type 1 fibers with a predominance of type 1 fibers. This disorder begins in infancy and often improves over time. Contractures, scoliosis and hip dislocation are common. The strength and function improve over time. The genetic defect is unknown.

METABOLIC MYOPATHIES

Infantile Acid Maltase Deficiency

This disorder results from a deficiency of acid maltase, a lysosomal enzyme. The myocardium, neurons and other several organs are involved besides the muscle. The

myopathic symptoms are prominent and the affected babies present with hypotonia and weakness and often heart failure from cardiomyopathy. Cardiomegaly on chest X-ray is often striking with evidence of left ventricular hypertrophy on EKG. The serum CK is high. Myopathic motor units and fibrillations are seen on needle EMG. Muscle fiber necrosis with regeneration and vacuolar change in cytoplasm of muscle fibers are prominent on muscle biopsies. The vacuoles contain PAS positive material and stain positively with acid phosphatase. The activity of acid maltase is severely reduced in muscle and similar reduction can be shown in leukocytes. DNA mutation studies can be performed on peripheral blood.

Treatment is supportive and mortality is high. Treatment trials with enzyme replacement are being evaluated.

Other Metabolic Myopathies

Disorders of fatty acids, medium and long chain fatty acid present in neonatal period with muscle weakness, encephalopathy and elevated serum CK. The neonatal form of carnityl palmityl transferase 2 present with hypotonia and elevated serum CK and episodes of myoglobinuria can be brought on by periods of fasting.

Myopathy and encephalopathy are clinical presentations of mitochondrial disorders in the neonatal period. They can result from deficiency of complex 1, 3, 4. These patients have lactic acidosis from birth. Some of these phenotypes are fatal. One phenotype of complex 4 deficiency causes severe muscle weakness in the neonatal period and then spontaneously reverses by age 1.

OTHER MYOPATHIES

Primary inflammatory myopathies are rare in neonates. There are few reports of neonatal idiopathic polymyositis. The diagnosis in these patients has been made on routine histochemical stains and have not had full battery of immunocytochemical staining for cytoskeletal proteins, hence it is not certain if they have primary autoimmune inflammation or if the inflammatory reaction is a secondary process.

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Advances on Rotavirus Disease

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Rotaviruses are the most common cause of severe diarrheal disease in infants and young children worldwide.

Rotavirus is a nonenveloped Ribonucleic acid (RNA) virus discovered in 1973 by Ruth Bishop and colleagues, at the Royal Children's Hospital in Melbourne, Australia. In 2004, rotavirus infections were estimated to cause approximately 527,000 (475,000—580,000) deaths, predominantly in developing countries. Although the viral strains show considerable diversity, 5 serotypes are responsible for the majority of human rotavirus disease. Rotaviruses cause gastroenteritis especially among children of less than 5 years age worldwide and acute diarrhea in the young ones of many other mammalian species (calves, piglets, lambs, rabbits, etc.) and of birds.

ROTAVIRUS STRUCTURE, STRAINS AND SERODIVERSITY¹⁻⁸

The structure of rotavirus is complex. It is called as rotavirus due to its wheel-like structure when observed under electron microscope. (Rota = wheel in latin).

Rotavirus genome has 11 segments of double stranded RNA. This genome codes for six structural proteins (VP1-VP4, VP6, VP7) and six nonstructural proteins (NSP1-NSP6).

Following are the layers that surround the genome (Fig. 1):

Core: Inner layer that surrounds the genome and has viroproteins VP1, VP2, VP3.

Inner capsid: Intermediate layer made-up of VP6.

Outer capsid: Outer layer that has VP7 at surface and VP4 as projections.

The viral antigens like VP4 (also called P because it is lysed by intestinal protease during viral entry), VP7 (Also called G because it is a glycoprotein), VP6 (that forms inner capsid) and NSP4 (which acts as enterotoxin) are

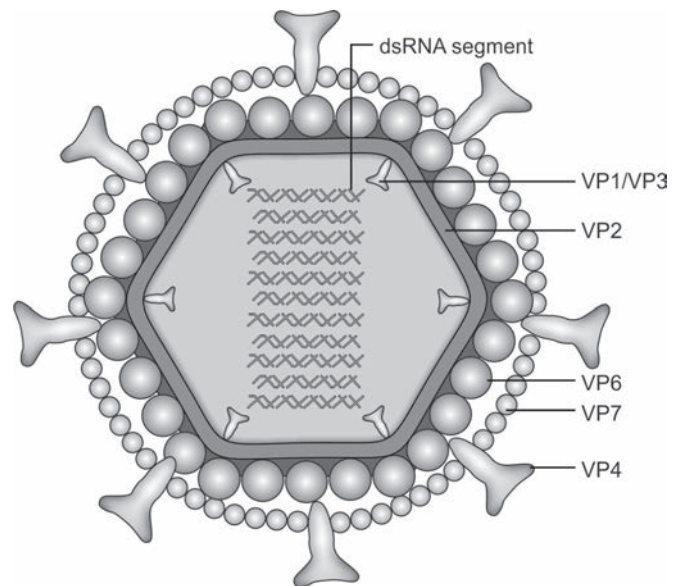


Fig. 1: Schematic presentation of rotavirus vaccine

important in the pathogenesis of disease and also in the protection against rotavirus infection. VP4 and VP7 elicit neutralizing antibodies and therefore considered to be involved in immune protection. Also these antigens are of importance in understanding classification and nomenclature of rotaviruses.

CLASSIFICATION OF ROTAVIRUSES

Based on inner capsid protein (VP6) there are seven groups of rotaviruses (A to G) Group A, B and C all of which cause human infection, the most common being group A. Within group A, rotaviruses are classified using a binary system (similar to influenza). For this the serotyping and genotyping methods are used.

G types: For G types, antigen serotype and genotype matches and therefore these types are mentioned based on serotype alone as G1, G2, G3, etc.

P types: For P types, there is greater number of genotypes than serotypes and concordance between serotype and genotype is rare. Hence P type is denoted as serotype, followed by the genotype (mentioned in brackets), e.g. P1(4), P1(8).

Nomenclature of Rotavirus

Binary nomenclature of rotavirus strain is used based on G and P type of that virus, for example, G1P1(8), G2P1(4). In short it can be mentioned only using genotype of P, e.g. G1P(8) G2P(4).

Serodiversity of Rotavirus Strains

The segmented nature of rotavirus genome allows for gene reassortment when a single cell is coinfecting by two different rotavirus strains. Theoretically this property has potential to generate two raised to power 11 different combinations of G and P proteins. In practice the number of G and P combinations is less.

Peculiarity of rotavirus is that the predominant strains show diversity with regards to region.

Globally Common Strains of Rotavirus

Four common G types (G1, G2, G3 and G4) in conjunction with P[8] or P[4] form over 88 percent of the strains analyzed worldwide. In addition, serotype G9 viruses associated with P[8] or P[6] were shown to have emerged as the fourth globally important G type with the relative frequency of 4.1 percent.

Common Strains in India

The Indian Rotavirus Strain Surveillance Network was established with four laboratories and 10 hospitals in seven different regions of India.

In this network, the stool samples of hospitalized cases for age in children <5 years were tested. From December 2005 through November 2007, Rotavirus was markedly seasonal in northern temperate locations but was less seasonal in southern locations with a tropical climate.

The most common types of strains were G2P[4] (25.7 percent of strains), G1P[8] (22.1 percent), and G9P[8] (8.5 percent); G12 strains were seen in combination with types P[4], P[6], and P[8] and together comprised 6.5 percent of strains. This study showed the regional diversity in rotavirus strains.

As opposed to global scenario wherein G1P8 strain was most common; this landmark study established that in India the scenario was a little different with G2P4 being the most common strain.

There are studies across world which found different emerging strains of rotavirus like G9, G10, G12. Out of emerging strains, only G9 has gained epidemiological importance.

Rotavirus Burden and Epidemiology^{4,9-13}

Rotavirus is the most common cause of severe gastroenteritis in infants and young children less than 5 years worldwide.

Clinical spectrum of rotavirus gastroenteritis (RVGE) ranges from mild to severe watery diarrhea with abrupt onset of fever and vomiting. (Vomiting precedes diarrhea in most cases).

It can result in dehydration, electrolyte disturbances, shock and even death.

Most common age group for severe gastroenteritis is in children aged 6 to 24 months.

The disease is of universal occurrence across developed and developing world.

Clean water supplies and good hygiene have not had a substantial effect on control of RVGE.

Global Rotavirus Burden

Rotavirus accounts for annual 6,10,000 deaths, 2.4 million hospitalizations, 24 million clinic visits and 114 million of rotavirus disease episodes.

Rotavirus epidemiology in developing world is characterized by a high mortality (about 85% of global mortality occurring in developing countries), serodiversity of strains, occurrence of coinfection by other enteric pathogens and earlier age of severe disease.

Rotavirus Burden in India

Burden of disease: Rotavirus diarrhea is one of the largest causes of child mortality in India. Amongst total rotavirus mortality in world, India accounts for the highest number of deaths due to RVGE. As per recent surveillance, rotavirus is associated with 39.2 percent of all diarrhea-related hospital admissions among children aged <5 years in India.

Every year in India, rotavirus diarrhea causes an estimated 122,000 to 153,000 deaths, 457,000 to 884,000 hospitalizations and 2 million outpatient visits in children <5 years of age.

As per recently published estimates for rotavirus global mortality, in 2008, diarrhea attributable to rotavirus infection resulted in 453,000 deaths (95% CI 420,000–494,000) in children younger than 5 years—37 percent of deaths attributable to diarrhea and 5 percent of all deaths in children younger than 5 years.

Five countries accounted for more than half of all deaths attributable to rotavirus infection: Democratic Republic of the Congo, Ethiopia, India, Nigeria, and Pakistan, India alone accounted for 22 percent of deaths (98,621 deaths).

Protection Against Rotavirus After Natural Infection¹⁴⁻¹⁶

Immune mechanisms that are responsible in rotavirus disease occurrence or protection from it are complex and not completely understood. Also there is no defined correlate of protection for rotavirus disease. There are multiple studies which involved follow-up of birth cohort to evaluate if the previous infection with rotavirus (symptomatic or asymptomatic) offered protection against subsequent infection or disease. A study by Velazquez et al which had birth cohort of 200 new births that was followed up for 2 years, found that natural infection offers protection from subsequent disease. The protection is complete against the moderate to severe disease if there are two previous infections. This study formed the basis for developing rotavirus vaccines and its dosage.

In a recent landmark study by Gladstone et al which was conducted in Vellore, the birth cohort of about 400 newborns was followed up for 3 years. It was found that the protection offered by the natural rotavirus infection against moderate to severe diarrhea is only 79 percent after 3 previous rotavirus infections. Reinfections were common and subsequent infections were not always mild or less in severity. Based on these results, authors of the study were of the opinion that more number of doses or increasing the dose or early (neonatal or maternal) vaccination may be options to get better efficacy of rotavirus vaccines in Indian setting where efficacy of the vaccine (and in general other oral vaccines) is found to be less as compared to developed world.

Available Rotavirus Vaccines: Efficacy, Effectiveness and Safety¹⁷⁻²⁶

The much publicized previous attempt at a vaccine, Rotashield was licensed in the United States in 1998. It had been shown to be efficacious in reducing the frequency of severely dehydrating rotavirus. Furthermore, it was cost effective and the strategy was clear; to use the high-priced vaccine routinely in industrialized countries to subsidize its use in developing countries. However, postmarketing surveillance detected an apparent increase in a relatively rare event, intussusception. The relationship was most strong when the first dose of vaccine was given with the first or second dose of the diphtheria—pertussis—tetanus vaccine. In the ensuing controversy, there was a reversal of the recommendation for universal immunization in the United States, leading to a withdrawal of the vaccine from the market, precluding the possibility of its deployment in developing countries.

Undeterred by the failure of Rotashield, pharmaceutical companies have persisted in developing alternatives. There were two vaccines that were developed later: RotaTeq which is a human bovine pentavalent vaccine and it is recommended to be used in three dose schedule that fits into the ongoing primary vaccination schedule. RotaTeq is ready to use fully liquid vaccine, available in latex free dosing tube.

Another vaccine, Rotarix is monovalent attenuated human rotavirus vaccine and it is recommended to be used in two doses. In India, the available formulation of Rotarix needs reconstitution. In China, there is a lamb derived rotavirus vaccine which is not licensed outside China and not much data is available about this vaccine.

The two vaccines: RotaTeq and Rotarix underwent robust clinical trials before approval for use. Each of these two trials recruited and followed more than 60,000 infants, making them the largest prelicensure vaccine trials conducted to evaluate vaccine safety (intussusception in particular). Importantly, neither of the trials have noted a significant difference in cases of intussusception (or other serious adverse events) between vaccine and placebo based on which the global bodies have declared the vaccines to be safe.

RotaTeq phase III clinical trial was conducted in 11 countries across three continents and it showed efficacy of 98 percent against severe RVGE and 74 percent against any severity of RVGE. It also demonstrated efficacy against different rotaviruses prevalent in the region.

Rotarix phase III clinical trial was conducted in 11 Latin American countries and Finland. The efficacy of the vaccine against severe rotavirus gastroenteritis and against rotavirus-associated hospitalization was 85 percent and reached 100 percent against more severe rotavirus gastroenteritis.

The results from both vaccines cannot be compared to determine which vaccine is superior as the studies were conducted in different settings and countries and also the scales used for scoring severity of gastroenteritis were different. Till date there is no head to head comparison study of RotaTeq and Rotarix.

The development rationale of these two vaccines differed. Both the vaccines try to simulate protection after natural rotavirus infection. RotaTeq followed the modified Jennerian concept and developed human-bovine reassortant vaccine. Bovine strain is naturally attenuated for human infection and pathogenesis and with the bovine genetic background, the vaccine has human antigens as G1, 2, 3, 4 and P(8) so that the vaccine would be safe and also immunogenic and efficacious. It included the most common rotavirus antigens that are prevalent globally. The three doses schedule was used based upon the earlier studies that showed good immunogenicity of three doses and finding from Velazquez study that at least two natural infections are essential to offer protection against severe disease and three infections to offer protection against mild disease.

Rotarix is an attenuated human rotavirus vaccine. It contains a single attenuated human rotavirus strain G1P(8). It was developed as two dose vaccine based on results of study on protection after natural rotavirus infection (Velazquez et al) that showed complete protection against severe disease after two natural infections.

Both the vaccines also demonstrated good efficacy in reducing health care resource utilization (HCRU) for

rotavirus gastroenteritis. In post-licensure period also, the vaccine has proven to be highly effective in developed world and the seasonal epidemic peaks of rotavirus disease in US are now almost absent.

Safety of vaccines was also established in post-licensure surveillance studies. In Australia, there was a small increased risk of intussusception found for both the vaccines. In Mexico and Brazil, monovalent vaccine was found to be associated with small increased risk of intussusception after vaccine administration, that led to label change of monovalent vaccine by US FDA.

For pentavalent rotavirus vaccine, such increased risk was not found in US.

However, it is noteworthy that this small increased risk in some settings is definitely not a cause of concern as the vaccines are highly effective and benefits outweigh the risk.

In developing countries also, these vaccines were evaluated and though the efficacy of both vaccines was less as compared to developed world, the impact can be substantial looking at the burden of disease in these countries. WHO also has endorsed the use of rotavirus vaccines in national immunization schedule at global level after reviewing this data of developing countries clinical trials of RotaTeq and Rotarix. Rotarix was evaluated in South Africa and Malawi while RotaTeq was evaluated in Africa (Ghana, Kenya, Mali) and also in Asia (Vietnam and Bangladesh). Efficacy for protection against severe RVGE ranged between 51 to 64 percent in these trials.

Vaccines in Pipeline for Rotavirus¹⁷

Research is continuing in the field of rotavirus vaccine. Presently some vaccines are in the clinical trial. These include: A human neonatal P[6]G3 strain, RV3, developed by Bishop and colleagues in Australia, a human bovine reassortant vaccine developed by Albert Kapikian and presently undergoing development and trials at different countries and a neonatal strain vaccine (G9P11) being developed by Bharat Biotech in India. This G9P(11) virus strain has the VP4 of bovine rotavirus origin, and all other segments of human rotavirus origin. Other approaches to the development of rotavirus vaccines are also being pursued. Rotavirus antigens for parenteral delivery have received some attention as virus-like particles prepared in baculovirus, expressed antigens, DNA vaccines, and killed virus. These novel approaches are being pursued using animal models.

SUMMARY

There is definite role the rotavirus vaccines have played in developed world. Now, it is the turn of developing countries like India where rotavirus disease burden is the highest to get the benefits of the rotavirus vaccines.

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